Fusion of Magnetic Resonance Imaging and Cone-Beam Computed Tomography: A New Approach to Diagnostic Imaging of Temporomandibular Joints.

By

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Abstract

Aims: to develop a reliable and accurate method to co-register magnetic resonance imaging (MRI) and cone-beam computed tomography (CBCT) images for improved assessment of TMJ internal derangement in adolescents and adults, and to utilize this MRI-CBCT co-registration tool to quantify TMJ changes in several clinical settings. The TMJ articular disc derangement is a three-dimensional (3D) problem that is commonly described and diagnosed from two-dimensional (2D) images. This project also aimed to construct 3D models of the TMJ to enable quantitative analysis of tissue changes in all directions.

Methods: 1) Two techniques of the MRI-CBCT image co-registration were tested for image quality, and the technique with the highest image quality was tested for accuracy. 2) Reliability of evaluation of TMJ disc position and osseous pathology from MRI alone, CT alone, and fused MRI-CBCT images was tested among radiologists. 3) Accurat and reliability of assessment of TMJ disc position by novice examiners from MRI-CBCT images was tested. 4) Applicability of the MRI-CBCT images to evaluate the TMJ disc position in adolescents was tested. 5) Feasibility of using MRI-CBCT image co-registration as a tool to reconstruct 3D models of the TMJ to evaluate changes of the TMJ articular disc and condyle was tested in patients pre- and post-surgical treatment of oropharyngeal cancer.

Results: 1) The intrinsic MRI-CBCT image co-registration technique produced high image quality to visualize TMJ and was proved accurate. 2) The MRI-CBCT images improved the reliability among examiners of varying experience levels in classifying disc position compared to MRI alone. The diagnostic value of the MRI-CBCT images to detect osseous abnormality is comparable to CBCT alone except for small osseous changes such as erosions. 3) The MRI-CBCT images improved the reliability of novice examiners to evaluate the TMJ disc position compared to MRI alone. 4) The examiners' reliability to evaluate the disc position in adolescents was not improved due to the low quality of the CBCT images obtained for adolescents. 5) Using the TMJ 3D reconstructed models were useful to quantify disc and condyle position and morphology changes after oral cancer surgical treatment.

Conclusions: The MRI-CBCT image co-registration is a reliable and accurate tool to assess the TMJ internal derangement that may be particularly helpful for readers inexperienced in MRI, and provides a 3D representation of TMJ tissues that allows quantification of changes in TMJ soft and hard tissues after treatment and over time. The MRI-CBCT image co-registered images are seem to be useful for TMJ diagnostic research and educational fields, and has a great potential a routine clinical application to evaluate the TMJ soft and hard tissues.

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Chapter 1: Introduction

1.1 Literature Review

1.1.1 Anatomy of the Temporomandibular Joint

The Temporomandibular Joints (TMJ) are bilateral synovial joints that articulate the mandibular condyles below with the socket in the base of the skull (glenoid fossa) above. The squamous part of the temporal bones forms the superior part of the mandibular fossa, and the tympanic part contributes to the posterior surface of the fossa. The inferior surface of the zygomatic process of the temporal bone forms the articular eminence in front of the glenoid fossa. The mandibular condyles fit inside the glenoid fossa of the temporal bone. The condyles are ellipsoid in shape, and peripheral projections are called medial and lateral poles. In the coronal view, the condyles are slightly rotated, with a medial pole extending medially and posteriorly toward the foramen magnum to perfectly fit into the glenoid fossa of the temporal bone. The articular disc is the third articulating component that interposes between the condyle below and glenoid fossa/articular eminence above. Figures 1.1 and 1.2 illustrates the anatomical structures of the TMJ.

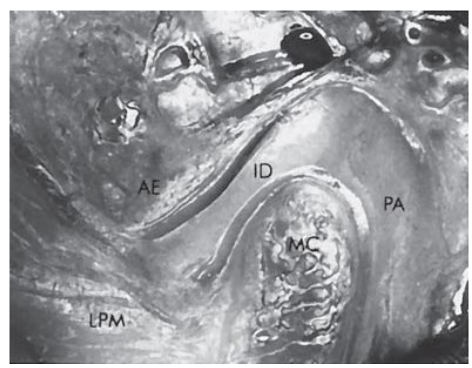

Figure 1.1: Sectioned cadaver specimen illustrates TMJ anatomy in a sagittal view. *AE*: Articular eminence; *ID*: Intra-articular disc; *LPM*: Lateral pterygoid muscle; *MC*: Mandibular condyle; *PA*: Posterior attachment. *(Courtesy Dr. W.K. Solberg, Los Angeles, CA*).[1]

During function, the condyles rotate around their horizontal axis inside the glenoid fossa in a hinging movement, and translate down the posterior slope of the articular eminence in a gliding movement, which makes the TMJ a "*ginglymoarthrodial joint"*.[2] The articulating surfaces are enclosed within the joint capsule and are lubricated with a synovial fluid during function. Each of these structures is discussed later in this chapter.

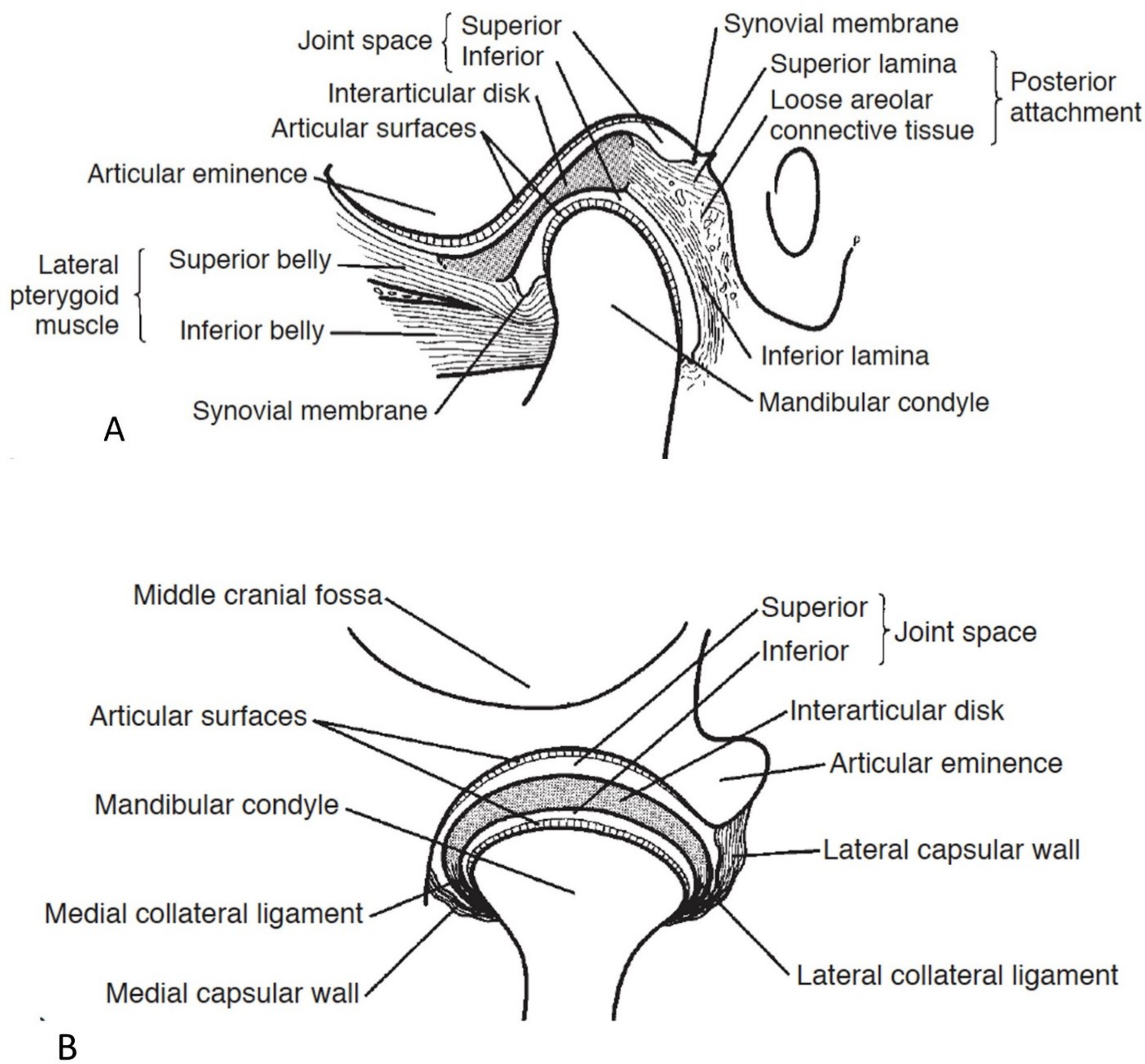

Figure 1.2: TMJ anatomy. A: Sagittal view of the TMJ. B: Coronal view of the TMJ. *(Reproduced from Pharoah; Courtesy Dr. W.K. Solberg, Los Angeles, CA)*.[1]

1.1.1.1 Skeletal components of the temporomandibular joint

The condyle is covered with a secondary cartilage that is responsible for its adaptive growth in response to the functional demands by the developing mandible. The secondary cartilage maintains the condyle's proper anatomic relationship with the temporal bone and is composed of four histologically different layers (Figure 1.3). The most superficial layer is the *articular zone* layer. This layer is formed of dense fibrous connective tissue, in which the collagen fibers are tightly packed in bundles that are organized in a parallel pattern to the articular surface. The *articular zone* layer is designed to withstand the shearing forces during the joint movement, making it less susceptible to break down over time, and has better ability to repair than hyaline cartilage. The second layer is the *proliferative zone*. It contains undifferentiated mesenchymal cells that are responsible for the fibrous connective tissue proliferation, in response to the functional demands. The third layer is the *fibrocartilaginous zone*. It contains collagen fibrils that are arranged in random orientation and provides resistance against compression forces. The *fibrocartilaginous zone* layer thickness varies according to its position in the joint and the individual's age, and it continues outside the boundaries of the joint space to merge with the external fibrous layer of periosteum covering the condylar neck. The deepest layer is the *calcified cartilage zone*. It is composed of chondrocytes and chondroblasts that form bone cells in a scaffold extracellular matrix. It becomes continuous with the outer or osteogenic layer of the periosteum (Figure 1.2).[3] In the adults, the periosteum covers the cortical bone which is supported by underlying trabeculae. The cortical bone is absent in growing adolescents, and space is occupied by a cartilaginous layer that is responsible for matrix formation, cartilage replacement, and mineralization. Endochondral bone formation replaces the forming cartilage at the resorptive interface between the developing the cartilage and the newly formed bone.

The condylar secondary cartilage is avascular and has non-innervated regions. No pain can be perceived directly from the condylar cartilage, and the synovial fluid provides the required nourishment. The structure of the posterior slope of the articular eminence and roof of the glenoid fossa are identical to the surface of the condyle.

The condyle undergoes continuous change during the active growth and development age. The tissue alterations such as tissue thickness, composition, and degree of calcification continue throughout adult life mainly due to changes in dental occlusion, mandibular function, and increasing age. Age-related condylar remodeling is a balance between bone formation and resorption, and the condylar cartilage adaptive role is important in maintaining the facial balance throughout the adult life. Reduced adaptive capacity results in tissue breakdown consistent with osteoarthrosis and degenerative joint disease.

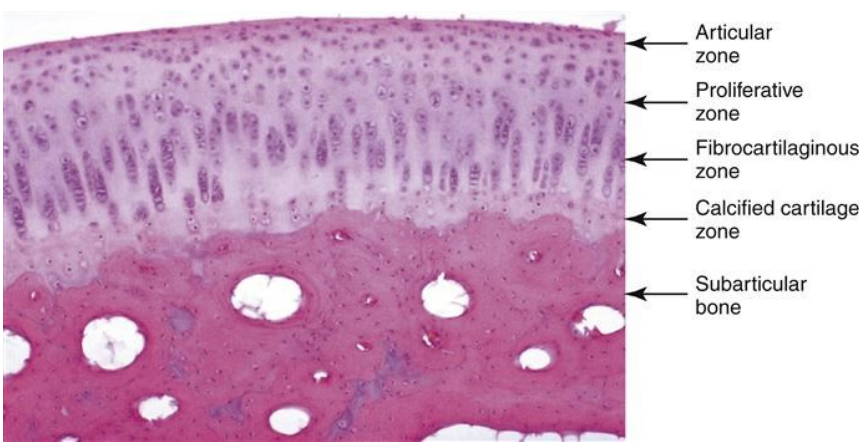

Figure 1.3: Histologic section of the superior surface of the condyle illustrating the different zones of the secondary cartilage. *(Reproduced from Cohen B, Kramer IRH, editors: Scientific Foundation of Dentistry. London 1976, William Heinemann*).[4]

1.1.1.2 Articular disc

The articular disc is an avascular, non-innervated, biconcave (wedge-shape) body that is composed of dense fibrous connective tissue. The articular disc is anatomically interposed between the mandibular condyles and the temporal bones to facilitate the complex movement of the joint, prevent direct bone contact and serve as a shock absorber during the joint's functions. In the sagittal view, the articular disc is divided into three regions according to the thickness (Figures 1.1 and 1.2). The middle region is the thinnest one, and it is called the *intermediate zone*, which is anatomically interposed between the condyle and the posterior slope of the articular eminence. The anterior region is thicker and is referred to as the anterior band, the posterior region is known as the *posterior band* and is slightly thicker than the *anterior band*.[2] The intermediate zone is the thinnest region and a load-bearing zone that is rich in dense collagen fibers. The load-bearing region also has high concentration of the proteoglycans, glycoproteins, and enzymes.[5] The collagen fibers are in a sagittal orientation parallel to the surrounding articular osseous surfaces in the middle, and fan out as they enter the anterior and posterior band regions (Figure 1.4). The posterior band is the thickest region and it lies between the posterior surface to the condylar head and at the anterior part of glenoid fossa (Figure 1.1). The anterior band is thinner than the posterior band and lies in the region anterior to the condylar head and the posterior slope of the articular eminence.

The collagen fibrils counteract the swelling pressure caused by the interstitial fluid that contributes to joint loading equilibrium.[6] The proteoglycans connect with hyaluronic acid chains and form hydrophilic proteins that attract water to the intercellular matrix. As the joint loading increased, the interstitial fluid flows out the disc, and as the loading decreases the fluid is absorbed. This fluid flowing action is the mechanical base of the *weeping lubrication* of the articular tissue (Figure 1.4).[7] In summary, the collagen fibrils network resists the tensile forces of the interstitial fluid swelling pressure; the proteoglycans resist the compression/loading forces of the joint, and the fluid absorption mechanism resists the fluid diffusion out of the disc when loading forces are released.[7]

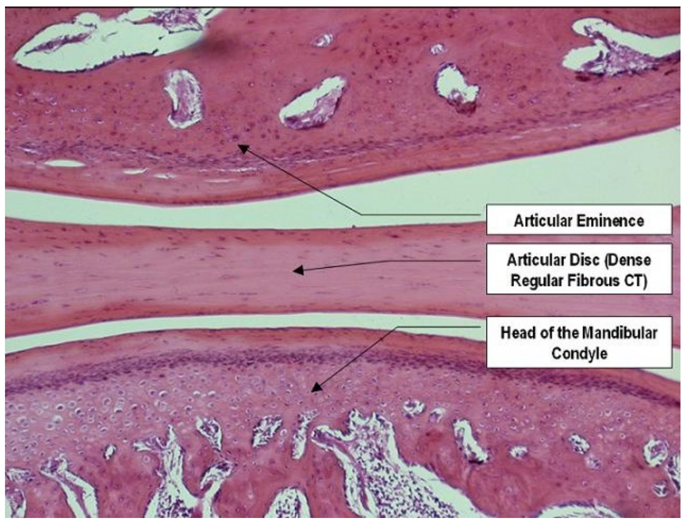

Figure 1.4: Histologic sagittal section of a healthy articular disc, eminence and mandibular condyle. *(Reproduced from* <u>*learn.dentistry.utoronto.ca*</u>*, Courtesy of University of Toronto oral histology department*).

The articular disc divides the joint space into superior and inferior compartments. In the coronal view, the medial region of the articular disc is thicker than the lateral region to correspond with the increased medial space between the condyle and the glenoid fossa. The articular disc is attached posteriorly to the *retrodiscal tissue*, which is a highly vascularized and innervated loose connective tissue. The *retrodiscal tissue* is surrounded superiorly by a connective tissue lamina that contains many elastic fibers and is referred to as the *superior retrodiscal lamina.* Inferiorly, the retrodiscal tissue is surrounded by a similar lamina that is mainly composed of collagen fibers and called the *inferior retrodiscal lamina.* The *superior retrodiscal lamina* connects the disc's superior posterior border to the tympanic membrane, and the *inferior retrodiscal lamina* connects the disc's inferior posterior border to the posterior surface of the condylar neck. Anteriorly, the articular disc is attached by two collagenous, superior and inferior, attachments that connect the disc to the surrounding capsular ligament. The *superior attachment* connects the disc to the anterior margin of the articular eminence of the temporal bone, and the *inferior attachment* connects the disc to the anterior surface of the condylar neck. The region between the *superior* and *inferior attachments* of the disc is attached to the lateral pterygoid muscle by tendinous fibers. However, recent studies denied the attachment between the lateral pterygoid muscle and the disc.[8,9] The medial and lateral margins of the articular disc are attached to the medial and lateral poles of the condyle by *collateral/discal ligaments* that are composed of collagenous connective tissue fibers. The *collateral ligaments* are fused with the joint capsule and secure the side margins of the superior and inferior joint compartments.[10,11]

1.1.1.3 Capsule

The TMJ is surrounded with a capsular ligament that consists of dense non-elastic collagenous connective tissue fibers. The capsular ligament is a conical shaped ligament with a superior wider-end attached along to the margins of the temporal bone articular surfaces, and an inferior narrower-end attached to the neck of the condyle. The articular disc collagen fibers merge into the lateral wall of the capsule. The capsular ligament passively restricts excessive joint movement outside its anatomical limits, protects the joint from any disruptive external forces and retains the joint's synovial fluid. The capsule is innervated by branches of the trigeminal nerve that travel with the blood vessels to the anterior and posterior discal attachments.[12]

1.1.1.4 Synovial membrane

The non-articular surfaces of the joint are lined with a synovial membrane that produces synovial fluid in the joint compartments (Figure 1.2). The synovial fluid lubricates the articular surfaces and reduces friction during function. The joint lubrication occurs in two forms: *boundary lubrication* when the synovial fluid runs through the joint compartment during function, and *weeping lubrication* when the synovial fluid is squeezed out the articular tissues under compression.[13] The synovial membrane is composed of an external cellular layer called synovial intima and a deep layer called the subintimal layer. The subintimal layer consists of collagen fibrils, intercellular matrix, and fibroblasts. It is a permeable layer that merges with the joint capsule tissues. The intimal layer comprises of several layers of synovial endothelial cells that are responsible for synovial fluid production and absorption. The synovial membrane is free of nerve supply, but is highly vascular.

The synovial fluid is a transudate of blood that is rich in proteins. The synovial membrane intimate cells produce hyaluronic acid and proteoglycans molecules which increase the viscosity of the synovial fluid.

1.1.2 Function and Biomechanics of the Temporomandibular Joint

The TMJs are bilateral joints that are connected to one bony frame “mandible”. Despite the fact that joints can function separately, each joint is influenced by the other during the function. The function of the TMJ is structured into two forms:

1. Hinging or rotational movement: the articular disc is attached to the condylar head by the medial and lateral ligaments forming the *condyle-disc complex*. The condyle rotates within the inferior joint compartment, against the articular disc and inside the glenoid fossa of the temporal bone. This movement of the condyle allows a maximum mouth opening of about 25 mm, and only limited lateral movements.
2. Gliding or translational movement: the *condyle-disc complex* rotates and travels within the superior joint compartment, outside the glenoid fossa and against the posterior slope of the articular eminence of the temporal bone. This movement of the *condyle-disc complex* allows the maximum mouth opening possible (45-59 mm), and lateral movements of about 10-15 mm.[2]

During the function, the articular disc facilitates the movement between the incongruent articulating surfaces. At maximum intercuspation, the intra-articular pressure increases, the condyle fits itself inside the intermediate zone between the two thicker bands and the *condyle-disc complex* is squeezed against the temporal bone. At the wide mouth opening, the *condyle-disc complex* is pulled forward against the articular eminence, the superior retrodiscal lamina becomes increasingly stretched and applies posterior retraction pressure on the articular disc. The disc morphology and intra-articular pressure maintains the condyle’s self-positioning inside the intermediate zone, allows the *condyle-disc complex* to translate against the articular eminence and prevents the disc from being over retracted posteriorly.

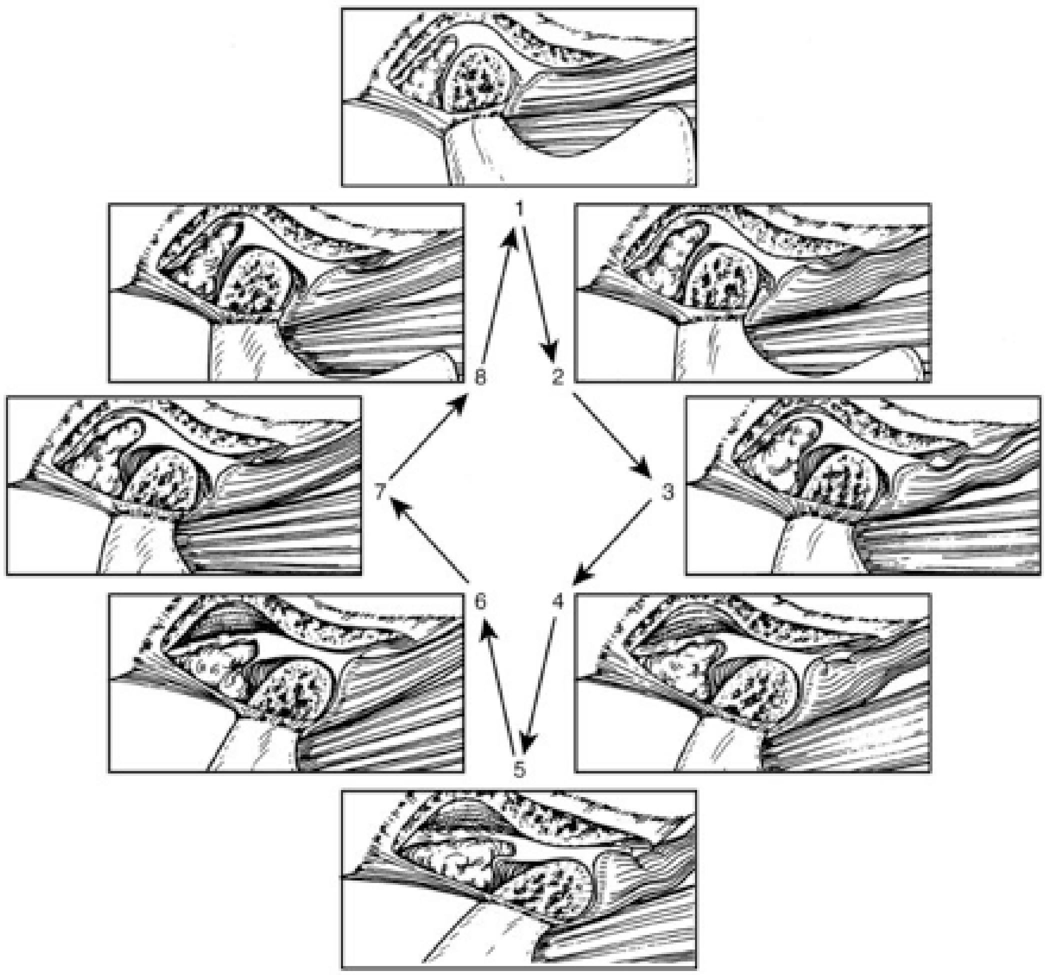

Figure 1.5: Normal functional movement of the condyle and disc during the full range of opening and closing. The disc is rotated posteriorly on the condyle as the condyle is translate out of the fossa. The closing movement is the exact opposite of opening. The disc is always maintained between the condyle and the fossa.[2]

During mouth closing, the superior lateral pterygoid muscle contracts in conjunction with the elevator muscles. The fibers of the superior lateral pterygoid muscle which is attached to the anterior border of the disc protract the disc anteriorly and medially into a resting position. However, the role of the lateral pterygoid muscle was debated in the literature, and recent reports denied any attachment of the lateral pterygoid muscle fibers to the anterior surface of the disc.[8,9] At rest, the intermediate zone of the wedge-shaped articular disc passively interposes between the condyle and the posterior surface of the articular eminence. The *condyle-disc complex* is seated inside the glenoid fossa in an orthopedically stable position by the masticatory muscles that are in a tonus state (mild contraction). The low intra-articular pressure allows the articular space to widen and the disc to slightly move in an anterior position permitted by the available space. The condyle is now in contact with the intermediate zone and the posterior band of the articular disc. Therefore, the proper pressure during function is necessary to maintain the normal condyle-disc relationship. During mastication, the intra-articular pressure increases with the rotational movement of the condyle. The histological structure of the articular disc plays an important role in absorbing and distributing the intermittent loads by the mastication movement, maintaining joint stability and spreading synovial fluid on the articular surfaces by weeping lubrication. The normal disc position relative to the condyle is essential for articular tissues health and hydration.

It is important to mention that the other collagenous ligaments attached to the articular disc do not actively participate in controlling functional disc movements. Their role is to restrict TMJ extreme border movements. Only when disc position and morphology are substantially altered, can the disc attachment ligaments affect joint biomechanics and subsequently lead to joint dysfunction.

1.1.3 Arthritides of the Temporomandibular Joint

Arthritides is a term describing a group of disorders that involve destructive osseous changes in a joint. The arthritides of the TMJ are classified into arthritis and polyarthritides.[2]

1.1.3.1 Osteoarthritis or Degenerative Joint Disease (DJD)

DJD is a non-inflammatory disorder that represents proliferation and deterioration process of the TMJ osseous surfaces. Some authors consider DJD a low-inflammatory condition that is classified as primary when no direct cause/etiology, or secondary to trauma or overload situations.[14] Others do not consider it a true inflammatory condition due to the adaptive ability once joint loading is decreased.[15] In an acute condition, the deterioration process dominates, and erosive changes are noticed. In a chronic condition, the proliferation process dominates, and more adaptive and sclerotic changes are noticed.[16-18] The degenerative changes of the articular surfaces, such as erosions, loss of cortex and subchondral cysts are characteristics of DJD, and are best depicted on computed tomography (CT) and cone-beam computed tomography (CBCT).[17] The osseous changes usually affect the anterosuperior surface of the condyle and posterior surface of the articular eminence and move from lateral region to the central and medial regions as DJD progresses.[19] Only large changes may be seen on magnetic resonance imaging (MRI).[20,21]

A proliferation process may take place and increase the articulating surface area, as an adaptive response to the excessive loading forces.[2] The newly formed bone at the periphery known as an osteophyte, may break off as a loose body in the joint space (joint mice) in severe cases. In advanced conditions, a narrowed joint space and bone-bone contact are associated with internal disc derangement or perforations. In chronic conditions, surface flattening and an increase in trabecula's number and density (subchondral sclerosis) take place to distribute and withstand the applied forces.[19] Alteration/remodeling of the condyle and articular eminence are evident in chronic conditions, and are often considered a normal physiologic aging feature of the joint.[19]

Controversy in the literature regarding the relationship between DJD and internal disc derangement still exists.[22,23] Some suggested that the internal disc derangement alters the force dynamics inside the joint and stimulates an adaptive response, and degenerative change begins when excessive loading forces exceed the adaptive ability of the joint.[14] However, this sequence of events is mostly outdated and is opposite to that described by others.[24,25] Others report that the degenerative changes could be a response to excessive loading forces of the joint and can occur before the onset of the internal disc derangement.[24,25] Therefore, there is no consensus in the literature on the relationship between the internal disc derangement and DJD, and both cause and effect are possible.The pathophysiology of DJD and the internal disc derangemet is explained later in this chapter.

Pain or crepitus on jaw movement is common symptoms of DJD.[21] The signs and symptoms gradually develop and become more noticeable in the later stages of the disorder.[22] Other signs and symptoms of advanced DJD are a loss of TMJ function and stability, ankylosis, loss of mandibular vertical height, and facial deformity.[26]

1.1.3.2 Polyarthritides

Unlike osteoarthritis/DJD, polyarthritides are uncommon and usually unrelated to the functional loading of the TMJ. They have specific causes and usually are painful. Mercuri *et al* consider the polyarthritides as high inflammatory types of bone degeneration.[14,27] Laboratory findings are consistent with the high level of inflammatory activity with high leukocyte counts in the synovial joint fluid of the affected patient. The most common types are juvenile arthritis and rheumatoid arthritis. Other kinds include traumatic arthritis, infectious arthritis, psoriatic arthritis and ankylosed spondylitis.[1,2,27]

The juvenile arthritis is the most common autoimmune inflammatory disease that affects adolescents before the age of 16 years. It affects 1 in 1000 children worldwide.[28] It characterized by chronic synovial inflammation that causes joint effusion, swollen and painful MTJ. Affected patients suffer from impaired mandibular growth, destroyed condyle (pencil-shaped), decreased density of the TMJ osseous components (osteopenia) and secondary DJD radiographic signs.[29]

The rheumatoid arthritis is a systemic inflammatory disease that affects the synovial membrane of multiple joints in the body. It characterized by generalized osteopenia, multiple erosion of the condyle and reduced joint space. The TMJ is the least affected joint when compared to more load-bearing joints such as knees, shoulders or spine. The signs of TMJ pain or functional limitation was reported to range between 40 -50 % of the affected population.[30] However, the symptoms of pain and discomfort seem to decrease substantially in older patients (over 65 years).[30]

Idiopathic condylar resorption or progressive remodeling is a severe form of destructive changes of the TMJ. Arnett *et al.* proposed an explanation of the possible etiology of this condition that could be either excessive or sustained physical stress on the joint, or decreased adaptive capacity of the joint due to systemic disease such as rheumatoid arthritis and hypothyroidism.[31,32]

Traumatic arthritis is caused by trauma to the TMJ that leads to sudden loss of the subarticular bone and may change the occlusion.[33] Arthritis can result from a bacterial infection through surgery or injections that cause infections arthritis. Infection spread from adjacent tissues is also possible.[34] Psoriasis and ankyloses spondylitis are rare inflammatory conditions that affect about 1% of the population. The TMJ arthritis affects around 6% of the psoriasis patients and 4% of the ankylosed spondylitis patients.[35]

Radiographic imaging is the choice to rule out the degenerative changes at the TMJ. The type of the selected imaging technique relies on the specific clinical problem and the amount of the needed information. The panoramic projects provide an overall view of the teeth and jaws, however, the thick overlapping layers and the oblique distorted view of the joints made of limited value in TMJ osseous changes diagnosis. Computed Tomography (CT) and cone-beam CT (CBCT) provide detailed image slices and three-dimensional images of the osseous structures of the TMJ. It is also useful in evaluating the severity of the degenerative changes, the presence of ankyloses, complex fractures and the extension of neoplasm. A proper diagnosis and monitoring of the osseous changes is the key to adequate treatment and management.

1.1.4 Internal Derangement of the Temporomandibular Joint

The TMJ internal derangement (ID) is defined as abnormal relationship of the disc relative to the condylar head and posterior slope of the articular eminence, with the disc usually displaced in an anterior or anterio-medial position at maximum intercuspation.[17,36-39] The disc in normal position functions as a shock-absorber and load distributer during joint functions, and provides lubrication and nutrition to the articular fibrocartilage. The internal disc derangement disrupts the normal function provided by the disc. The internal derangement may vary in severity and can affect the joint to different degrees. The minimal disc displacement allows normal disc-condyle relationship in the most of the functional movements. Similarly, the displaced disc that reduces back to the normal position allows the normal sliding movement of the disc-condyle complex, and preserves the integrity of the retrodiscal tissues and disc attachments. In contrast, the disc displacement without reduction may be associated with severe changes of the joint articular tissues due to the excessive loading forces applied.

The different theories of the internal derangement etiology and its cause- effect relationship to the joint degenerative changes are discussed below.[40]

1.1.4.1 Pathophysiology

The apparent association between the articular degeneration and the disc displacement has led to the theory that the degeneration process may be a predisposing factor and the disc displacement is a consequence rather than a cause.[31,32,41,42] Others suggested an opposite sequence, where the disc displacement disrupts the biomechanical forces inside the joint and initiate degenerative response of the articular tissues.[43,44] However, the cascade of the molecular events that underlie the evident joint changes does not support the latter claim.[31,32,41,42]

Remodeling of the articular tissues is an important biological response to the normal functional demands that ensures the joint integrity and function.[45] Arnett *et al.* reported that the degenerative changes, as a result of failed remodeling process, are due to: 1. Decreased adaptive capacity of the articular structures, or 2. Excessive or sustained physical stress that exceeds the normal adaptive capacity of the articular structures.[31,32] Milam *et al.* suggested that the direct mechanical injury due to the excessive or sustained stresses facilitates hypoxia and subsequent inflammation of the TMJ and mediate the degradation process associated with the osteoarthritis.[42]

Under the excessive compressive loading, the chondrocytes in the condyle articular cartilage upregulates the production of the vascular endothelial growth factor (VEGF). The VEGF is linked to activation of the hypoxia-induced transcription factor-1 that leads to hypoxia and inflammation of the articular cartilage. The mechanical injury induced inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1 and -6 were reported to accelerate cartilage degradation and promote bone resorption by differentiation and activation of osteoclasts.[46] Moreover, the VEGF stimulates chondrocytes to produce imbalanced levels of the matrix metalloproteinase (MMP-13) and the tissue inhibitor of matrix metalloproteinases (TMP-1) and activates osteoclasts to induce more destruction of the articular cartilage.[47] The MMP-13 and TIMP-1 are effectors of the extracellular matrix remodeling, and their imbalanced production results in rapid degradation of the extracellular matrix, collagen fibers and proteoglycans, which lead to the condylar cartilage distruction.[48]

As inflammation progresses, increased permeability of the inflamed synovial membrane allows large molecules to influx into the joint space and increases the intra-articular pressure. With the joint overloading, the intra-articular pressure may be further elevated and exceed the capillary perfusion pressure to reduce fluid perfusion and result in a temporary hypoxia. The reduced perfusion affects the delivery of nutrients and oxygen to the articular surfaces and results in accumulation of oxygen free radicals and metabolic waste products within the joint.[49] The oxygen free radicals contribute to the persistence of the chronic inflammation and the damage of the proteins and immunoglobulin IgG, a process known as “hypoxic-reperfusion”.[50,51]

With continual joint function, the hypoxia-reperfusion cycle inhibits biosynthesis of the hyaluronic acid and reduces the viscosity of the synovial fluid.[52] Also, the process of hyaluronic acid regulation is controlled by the inflammatory cytokines. Several cytokines including interleukin-1β, TNF-α, interferon-ɤ and transforming growth factor-β, were found to degrade the hyaluronic acid and proteoglycans. The cytokines alter the synovial fluid’s viscosity and lubrication ability in patients suffer from DJD and internal disc derangement.[53,54] The synovial fluid is crucial for joint lubrication and nutrition. Highly viscous synovial fluid prevents proper nutrients and oxygen perfusion to the articular surfaces and results in hypoxic-reperfusion joint damage.[49] The collapse of the joint lubrication system increases the shear stresses between the articular surfaces, within the disc and articular cartilage, and leads to fatigue of the tissues and irreversible damage.[55,56] The reported findings suggested that the cytokines in the viscous synovial fluid play in important role in the pathogenesis of the cartilage degradation and may extend more deeply to involve the osseous tissues. This process of tissue breakdown may be responsible for the onset and progression of the degenerative changes in the TMJ.[57]

The impairment of the joint lubrication and nutrition with the associated hypoxic-reperfusion and inflammation affects the regenerative capacity in the chondrocytes in the condylar cartilage. The reduced regenerative capacity of the chondrocytes results in a reduction of the normal extracellular matrix, collagen fibers, and proteoglycans with an overall decrease in articular cartilage integrity. These changes alter the dynamics of force distribution over the cartilage layer, which increases functional forces per unit area and may lead to tissue fatigue, fluid tissue loss, and reduced cartilage compressibility. Continuous loading breaks down the articular cartilage, which has minimal ability to repair, and may fracture the underlying trabeculae due to excessive point localization of loads and damaged overlying cartilage. The fractured trabeculae may be resorbed leaving inflammatory microcytes, and as inflammation progresses to deeper layers, the osteoclasts and osteoblasts are activated. Also, the fractured trabeculae may be repaired and induces the formation of reparative callus that leads to bone thickening and subchondral sclerosis.[57]

Similarly, the inflammatory cytokines infiltrate the articular disc and affect the collagen production and matrix synthesis by the fibrocytes. Interleuki-1 is a potent inhibitor of matrix synthesis and proliferation and breaks down the collagen fibrils of the disc. The collagen fibrils are crucial to counteract the swelling pressure caused by the interstitial fluid that contributes to joint loading equilibrium.[6] The loss of the lubrication fluid provided by the disc along with the increased shear stresses between the articular surfaces disturbs the coordinated movement of the disc relative to the condyle. During some stages of the joint loading, the intermediate zone of the disc does not remain interposed between the condylar head and posterior slope of the articular eminence. When the disc is partially anteriorly displaced, the condylar head loading will be applied to the thick posterior band of the disc. In the normal condition, the collagen fibrils are arranged in a transverse direction in the posterior band of the disc, which makes it less capable to resist functional forces compared to the disc intermediate zone. In the condition of joint inflammation, the damaged collagen fibrils do not support the disc rigidity and allows the posterior band to “squeeze” between the condyle and the articular eminence, which promote further joint instability and disc displacement over time. In the closed mouth position, the displaced disc lies in the space anterior to the condylar head and at the height of the articular eminence. During mouth opening, the condyle pushes the disc forward without reduction. The posterior band shows an increase in its thickness due to the continual pressure of the condylar head. The fluid content of the posterior band may increase as well due to the loss of the collagen fibrils network. The limited space available for the displaced disc is not enough to contain its fully extended form. Therefore, the disc often buckles in the region of the intermediate zone which potentially adds more damaging effect on the collagen fibrils network and disc turgor and morphology.[58,59]

With the anteriorly or anterio-medial disc displacement, the retrodiscal tissues assume the function of the displaced disc and interposes between the condylar head and glenoid fossa. The retrodiscal tissues are unable to provide normal load dissipation, and in the situation where functional loading is not excessive, a physiologic adaptive process occurs. The collagen fibrils become more arranged, proteoglycans content increases, nerves degenerate, vascular plexus become occluded, and finally the scarred tissues become fibroused. The retrodiscal tissues remodel into a functional "*pseudo disc*" to establish a new joint loading equilibrium.[2]

The TMJ articular cartilage and the articular disc do not contain nerve endings, and the damage of these tissues is not experienced as joint pain. The TMJ is innervated by multiple nerve supply, auriculotemporal, masseteric and posterior deep temporal nerves.[60] The nerves endings innervate the joint capsule, the retrodiscal tissues and the periphery of the articular disc. Pain is experienced when the joint capsule is vigorously twisted or stretched; when the retrodiscal tissues are acutely inflamed "*retrodiscitis*"; and when the inflammatory products stimulate nerve endings in the medullary spaces.[49]

1.1.4.2 Etiological factors

The TMJ internal disc derangement is a problem with multifactorial etiology, as evidenced by the combination of factors altering the functional balance between the TMJ articular structures, masticatory muscles, and dental occlusion. Factors were grouped into three categories:[61] 1. Predisposing factors that increase the risk of having internal disc derangement, 2. Initiating factors that cause the onset of the internal disc derangement. 3. Perpetuating factors that interfere with the healing process or support the damage progression. A single factor may be considered in one or all three categories.[61]

Macrotrauma

Macrotrauma can be a predisposing and/or initiating factor, and it involves any sudden excessive force result in structural damage of the TMJ. Excessive traumatic forces can result in serious and irreversible damages to the TMJ tissues. Sudden and severe mandibular trauma at resting position such as a blow to the chin can result in condylar neck fracture, capsular laceration, ligaments elongation, and disc displacement.[62,63] Iatrogenic over-extension of the mandible during intubation in general anesthesia, extended dental procedure, orthognathic surgeries, were also reported to cause or increase the symptoms the TMJ dysfunction.[64] Moderately excessive trauma, such as neck or cervical whiplash injuries, was reported to cause delayed symptoms of the TMJ internal derangement.[65]

Oral and oropharyngeal cancer transmandibular surgeries result in impaired oral functions and are expected to cause internal disc derangement. However, only a few and inconclusive data were reported regarding this issue. The literature regarding the morphological and the functional changes of the TMJ is systematically reviewed and analyzed in **Chapter 10**.[66]

Parafunctional activities (microtrauma)

Microtrauma is the small forces repeatedly applied over an extended period of time. Parafunctional habits such as clenching, grinding, bruxism, are the most common microtraumas related to oral-functions and muscular hyperactivity. Studies in the literature suggests that the functional overloading associated with the parafunctional activities is a crucial factor to predispose, initiate and/or perpetuate the TMJ internal derangement and DJD.[67-70] The excessive/sustained overload may vary in severity and can affect the joint to different degrees. Milam *et al* suggested that the sustained mechanical overload and the hypoxia-reperfusion injury result in oxidative stress and accumulation of free radicals over the articular surfaces and the synovial fluids.[42] The lack of the adequate nutrients and oxidation initiate a cascade of pathophysiological events that result in subsequent tissues degeneration and joint dysfunction.[71,72] However, most of the research supporting the view that parafunctional activities occurs at elevated rates in TMD patients relies on self-reporting data rather than well-documented diagnostic imaging or muscular activity recording data.

Dental malocclusion and orthodontic treatment

Dental malocclusion and related orthopedic instability were considered the most controversial predisposing factor of internal disc derangement.[61,73,74] Most studies considered dental malocclusion merely a potential risk factor for TMJ dysfunction.[61,75,76] This controversy has influenced and limited treatment options for TMD. Anterior open bite is generally considered a consequence of the condylar remodeling rather than a TMD etiological factor.[77] Other studies detected positive association between occlusion discrepancy, condylar displacement and symptoms of joint dysfunction.[78,79]

Some studies suggested that certain orthodontic treatment can result in internal disc derangement.[80,81] However, long-term studies of orthodontic treated patients were not supportive to this concern.[82,83] The incidence of TMD symptoms in patients received orthodontic treatments was not greater than untreated individuals. Different treatment techniques and extraction options did not reveal a greater incidence of internal disc derangement.[84,85] The functional mandibular anterior repositioning appliances effect on the TMJ in adolescents has been greatly controversial. The available literature regarding the associated TMJ changes is systematically reviewed and analyzed in **Chapter 7**.[86]

Joint laxity and hyperactivity

Controversy in the literature regarding the joint laxity and hypermobility was evident as well. Both generalized hypermobility and TMJ hypermobility have been reported to be predisposing factors of TMJ disc derangement.[87,88] One study reported no association between the generalized hypermobility and TMD, or between the generalized hypermobility and TMJ hypermobility.[89]

Genetic and hormonal factors

Little is yet known about the genetic predisposition to the development of internal disc derangement or TMD. Michalowicz *et al.* suggested examined different groups of monozygotic and dizygotic twins for similarities in TMJ dysfunction signs and symptoms. The authors concluded that genetic factors were not related to the TMJ dysfunction symptoms.[90]

Despite weak evidence, the relationship between the estrogen hormone in females and the TMD symptoms seem to be less controversial. The TMD symptoms are more common in females than males.[91] It was hypothesized that estrogen receptors increase the ligaments laxity of the TMJ and susceptibility to painful stimuli.[92] Estrogen and relaxin were reported to contribute to the degradation of the TMJ articular cartilage by attacking collagen and proteoglycans in the cartilaginous matrix.[93] However, clear explanation of the mechanism by which the estrogen affects the TMJ tissues is not yet understood.

1.1.4.3 Prevalence

The prevalence of internal disc derangement varies depending on the parameters used and the studied population.[75,94-99] Nebbe *et al.* reported a high rate of disc displacement in asymptomatic adolescents. Normal joints were found in only 24% -29 % of girls and 50% of boys, and the frequency of normal joints increased with age increasing.[75] Other studies reported approximately 30% of the asymptomatic adolescents have anterior disc displacement.[96-98] Furthermore, 82% of the adult patients presented with TMJ pain and dysfunction, and about 13-22% of the asymptomatic adults were found to have internal disc derangement.[96,98,100]

Joint sounds (clicking and popping) are frequent findings associated to the internal disc derangement. However, they do not represent a useful epidemiologic tool as they are noticed in approximately 35% of the asymptomatic population.[75,95]

1.1.4.4 Types

In the normal function, the articular disc anterior movement is limited by its morphology (thick and firm posterior band) and length of the posterior retrodiscal lamina. In the condition of joint inflammation, the decreased and viscous synovial fluid together with the hypoxia-reperfusion injury model act as damaging factors to the TMJ articular tissues. The friction and the shear stresses between the articular surfaces and the disc increase subsequently. The coordinated movement of the disc-condyle complex become disturbed, and the intermediate zone of the disc does not remain interposed between the condylar head and posterior slope of the articular eminence. When the disc is slightly anteriorly displaced, the condylar head loading will be applied to the posterior band of the disc that gets squeezed between the condyle and the articular eminence, which promote further joint instability. In the closed mouth position, the displaced disc lies in the space anterior to the condylar head and at the height of the articular eminence. During mouth opening, the condyle moves forward and the disc either successfully re-establishes the normal disc-condyle relationship or resists the condyle pushing forces. The functional displacement of the disc is categorized into two types according to the disc ability to re-establish the normal disc-condyle relationship during function.

1. ***Disc displacement with reduction****:* during opening movement, the condyle rotates forward to fit into the intermediate (thinnest) zone of the displaced disc and the normal condyle-disc complex union is re-established a process also known as *disc reduction*. An associated short lasting sound "*click or pop*" may be created. In some cases, this sound occurs again during mouth closing when the condyle-disc complex is separated again and is referred to as "*reciprocal or closing click*". The arthokinetics of the disc displacement

with reduction is illustrated in Figure 6.[102] Clinically; this condition can be associated with initial midline line deviation and limited vertical mouth opening, which disappear once the disc is reduced and the condyle-disc complex is re-established again. [2]

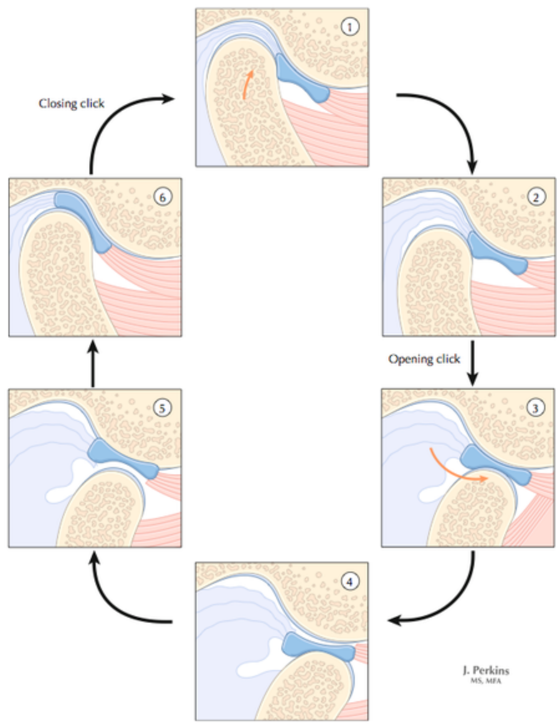

Figure 1.6: Arthokinetic cycle of the TMJ disc displacement with reduction. 1and 2: during opening, condyle passes over the posterior band of the anteriorly displaced disc toward the disc's intermediate zone causing a click sound; 3 and 4 The condyle-disc complex is re-established during the mouth opening; 5, 6 and 1: during closing the condyle-disc complex goes back to normal position before the disc displaces to more anterior position causing a reciprocal/closing click.[102]

2. ***Disc displacement without reduction (closed lock)**:* In this condition, the condyle-disc complex separation is more severe. The disc is further displaced and distorted and interferes with the translation movement of the condyle during the mouth opening. The condyle is never able to recover the normal relationship with the disc, but instead, pushes the disc forward during the mouth opening. In acute inflammation conditions, the full mouth opening is lost and may be associated with painful mouth oral functions. The arthokinetics of the disc displacement without reduction is illustrated in Figure 7.[102]

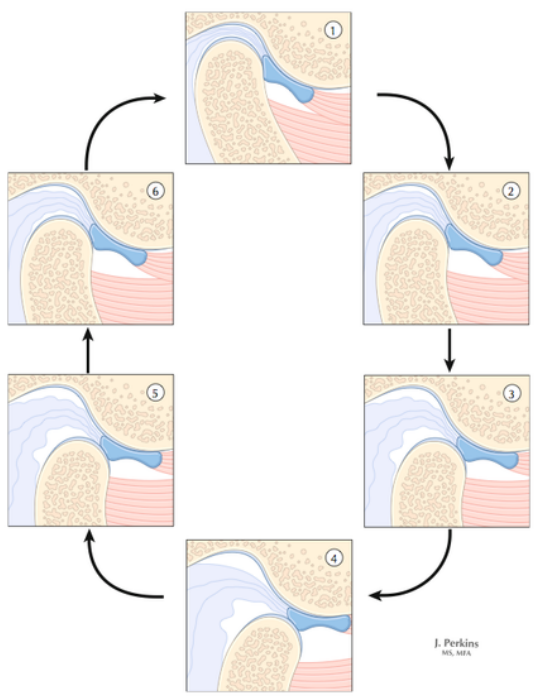

Figure 1.7: Arthokinetic cycle of the TMJ disc displacement with reduction. 1and 2: during opening, condyle passes over the posterior band of the anteriorly displaced disc toward the disc's intermediate zone causing a click sound; 3 and 4 The condyle-disc complex is re-established during the mouth opening; 5, 6 and 1: during closing the condyle-disc complex goes back to normal position before the disc displaces to more anterior position causing a reciprocal/closing click.[102]

1.1.4.5 Classification

The sagittal view of the TMJ (Figure 1.2, A) appears to be the most descriptive view for the condyle-disc complex and the joint functional movements. Drace and Enzmann described a method to define the normal disc position in relation to the condyle in sagittal MRIs of the TMJ.[103] In the maximum intercuspation position, the position of the posterior band of the articular disc relative to the superior aspect of the head of the condyle should be at a 12 o'clock position (± 10 degrees). Nebbe *et al.* used the intermediate zone of the disc that is interposed between the condylar head and the posterior slope of the articular eminence to describe the normal condyle-disc relationship.[104] The 12 o'clock evaluation method has been endorsed by many studies in the assessment of internal derangement.[105-108] However, the 12 o'clock parameter does not take in account the anatomical variation of the articular structures (depth of the glenoid fossa, inclination of the condyle and articular eminence), and introduces an overestimation/underestimation bias to disc position evaluation. The 12 o'clock position was considered responsible for the high reported prevalence (approximately 22%) of disc displacement in asymptomatic patients.[97,109] The disc's intermediate zone is more meaningful regarding functional orientation and normal positioning evaluation.[97,109] The anterior disc displacement was classified to normal, mild, moderate, severe based on the displacement of the intermediate zone.[104] This classification was used to evaluate the disc position in the projects of this dissertation, and details are explained in **Chapter 3, Figure 3.5**.

Coronal view of the TMJ (Figure 1.2, B) are used to depict the disc lateral displacements. Katzberg *et al* reported that coronal MRIs provided auxiliary information to the sagittal MRIs, and revealed about 10% of false-negative evaluation of normal disc position.[106,110] However, it is not possible to detect the normal from abnormal disc position using coronal MRI solely.[111] A combination of two directional disc displacements (antero-posterior and medio-lateral) are more common than one direction disc displacement. Three-dimensional imaging of the TMJ seems to be ideal in detecting the disc position and its functional relationship.

1.1.4.6 Clinical examination

A clinical evaluation to determine internal disc derangement is necessary to investigate signs and symptoms arise from the TMJ and surrounding musculature. Adequate assessment of the disc derangement allows effective management of the condition and prevent further damaging to the TMJ. Research Diagnostic Criteria for TMD (RDC/TMD) provided standardized, evidence-based criteria for clinicians to diagnose and differentiate the intra-capsular from muscle related symptom, and have been the most widely used diagnostic guide for TMD since it was introduced in 1992.[112]

The clinical exam starts with evaluating the quality of the mouth movement is terms of mandibular deviation or deflection during mouth opening. Mandibular deviation is a result of unilateral irregular condylar translation, which is typically related to disc displacement with reduction. Mandibular deflection is a result of unilateral lack of condylar translation, which is typically related to acute disc displacement without reduction. Tenderness and tonicity of the elevator muscles can cause similar signs of mouth movement limitation, deviation, and deflection during mouth opening. The mouth movement limitation due to muscle spasm is usually described as soft-end feel compared to hard-end feel caused by acute disc displacement without reduction "*acute closed lock*". Capsular tenderness upon palpation may be associated with the limited mouth movement as a sign of acute inflammation "*capsulitis*". Measuring the maximum vertical mouth opening is a standard diagnostic protocol to evaluate the association between the mouth opening limitation (interincisal distance is <40mm ± overbite/open-bite measurement) and disc displacement or muscular spasms. Measuring the maximum vertical mouth opening in millimeters is sensitive to over-time change and has excellent reliability to determine the severity of the limited jaw movement.[112,114,115]

Based on the available literature, internal disc derangement is highly prevalent, and unless pain or functional limitation are reported, the clinical examination is not always reliable.[112,113] The history and clinical presence of the joint noises such as clicking, popping and crepitus are limited diagnostic signs. The clicking noise suggests the presence of disc displacement with reduction with high specificity (92% - 98%); However, the absence of clicking noises is not an evidence of the lack of disc displacement (low sensitivity, 34% - 38%).[38] For example, in the condition of disc displacement without reduction, the condyle may translate during mouth opening without moving over the disc posterior band. The absence of the clicking noise, in this case, may be mistakenly considered as a sign of a normal disc position (false negative). Also, the fine crepitus noise can be missed during clinical examination, and was reported to have low sensitivity (55%), and specificity (61%) in ruling out DJD.[38] The subjectivity nature of the clinical findings and the ambiguity of the reported signs and symptoms complicate the diagnostic interpretation and may lead to poor reproducibility and reliability of the clinical examination.

Nonetheless, imaging using MRI is required for definitive diagnosis of internal disc derangement, and CT/CBCT is required for definitive diagnosis of DJD. However, two exceptions should be considered, the disc displacement without reduction with associated limited mouth opening "*acute closed jaw lock*", and condyle-disc complex complete dislocation "*open jaw lock.*" The *acute closed jaw lock* (sensitivity 80%, specificity 97%) and the *open jaw lock* (sensitivity 98%, specificity 100%) showed high validity of the clinical examination without required imaging.[38]

On the other hand, evaluation of TMJ impairment and dysfunction severity has been approached using different qualitative assessment tools. The most common tools used in the literature were Helkimo index, craniomandibular/temporomandibular index and jaw function limitation scale (JFLS).[116-120] These tools allow patients to assess how their oral functions became altered due to TMJ dysfunction using a simple numerical scale, where 0 indicates no difficulty and 10 indicates extreme difficulty. However, Helkimo index and the craniomandibular/temporomandibular index are lengthy (50 questions), and suffers of cognitive bias limitations and lack of generalizability. Ohrbach *et al* developed the JFLS to overcome these limitations.[117] The JFLS contains 10 questions only (Table 11.1), and was validated and tested for reliability to determine the impact of the diagnosed pathology of the TMJ on its functions.[116,117] Ohrbach *et al* reported that the JFLS was independent of psychosocial dysfunctions, such as depression and somatization, and was sensitive to clinical change.[117] The JFLS can be used as additional tools to both clinical examination and diagnostic imaging.

1.1.5 Temporomandibular joint diagnostic imaging

"*The purposes of TMJ imaging are to evaluate the integrity and relationships of the hard and soft tissues, confirm the extent or stage of progression of known disease, and evaluate the effects of treatment.*"[1] TMJ imaging supplements information obtained from the clinical examination when an osseous abnormality, infection, and trauma are suspected, or significant alteration in occlusion, dysfunction, and limited range of motion are evident. Ineffective conservative treatments also require further investigation with diagnostic imaging. Selecting the appropriate imaging technique depends on the examined tissue type, clinical problem, amount of the diagnostic information requested, cost and radiation dose.[1]

Radiographic imaging is the best technique to depict osseous tissues. Panoramic radiograph serves as a screening projection to identify substantial osseous changes, asymmetries, tumors, fractures, or dental disease that could be a source of TMJ symptoms. However, the distorted view of the condyles and heavy superimposition of the skull base and zygomatic arch severely obscure the mild/moderate osseous changes and limit the image quality. Tomography radiograph produces multiple thin sections depicting the condylar head and temporal bone structures of the TMJ, which are free of other bony superimposition. Computed tomography (CT) also known as "Medical CT" provides detailed image slices and three-dimensional images of the shape and internal structures of the osseous components of the joint. However, CT is a much higher radiation dose than tomography CT is useful in evaluating neoplasms and complex fractures in the TMJ area. Cone-beam computed tomography (CBCT) provides excellent images of the osseous structures in three dimensions, with much lower radiation dose than the CT. CBCT has gradually replaced tomography and is now considered the imaging technique of choice to assess osseous components of the TMJ.

Although medical CT has a soft tissue imaging window, it does not produce accurate images of the articular disc. The double contrast arthrography was the first imaging modality used to show the articular disc by the means of negative space. Arthroscopy is still the best technique to detect articular disc perforation, however, injecting a contrast agent into the joint spaces is a painful and invasive procedure. MRI has replaced arthroscopy and is now considered the technique of choice to image and assess the TMJ inflammatory activity and internal derangement. MRI can display the TMJ osseous structures however not in the comparable detail seen in CBCT. MRI is not invasive technique and does not use ionizing radiation.

1.1.5.1 Cone-beam computed tomography (CBCT)

CBCT was first used to examine the TMJ pathology in 2001.[121] Over the past decade; the CBCT has emerged as a cost and dose-effective alternative to the medical CT in TMJ examination. The diagnostic potential of the CBCT was discussed in the literature in 4 main areas: early and late osteoarthritis (DJD), fibro-osseous ankyloses, condylar hypo/hyperplasia and intra-articular fractures.[121-124]

1.1.5.1.1 Advantages and disadvantages

The CBCT is readily available to dentists. It is free of superimposition of overlapping structures, and provide ten times less ionizing radiation (~87-100 µSv for 12 cm field of view), compared to Medical CT (~860 µSv for 12 cm field of view) using its broad cone-shaped x-ray beam.[125] Most CBCT units acquire images in the seated position. Caveats to CBCT include the suboptimal resolution due to scattering radiation (inherent noise), sensitivity to motion artifact, lack of soft tissue delineation, harmful ionizing radiation if the protocol is not adequately customized on individual bases.

1.1.5.1.2 Diagnostic accuracy

The CBCT was found to provide accurate measurements of TMJ bony structure dimensions (1:1 size ratio) due to its small isotropic pixels.[126,127] Zhang *et al* confirmed that the measurement of the joint spaces is very similar to the actual spaces of the joint.[128] Honda *et al* found that the CBCT showed high sensitivity (80 %) for detecting osteophytes and surface erosions using an autopsy material. Compared with medical CT, the authors reported that the sensitivity was not significantly different between the two modalities.[129] Using fresh pig mandibular condyles, Patel *et al* reported a high sensitivity value (87%) for detecting condyle osseous defects.[130] However, osseous defects smaller than 2mm were difficult to detect. Moreover, the authors found that sensitivity was improved significantly, for defects smaller than 2mm, with increased scanning resolution (from $0.4mm^3$ to $0.2mm^3$ voxel size).[130] Librizzi *et al* compared the different field of views, 12 inches ($0.4mm^3$ voxel size), 9 inches ($0.3mm^3$ voxel size) and 6 inches ($0.2mm^3$ voxel size) to evaluate the diagnostic efficacy for detecting condylar erosions.[131] The authors found that the smallest field of view showed the highest diagnostic efficacy.[131]

The CBCT seem to have an excellent diagnostic accuracy in detecting the osseous changes, and is comparable to the high-resolution Medical CT.[108] Most studies reported high specificity as well. The examiner's agreement was found to be influenced by the image resolution and the defect size. Small osseous defects (< 2mm) were found to be frequently missed. Of note, different scanners and imaging protocols produce images with different resolution and quality. Thus, studies should be compared with caution.

1.1.5.1.3 CBCT interpretation of the TMJ

The CBCT images were extensively used in the literature to observe the changes in TMJ and their association with clinical symptoms and treatment outcomes. Harris and Heaney reported that a decrease of 30% – 50% of the skeletal mass is required to detect erosive lesions in the radiograph.[132] The gradual demineralization of the bone matrix, however, is a slow process that takes a number of weeks in humans. Despite the uncertainties of the calcium reduction kinetics and techniques, it was demonstrated that the bone mass loss is influenced by many factors including age, dysfunctions and hormonal disturbance. The radiographic signs of the TMJ osteoarthritis were first described by Lihrem *et al* in 1980,[133] and different grouping, classifications, and descriptions of the TMJ osteoarthritis signs were reported in the literature.[134-136] Nah reviewed CBCT images of 220 patients with TMJ pain and/or noises (age range from 11 -78 year), and reported that subchondral sclerosis and surface erosions were the most observed findings (30% of the cases), followed by flattening (12%), osteophyte (8%) and Ely's cyst (5%).[137] Twenty-seven percent of the assessed joints had at least one observation. TMJ osteoarthritis is characterized by the presence of more than one feature of bone proliferation and destruction; single small changes should be interpreted with caution.[135,138] Erosive osteoarthritis are characterized with severe erosions and often are mistaken with rheumatoid arthritis.[139] It seems to be impossible to diagnose the rheumatoid degenerative changes of the TMJ based on imaging alone, and without confirming the plasma glutamate levels.[140] Alexiou *et al* reported that the TMJ degenerative changes are age-related, and the progression and severity of the degenerative changes increased with age.[141] Other studies indicated that the TMJ degenerative changes were observed more in females than males,[142] correlated poorly to pain and reduced joint space,[143,144] and correlated highly to TMJ clinical dysfunction,[145] and class II jaw skeletal discrepancy.[146] Moreover, the cortical bone thickness of the glenoid fossa of the temporal bone did not correlate to different condylar head shapes, patients' age or gender.[147,148] However, the thickness of the cortical bone increased by 1.2 mm when osteoarthritis signs were observed in the sagittal view of the condyle.[148]

Young children do not necessarily have continuous and compact cortex outline of the TMJ, which makes difficult to distinguish a degenerative disease from a remodeling process. Only a few studies in the literature investigated the TMJ's osseous changes in adolescents and preadolescents populations. Juvenile osteoarthritis was found to be higher in symptomatic than asymptomatic children and more in females than males.[149] Juvenile idiopathic arthritis (JIA) in adolescents younger than 16 years old was reported to potentially cause facial deformities with associated TMJ surface flattening and erosions.[150,151] Junior *et al* found that 83% of the patients with JIA had TMJ osseous alterations detected on CBCT.[152] Koos *et al* classified the JIA based on the number and severity of the joint osseous alterations using CBCT and contrast–enhanced MRI.[153] Ikeda and Kawamura investigated the condyle position in the glenoid fossa using post-orthodontic CBCT images of young asymptomatic individuals.[154] The study revealed a relationship between the condylar position and the disc position on MRI. The interpretation of the condylar position inside the glenoid fossa and the joint space on CBCT can be influenced by many factors, which are related to image technique and joint anatomy. The clinical significance of the condylar position is controversial, and the joint space was found asymmetric even in healthy patients, and therefore should be interpreted with caution.[155]

Recently, three-dimensional quantification and assessment of the TMJ surfaces emerged in the literature. Cevidanes *et al* investigated the correlation between the condylar morphology and pain females with osteoarthritis compared to asymptomatic one.[156] The authors reported profound differences in condyle morphology between the two groups, and the extent of the condylar resorption paralleled pain severity and duration. Paniagua *et al* performed three-dimensional analysis of the condyle morphology of two groups of patients (symptomatic versus asymptomatic) who sought orthodontic treatment.[157] The study reported that osseous surface defects that ranged from 3-6 mm were accurately detected in the three-dimensional models of the condyle. Farronato *et al* and Stoustrup *et al* investigated the three-dimensional volume and morphological changes of the TMJ in children with JIA.[158,159] Arici *et al* and Le Corno *et al* investigated the effect of the mandibular anterior repositioning devices on condyle, glenoid fossa and joint space using three-dimensional models of TMJ.[160,161] These studies are discussed in details in **Chapter 7**.

The value of the CBCT images was emphasized in viewing expansion lesions, fractured and displaced condyles, trauma and developmental abnormalities. Also, the three-dimensional superimposition of the CBCT images was found reliable and useful in quantifying delicate surface changes of the TMJ articular surfaces.[162] The clinical usefulness of the CBCT in patients' management was clearly demonstrated, however, further research in this area is required.[163] Although CBCT is quite sensitive to motion artifact, it emerged as low dose- and cost-effective alternative to medical CT, and superior to conventional imaging and MRI in depicting TMJ osseous abnormalities.

1.1.5.2 Magnetic Resonance Imaging (MRI)

MRI provides information on the TMJ structures with excellent definition of the articular disc, muscles, fat, and fluids. Certain ultra-fast MRI sequences can provide dynamic imaging of the TMJ. However, MRI is not readily accessible to dentists and static image sequences take a long time to complete.

1.1.5.2.1 Advantages and disadvantages

MRI is the most desirable imaging for TMJ articular disc, as it has no ionizing radiation. It uses a magnetic field and radiofrequency pulses to produce multiple digital image slices. It allows construction of the TMJ in three dimensions without patient repositioning. It is non-invasive and pain-free compared to the arthrography. Caveats to MRI include sensitivity to motion artifact, distortion of signal intensity or void due to metallic dental materials (fillings, prosthesis or orthodontic brackets), a suboptimal signal of the osseous structures, and cross-talk artifact that requires spacing between the image slices.[164] MRI scanners are expensive, found in specialized imaging centers or general hospitals, and not readily available for dentists.

Also, MRI is contraindicated in patients who are pregnant, claustrophobic, unable to remain motionless in a supine position, have pacemakers, metal vascular clips or particles in vital structures.

1.1.5.2.2 Diagnostic accuracy

Westesson *et al* and Tasaki *et al* evaluated the MRI diagnostic accuracy using TMJ of fresh cadavers. The authors evaluated the disc position, configuration, and osseous changes and found that MRI has a sensitivity of 95%, specificity of 95% and accuracy of 93%.[165,166] However, images of cadavers are not equivalent to images obtain for living tissues at clinical settings where jaw motion artifact and pulsating vessels are encountered. As well, the fact that the clinical MRI has thick slices (3mm) with spatial inter-slice gaps may result in missing subtle osseous changes of the TMJ. Alkhader *et al* reported the limited value of the MRI in detecting osseous abnormalities of the TMJ with a sensitivity values between 30% to 80%.[167] The CBCT has greater accuracy in detecting osseous changes than MRI and is the reference standard to detect osseous changes in TMJ. However, some studies used MRI to detect the association between disc displacement and condylar surface erosions and osteophytes.[168,169]

The current standard of the internal disc derangement diagnosis seems to depend on the subjective evaluation of the examiner reading the image. The familiarity of the examiner with the MRI and TMJ anatomy and function substantially influence the examiner's diagnostic interpretation. The diagnostic quality, also, can be affected by the image quality, field strength of the magnet, surface coil, and the software of the MRI itself.[170] The accuracy and reliability of the MRI to evaluate the disc position has been a source of controversy in the literature.[135,171-176] There is strong reason to believe that examiners performance substantially influence the diagnostic accuracy of the disc position and joint effusion.[177,178] Takano *et al* reported moderate examiner agreement for anterior disc displacement without reduction and no joint effusion.[178] Different studies with different agreement values in detecting the articular disc displacement using MRI are discussed in **Chapter 5.**

1.1.5.2.3 Spatial encoding and pulse sequences

Magnetic resonance images are obtained by placing the nuclear magnetic field of the living tissues in a larger externally applied magnetic field (as applied by MRI magnet). An image of a living tissue is produced when the nuclear magnetic field of the hydrogen nucleus is temporarily excited to emit a signal. The hydrogen atom has a single proton nucleus with a strong magnetic field. The high water content in the human body (80%) deemed the hydrogen atoms most suitable to depict living tissues by MRI.[49] MRI magnets apply a radiofrequency pulse that is specific only for hydrogen atoms. Under larger external magnetic field (MRI magnet), the hydrogen atoms line up in a parallel direction to the external magnetic field with a continuous spin motion "resonance frequency" that creates another magnetic field. The magnet radiofrequency pulse forces the protons under effect to spin at a specific frequency and in a specific direction.[179] When the radiofrequency pulse stops, the stimulated hydrogen nuclei emit the absorbed energy in the form of radio waves that are detected by a radio antenna.[180]

The magnetic field is measured with a unit called Tesla. MRI magnets up to 3 Tesla are currently approved for medical imaging. A graded strength of magnetic field "gradient" creates different resonance frequencies of the stimulated hydrogen nuclei, which allows the differentiation of the various tissues. Images of different tissues are obtained through slice information of anatomical structures. Spatial encoding is the process of slice selection and formatting of the gathered information. When a gradient magnetic field is applied in a Z-axis, all hydrogen nuclei line up in a parallel direction to the Z-axis. In a specific single slice, a specific radiofrequency pulse is applied to deflect the hydrogen nuclei from the Z-axis (longitudinal) to the X-Y-axis (transverse). The larger the amplitude of the radiofrequency pulse, the greater the degree of the deflection (90º to 180º). At this point, the slice of tissue is localized, and the whole tissue unit resonates at same frequency without accurate information on the different tissue structures in that slice. An additional gradient magnetic field is applied, as another local encoding, to differentiate the tissue structures. The interactions of the hydrogen nuclei with the local encoding intensities cause them to resonate at different frequencies based on their position in a transverse slice of the tissue. The strength of the radio frequency resonance gives information on the amount of the hydrogen atoms present in that tissue and specific radiofrequency can be used to obtain different types of tissue contrast. The same process is repeated many times with exposing the same slice to radio waves in slightly different directions to get some parallel lines that will cross the slice plane at different spatial angles. Also, this process is repeated to collect information from different slices of the imaged tissue.[49,179,180]

When the hydrogen nuclei are stimulated and deflected to the transverse axis by the gradient magnetic field, the absorbed energy is emitted immediately after the stimulation gradient is removed and the atoms return to the longitudinal axis (relaxation). T1 relaxation is the time required for 63% of the hydrogen atoms to appear in the longitudinal plan after emitting energy as a signal. T1 relaxation is also called longitudinal relaxation or spin-spin relaxation. T1 relaxation time differs in different tissues. Water molecules are mobile and have long relaxation time, whereas solid tissues have short relaxation time due to their less mobile molecules. The reduction in the emitted signal (decay) by the relaxing hydrogen atoms occurs long before the atoms are back in the longitudinal plan. Signal decay occurs due to the disharmonious spinning (nuclei dephasing) of the hydrogen atoms in the transverse plan before finally relax in the longitudinal plane. This signal decay is called a T2 relaxation and defined as the time required for the magnetic resonance signal to decay irreversibly to 37% of its initial value. T2 relaxation is also called transverse relaxation or spin-lattice relaxation. Tissues such as fat, muscles and blood have shorter relaxation time in T2 than in T1.

The variation of the T1 and T2 relation times is used to provide an excellent source of tissues contrast and to distinguish healthy from diseased tissues. The timing of stimulation radio waves and pulse sequences can be modified to accentuate either T1 or T2 to obtain the best signals of the tissue of interest. The time between the successive excitation pulses applied to the same slice is called time to repetition (TR). The time point at which the radio-frequency signals of the target tissues are collected is known as a time to echo (TE). Both TR and TE are measured in milliseconds (ms). TR and TE can be adjusted to emphasize a particular type of signal contrast and regulating total scanning time. Short TR (< 1000 ms) and short TE (10-25 ms) are used to generate T1-weighted images. Long TR (> 1500 ms) and long TE (100- 125 ms) are used to generate T2-weighted images.[49,179,180] When TR is long, and TE is short, the differences in hydrogen magnetic relaxation and signal decay between different tissues are not distinguishable, and the resultant image is produced because of the proton density (PD) concentration that represent the contrast of the various tissues.[180]

The magnetization principles explained above are applied to the TMJ imaging. T1-weighted images depict the normal anatomy of the TMJ and articular disc morphology. If contrast material is used, T1-weighted images can be used to detect TMJ pathologies such as disc adhesion, pannus formation, and joint effusion. Due to the high water/fluid content in the diseased tissues, T2-weighted images are the best to depict joint effusion and tissue's pathology.[180,181] PD-weighted images, especially with fat-suppression sequence via short tau inversion recover (STIR), depict both anatomy and disease entity and provide the best depiction of the anatomy and tissue contrast of TMJ and articular disc.[182-184]

The principles of the magnetization are applied in the same way on each slice of the TMJ tissues. T1, T2, and PD all depict the same tissues with different pulse sequences, and therefore, same tissues appear differently in different sequences. The cortex layer of the TMJ osseous structures contains immobilized protons that are incapable of producing radio wave signal and therefore appears as a black line. The fat, lymphatic tissues, blood vessels and extracellular substance inside the medullary space have more mobile protons, than the outer cortex layer, and produce bright signals in short T1 sequence. Muscles such as lateral pterygoid and temporalis contain protons that are more mobile than the protons in bone and less than the ones in the fluid or fat. The muscles' attained signals produce an intermediate gray contrast divided by dark bands of the fascia. The articular disc comprised of condensed fibrous tissue and hydrophilic proteoglycans that attract water and fluid. Protons in the fibrous tissue are immobile; in contrast, protons of the fluids inside the disc are highly mobile. This combination allows a healthy disc to appear proportionally darker than a muscular tissue but brighter than cortex in a short T1 and PD sequences. An altered disc may lose its fluid content and appear darker than normal, and may not be easily distinguished from the cortex surrounding structures. The retrodiscal tissue appears with bright signal due its high fluid and fat contents. In an internal derangement, the retrodiscal tissue may be squeezed between TMJ osseous components, and tissue fibrosis generates a darker signal that resembles the articular disc and leads to a false-negative diagnosis.[179] The synovial fluid is contained within the TMJ capsule and circulates between the disc and the articular cartilage. It's bright signal, from the superior and inferior joint spaces separate the articular disc from the surrounding osseous structures. In a sagittal view, the lateral pterygoid muscle appears as an intermediate gray body fanning out from the condylar neck. The articular disc appears as a dark bow-tie body with thick anterior and posterior bands, and thin intermediate zone interposed between the condyle and the articular eminence of the temporal bone.

1.1.5.2.4 MRI interpretation of the TMJ

MRI for TMJ is preferably obtained in long TR and short TE (PD sequence) to best depict the disc derangement.[165,185,186] The long TR and long TE (T2 sequence) is appropriate for depict retrodiscal tissues' inflammation and joint effusion, but not appropriate to visualize anatomical structures. Small amounts of joint fluid can be seen in a normal joint. Abnormal joints appear with a significant amount of joint fluid that is referred to as joint effusion, which is usually associated with painful joint and functional limitation.[187] Ideally, oblique sagittal and oblique coronal views are preferred to assess the anteroposterior and mediolateral articular disc displacement. The axial view may be required if a lesion is suspected to be a neoplasm. Both open and closed mouth positions are necessary to detect the disc location relative to the condylar head.[185] Dynamic or echo-planner imaging are a real time imaging techniques that have suboptimal image quality but are useful in detecting intra-articular adhesion.[188] Contrast-enhanced MRI was found to improve visualization of lesions in the retrodiscal tissues and condylar bone marrow abnormalities.[189]

MRI has been extensively used in the literature to observe the changes in TMJ and their association with clinical symptoms and treatment outcomes. The MRI diagnostic findings are usually influenced by multiple factors such as imaging technique, imaging protocol, diagnostic criteria and examiners performance.[190] Although the imaging technique and protocols have become more and more similar in reported studies over the last two decades, the diagnostic criteria and classification systems of the articular disc varied significantly. Some studies adopted previously presented classification systems,[103,187,191] whereas others used their own classification systems.[192-194] Some studies reported the relationship between TMJ pain and anterior disc displacement,[195-197] and others found no such relationship.[97,198] The relationship between the disc position and the joint noises was also found to be low, with a prevalence of 13% in adolescents and 30% in adults.[114,199] Joint noises were found to fluctuate in adult life and increase with age and degenerative changes of the TMJ.[200,201] Disc displacement without reduction was found to relate strongly to reduced vertical jaw opening in millimeters.[202,203]

The radiation therapy effect on the masticatory muscles such as fibrosis, inflammation, and denervation atrophy was investigated using MRI findings.[204-207] However, the radiation therapy effect on the TMJ intra-capsular tissues was not reported in the literature.[208] The effect of the orthodontic mandible anterior positioning appliances on the TMJ articular disc of adolescent patients using MRI is reported and discussed in **Chapter 7**.

Arthroscopy, double contrast arthrography, and MRI can be used to visualize the hard and soft tissues components of the TMJ. MRI is the only non-invasive imaging modality that clearly depicts soft tissues of the TMJ. MRI is a paramount diagnostic tool when the TMJ internal disc derangement must be ruled out for diagnosis and treatment planning.

1.1.6 MRI and CBCT Image Co-registration

Image registration finds correspondence of each point in two images of different modalities and spatially aligns them after assuming one common coordinate for the both images. This process begins by determining the coordinates of each point in the MRI, transferred or sensed image, to its corresponding point on CBCT, reference image. This is based on reading intensities and intensities per one voxel. The sensed image is point-by-point resampled to the geometry of the CBCT image. This is a fast parameter screening providing initial preliminary overlap or registration that is refined using reading the intensities of both images and forming a joint histogram of reference and sensed image intensities. The joint histogram of two co-registered images appears the sharpest when the two images are completely and perfectly aligned. In the case of images from different modalities (such as MRI & CBCT), the images' intensities are entirely different, and finding a sharp joint histogram is not easily attainable. The mutual information theory utilizes the histogram spread "entropy" to calculate the statistical dependence between the image intensities of corresponding voxels in both images. After detecting the similarity between the two images, images are resampled using "linear interpolation" followed by iterative refinement to increase similarity between both images until optimal/final registration is reached. The final registered image preserves the same voxels' sizes and intensity of both MRI and CBCT images. The final fused MRI-CBCT image is displayed with alpha-blending intensity, a transparency tool, where a user can adjust the intensity-blending ratio as desired. The MRI-CBCT co-registered images provide a corresponding hybrid image of the soft and hard tissues of the TMJ. Application of MRI-CBCT registered images in the field of dentistry is discussed in **Chapter 2.**[209] The accuracy of the MRI-CBCT images co-registration is reported in **Chapter 4**,[210] and the registration technique details are reported in **Chapter 8**.

1.2 Statement of the problem

The TMJ internal derangement is defined as abnormal relationship of the disc-condyle complex.[17,36-39] The increased functional forces may result is hypoxia and inflammation of the joint tissues, which lead to tissues' fatigue, fluid loss and reduced ability to repair. As inflammation progresses, the articular surfaces may become subject to cellular activity of degeneration and remodeling of the articular cartilage and disc. Under abnormal disc-condyle relationship, the displaced articular disc is unable to provide proper load dissipation, which changes the dynamics of force distribution over the fibrocartilage layer of the condyle. Subtle changes in the disc-condyle complex may result in unfavorable developmental and functional long-term consequences.

The TMJ internal derangement is a problem with multifactorial etiology. A combination of initiating, predisposing and perpetuating factors may alter the functional balance between the TMJ structures, masticatory muscles, and occlusion. Based on the available literature, internal disc derangement is highly prevalent (about 13-22% in asymptomatic adults),[96,98,100] and unless pain or functional limitation are reported, the clinical examination is not always reliable.[113] The history and clinical presence of the joint noises are limited diagnostic signs. Diagnostic imaging is necessary to assess the integrity and the relationship of the disc-condyle complex, confirm the severity and progression of the abnormality and evaluate the effect of the treatment. An adequate evaluation of internal disc derangement allows proper diagnosis, adequate management planning of the underlying disease and prevention of further damage to the TMJ.

The osseous structures are best depicted with medical CT or CBCT images, which are required for definitive diagnosis of TMJ osseous abnormalities. MRI is considered the "gold standard" tool to view the TMJ articular disc and is required for definitive diagnosis of the internal disc derangement. The accuracy and reliability of the MRI to evaluate the disc position has been a source of controversy in the literature.[135,171-176] Disc position is often inconsistently reported on MRI and relatively low inter-examiner reliability for disc position classification has been reported in the literature.[135,171-176] There is a strong reason to believe that examiners performance substantially influence the diagnostic accuracy of the disc position.[177,178] Approaches such as increased image resolution, examiner's calibration, standardized categorization and quantitative assessment methods have been introduced to enhance diagnostic value and reduce decision-making errors when looking at TMJ articular disc position in MRI. Moreover, diagnosing articular disc and condylar changes from two separate images often lead to an incomplete understanding of tissue changes and may responsible for misdiagnosis. It is conceptually desirable to fuse MRI and CBCT images to accurately diagnose and understand the TMJ anatomical changes. Merging MRI and CBCT images result in a hybrid image that combines key features of both modalities and may allow better clinical interpretation of the TMJ characteristics. However, few points are worth to consider:

- Unlike co-registration of serial CBCT images, multimodality image co-registration between routine MRI for TMJ and CBCT is challenging due to differences in receivers, anatomical structure identification, FOV, voxel size and value, image-acquired orientation, slice thickness, image resolution, field inhomogeneity, patient position during imaging, and image artifacts. Although multimodality image co-registration is a popular technique in medical diagnostic imaging, it has not yet been deeply explored or tested for accuracy in the dental field or the TMJ diagnostic imaging.

- Regardless of the superiority of MRI for identification of the TMJ soft tissue structures, the difficulty in attaining and maintaining the examiners' reliability prevents the ideal interpretation of joint anatomy and the opportunity for improvement in joint imaging interpretation. The advancement in image registration technology enhances the definition of anatomical structures and may contribute to the examiners' knowledge, regardless their level of expertise, and reduce these sources of diagnostic errors in MRI interpretation.

- The TMJ articular disc derangement is a three-dimensional problem that is commonly described and diagnosed from two-dimensional images. The three-dimensional models of the TMJ enable quantitative analysis of tissue changes in all directions. Multiple attempts have been conducted to visualize the TMJ articular disc and osseous structures in three-dimensions using MRI.[211-214] However, differentiation of osseous contours from MRI is often insufficiently clear, especially in the TMJ region, which represents a significant limitation that is, yet, not addressed.

In adolescent and adult populations, can the MRI and CBCT image co-registration meet the research and clinical needs for simultaneous evaluation of soft and hard tissues at complex structures such as the TMJ? This needs to be answered!

1.3 Objectives and Hypotheses

Objective 1: To assess reliability and accuracy of the intrinsic MRI-CBCT image co-registration technique specific for TMJ tissues.

Hypothesis 1 (H_0): The intrinsic "mutual information-based" MRI-CBCT image co-registration is an accurate and reliable registration technique.

Objective 2: To assess the intra- and inter-examiners' reliability for experienced and novice users in evaluating the articular disc position and osseous pathology using MRI-CBCT co-registered images of adolescent and adult populations.

Hypothesis 2 (H_0): The MRI-CBCT co-registered images, from adolescent and adult populations, improve the intra- and inter-examiners' reliability compared to MRI alone.

Objective 3: To assess the usefulness of MRI-CBCT co-registered images in improving novice examiners' reliability in evaluating the articular disc position.

Hypothesis 3 (H_0): The MRI-CBCT co-registered images improve the reliability of the novice examiners' compared to MRI alone.

Objective 4: To assess feasibility and utility of reconstructing 3D models of the TMJ from the MRI-CBCT co-registered images as a means of evaluating the TMJ soft and hard tissue changes after mandibulotomy surgery in adults.

Hypothesis 4 (H_0): The MRI-CBCT is a reliable tool to reconstruct a 3D models that represent the TMJ soft and hard tissues; and can clearly quantify the morphological changes of the TMJ, in 3D, after mandibulotomy.

1.4 General Scope of the Dissertation

This thesis is presented in twelve chapters. This chapter, **Chapter 1**, represents a general introduction that reviews pertinent literature, states relevant problems, lists objectives, and proposed hypotheses, and finally, presents the general scope of the dissertation.

Chapter 2 represents a systematic review that discussed the importance, clinical applicability and practicality of the MRI and CT/CBCT image co-registration for TMJ assessment. The review highlighted the lack of sufficient data that supports the accuracy or the applicability of the MRI CT/CBCT co-registered images as a valid tool to assess the TMJ.

Chapter 3 represents a pilot study that aimed to explore the quality of two different techniques of MRI and CBCT co-registration (extrinsic versus intrinsic). The extrinsic co-registration was performed using multiple skin-surface fiducial markers, and the intrinsic co-registration was performed using the mutual information theory. Also, the study optimized the co-registered images to visualize and assess the soft and hard tissues of the TMJ. The co-registered images were evaluated by three experienced radiologists in diagnostic imaging of the TMJ.

In **Chapter 4,** the accuracy of the intrinsic (mutual information based) MRI-CBCT image co-registration is measured. Five fresh cadaver swine heads were imaged to mimic the human tissues in a clinical imaging set up. Multiple fiducial markers were fixed in the cadavers' skulls, and the linear distances between the markers were measured using a laser scanner, and compared to the linear distances in the co-registered images to confirm the accuracy and the marginal errors.

Chapter 5 represents the main experiment that evaluated the effect of the MRI-CBCT co-registered images on the inter- and intra-examiners' reliability when diagnosis the TMJ disc position. The reliability between the radiologists and over time was examined using two sets of images: 1. 50 MRI-CBCT co-registered images and 2. MRI alone.

Chapter 6 represents the usefulness of the MRI-CBCT images co-registration for young, inexperienced dental students to assess TMJ disc position was explored. The study aimed to emphasize the effect of the co-registered images on the students' reliability compared to MRI alone.

Chapter 7 represents a systematic review that analyzed the available data and discussed the lack of a reliable and universal tool to evaluate the TMJ changes in adolescents after treatment with orthodontic functional appliances. Although several studies have emerged recently, most if not all discussed shortcomings still apply.

Chapter 8 represents a pilot study that highlighted the applicability of the MRI-CBCT co-registered images as a valid tool to evaluate the TMJ disc position in adolescents who were undergoing orthodontic treatment.

Chapter 9 represents a systematic review that analyzed the available data and discussed the limited information on the morphological and functional changes of the TMJ after transmandibular surgeries in adults. The review highlighted the need for an accurate, valid and reliable tool to quantify the morphological changes after major trauma to the TMJ.

Chapters 10 and **11** represent two studies that introduced a new tool of 3D reconstructed models of the TMJ to quantify the TMJ changes. The 3D models of the TMJ were reconstructed from the MRI-CBCT co-registered images with an articular disc depicted from MRI and osseous structures depicted from CBCT. This tool was utilized to quantify the 3D morphological changes of the TMJ following two types of traumatic surgeries of oropharyngeal cancer resection.

Finally, **Chapter 12** provides a broad view of the performed studies in a general discussion, limitations and recommendations for future projects to further improve the MRI-CBCT image co-registration as an easily applicable and universal tool for TMJ assessment.

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Chapter 2: MRI and CBCT Image Registration of Temporomandibular Joint: A Systematic Review *

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Preface

This systematic review, which is a part of this thesis, is an original work. In this review, I conceived, prepared the study design and coordination. I ran the electronic search in the library electronic data bases, collected the information, summarized and critically appraised the findings and finally drafted the manuscript. The participating co-authors, Dr. J. Jaremko and Dr. N. Alsufyani (Department of Dentistry) contributed in the present review by evaluating the included articles. Drs. Lgravere, and Major were involved in concept formation, manuscript drafting, critical revision of the intellectual content and final approval for manuscript submission.

2. MRI and CBCT Image Registration of Temporomandibular Joint: A Systematic Review*

Abstract

Purpose: The purpose of the present review is to systematically and critically analyze the available literature regarding the importance, applicability, and practicality of (MRI), computerized tomography (CT) or cone-beam CT (CBCT) image registration for TMJ anatomy and assessment. **Data sources:** A systematic search of 4 databases; MEDLINE, EMBASE, EBM reviews and Scopus, was conducted by 2 reviewers. An additional manual search of the bibliography was performed. **Inclusion criteria:** All articles discussing the magnetic resonance imaging MRI and CT or CBCT image registration for temporomandibular joint (TMJ) visualization or assessment were included. **Results and included articles' characteristics**: Only 3 articles satisfied the inclusion criteria. All included articles were published within the last 7 years. Two articles described MRI to CT multimodality image registration as a complementary tool to visualize TMJ. Both articles used images of one patient only to introduce the complementary concept of MRI-CT fused image. One article assessed the reliability of using MRI-CBCT registration to evaluate the TMJ disc position and osseous pathology for 10 temporomandibular disorder (TMD) patients. **Conclusion:** There are very limited studies of MRI-CT/CBCT registration to reach a conclusion regarding its accuracy or clinical use in the temporomandibular joints.

2.1 Introduction

Merging different imaging modalities such as magnetic resonance imaging (MRI), multi-detector computed tomography (CT) and Positron emission tomography (PET) to display both osseous and soft tissues has been undertaken for about 20 years in neurosurgery.[1] Digital registration tools were employed to optimize image alignment. Other medical applications of image registration have been introduced including computer-aided robotic orthopedic surgeries and radiotherapies.[2-4]

Image superimposition to evaluate changes in facial soft tissues, skeleton and dentition has been performed for many years using two-dimensional (2D) radiographs.[5,6] However, the 2D radiographs suffered many limitations such as tissue overlapping, landmark obstruction, distortion, magnification and object displacement. The contribution of three-dimensional (3D) cone-beam CT (CBCT) to the field of dentistry is significant especially for diagnosis, treatment planning of craniofacial structures and assessment of the hard tissues of the temporomandibular joint (TMJ).[7,8] CBCT overcame the limitations of 2D radiography and allows 3D image superimposition. CBCT superimposition using anatomical landmarks in the skull base to analyze changes in craniofacial bones and airway tract has been validated.[9-11] Virtual 3D surface models have been developed to quantify tissue displacement between two time points using a color-coded scale.[12,13] Registration of CBCT images has evolved into automatic superimposition of 2 CBCT images using the mutual information registration concept and has recently been introduced as a new tool to evaluate the craniofacial changes and TMJ assessment.[14,15]

In 1998, Nebbe *et al* superimposed sagittal MRI to lateral cephalometric radiographs to evaluate the temporomandibular joint (TMJ) disc position.[16] CBCT and MRI are the most commonly used diagnostic imaging techniques used in the field of dentistry. CBCT is optimum for viewing skeletal and dental tissues, and MRI is the standard for viewing masticatory muscles, ligaments and the cartilaginous disc of TMJ. Unlike registration of serial CBCT images, multimodality image registration between MRI and CBCT is challenging due to differences in voxel size, pixel intensity, anatomical structure identification, image orientation and field of view (FOV). Nevertheless, this registration is desirable as it provides a complementary image of soft and hard tissues in one picture frame for optimum diagnosis, treatment planning, and evaluation of treatment outcome.

The purpose of the present review is to systematically and critically analyze the available literature regarding importance, applicability, and practicality of MRI, CT and CBCT image registration for TMJ anatomy and assessment.

2.2 Materials & Methods

Search strategy:

Systematic search of four major databases, MEDLINE (1946 to 2015 Jan 10), All EBM Reviews-Cochrane DSR, DARE, and American College of Physicians Journal Club (1980 through January 13, 2016), Scopus (1965 through Jan 18, 2016), and EMBASE (1974 to 2016 January 18), was conducted without language limitation. The search's key words used were *Magnetic resonance imaging, tomography, computed tomography, CT, cone-beam CT, registration, integration, merging, correlation, fusion, superimposition, image-processing, matching, temporomandibular joint, TMJ, temporomandibular disorder, TMD,* *craniomandibular disorder, TMJ articular disc, TMJ articular disk.*

MESH keywords and truncated terms were searched with help of a librarian. In addition, manual search of the references in the identified articles was performed to avoid missing relevant articles. An example of search terminology used in Medline is summarized in Table 2.1 (Search terminology for the included databases is provided in Appendix A).

Inclusion and exclusion criteria:

Studies of different designs (e.g., clinical trials, cohort studies, case-control studies, cross-sectional studies, prospective and retrospective studies, case series/reports) reporting MRI and CT/CBCT image registration for TMJ concerns were included. Reviews, editorials, letters, published errata and historical articles were not included. Articles describing multimodal image registration concerning head and neck oncology were excluded.

Screening process and data collection:

Three independent reviewers (M.A., H.S & N.A.) screened the search data thoroughly and identified the relevant abstracts for full-text article evaluation. When in doubt or unclear from the abstract, the full-text article was selected for evaluation. Preliminary selected abstracts/articles, were reviewed according to the inclusion/exclusion criteria. No clear conflict in the article selection between the two reviewers was reported. Image characteristics and registration type for the included studies were collected and summarized in Table 2.2.

Table 2.1: Midline database search results		
	Keywords	Number of articles
1	Magnetic resonance imaging or MRI	396,001
2	Computed tomography, CT, x-ray	439,315
3	Cone-beam computed tomography, CBCT	5,907
4	Temporomandibular joint	14,080
5	TMJ internal derangement, TMD	24,634
6	Image processing, computer assisted, registration	23,7947
7	Merging, fusion, matching, superimposition	23,9841
8	(1 or 2 or 3) AND (4 or 5) AND (6 or 7)	464

<table>
<tr><th colspan="5">Table 2.2: Description of the finally included articles.</th></tr>
<tr><th>Article</th><th>Subjects</th><th>Image characteristics</th><th>Registration model</th><th>Measured outcome</th></tr>
<tr><td rowspan="2">Lin et al 2008</td><td rowspan="2">1 patient
(2 TMJs)</td><td>CT: DICOM files.
• GE® multilayer spiral CT scanner; 120 kv; 250 mA; slice thickness 0.6mm.
• FOV, matrix size & voxel size were not reported.
• Supine scanning position.</td><td rowspan="2">• Extrinsic registration model (14 radio-opaque fiducial markers).
• Dicom Works® V1.3.5 software.</td><td rowspan="2">• Visualize 3D model of TMJ.</td></tr>
<tr><td>MRI: DCOM files.
• Signa® 1.5T MRI scanner.
• T1-weighted image; TR 23ms; TE 4.6ms; FOV 25cm; Matrix 256X128; slice thickness 1.5mm.
• Supine scanning position.
• Type of surface coil & voxel size were not reported.</td></tr>
<tr><td rowspan="2">Dai et al 2012</td><td rowspan="2">1 patient
(one side of TMJ)</td><td>Contrast-enhanced CT: DICOM files.
• Philips® multilayer spiral CT scanner; 140 kv; 287 mA; slice thickness 1.25mm; matrix size 512X512.
• FOV 23.8cm; pixle size 0.47mm.
• Contrast agent (Inhexol 300mg I/ml)
Supine scanning position.</td><td rowspan="2">• 2D sagittal slices were manually superimposed.
• Photoshop® software.</td><td rowspan="2">• Matched 2D sagittal slices of MRI and CT of a TMJ to visualize fused image of both modalities.</td></tr>
<tr><td>MRI: DICOM files.
• Signa® 1.5T MRI scanner. Head surface-coil.
• T1-weighted image; TR350-550ms; TE13-20ms; Matrix 512X512; slice thickness 4mm.
• Contrast-enhanced T1-weighted image; TR2000-3000ms; TE15-40ms; Matrix 512X512; slice thickness 4mm. (Gadopentetate dimeglumine 0.1mmL/kg).
• T2-weighted image; TR 2800-5000ms; TE 100-120ms; FOV 24cm; Matrix 512X512; slice thickness 4mm.
• Supine scanning position.</td></tr>
<tr><td rowspan="2">Al-Saleh et al 2015</td><td rowspan="2">10 patients with TMD symptom.
(20 TMJs)</td><td>CT: DICOM files.
• i-CAT® CBCT scanner; 120kv; 5mA; scan time 9sec; slice thickness 0.3mm; matrix size 512X512.
• FOV 17X23cm; voxel size $0.3mm^3$.
• Upright scanning position.</td><td rowspan="2">• Extrinsic marker-based registration.
(5 radio-opaque fiducial markers)
• Intrinsic registration (Mutual information-based registration).
• Mirada® software.</td><td rowspan="2">• Qualitative assessment of the registration models.
• Assess the reliability of evaluating TMJ disc position and osseous pathology in 20 TMJs.</td></tr>
<tr><td>MRI: DCOM files.
• Seimens® 1.5T MRI scanner. Head surface coil.
• T1-weighted image; TR 13ms; TE 4.8ms; FOV 46X36cm; Matrix 256X128; slice thickness 1mm; voxel size $1mm^3$.
• Supine scanning position.</td></tr>
<tr><td colspan="5">Abbreviation: TMJ: temporomandibular joint; CT: computed tomography; MRI: magnetic resonance imaging; DICOM: digital imaging and communication in medicine; FOV: field of view; TR: repetition time; TE: echo time; kv: kilovoltage; mA: milliAmber.</td></tr>
</table>

2.3 Results:

Data searched:

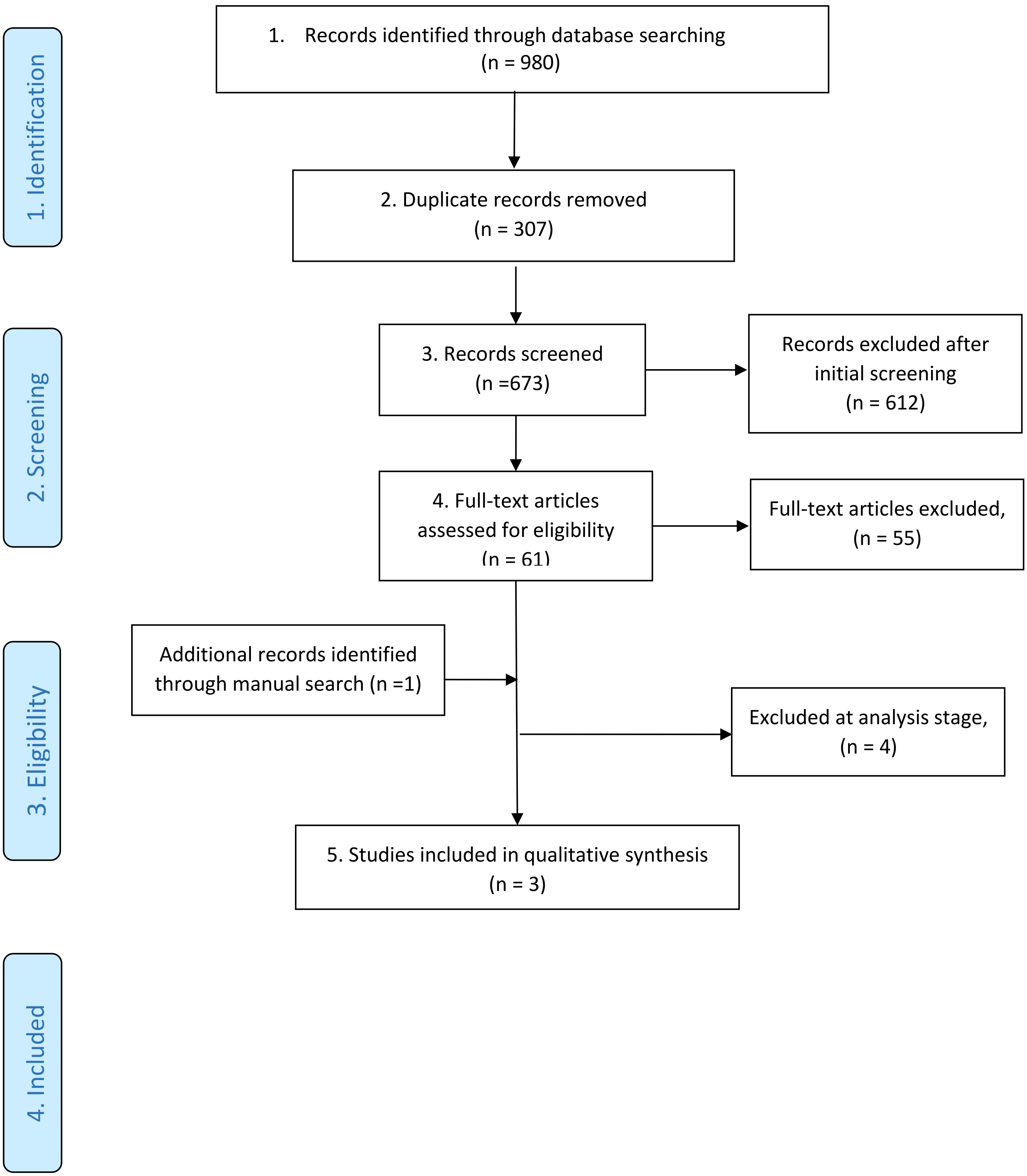
The database search resulted in a total of 673 articles. The initial review of the titles and abstracts resulted in 61 articles that were considered for full-text review. The full-text review resulted in 6 articles.[15,17-21] One more article was identified by manual search.[22] Figure 2.1 demonstrates a flow chart of the articles selection process. Only 3 articles met the inclusion criteria of this review. The 4 remaining articles from the final selection phase were excluded for the following reasons:

1. Measure accuracy of different multimodal image registration techniques. [17,18]
2. Introducing multimodal image registration to visualize the tumors in the head and neck region. [20,21]

Characteristics of the included articles

All included articles were published within the last 7 years. Two articles described MRI to CT multimodality image registration as a complementary tool to visualize TMJ. Both articles used images of one patient only to introduce the complementary concept of MRI-CT fused image. One article assessed the reliability of using MRI-CBCT registration to evaluate the TMJ disc position and osseous pathology in 20 TMJ's for 10 temporomandibular disorder (TMD) patients. Table 2.1 shows the imaging protocols and measured outcomes of the included articles.

Figure 2.1: PRISMA 2009 Flow diagram



2.4 Discussion

Multimodal image registration:

The essential goal of merging two images from different modalities is to utilize the complementary nature of the displayed information. Proper registration of the different images is crucial especially when used for clinical applications. The process of image registration is composed of two major steps: the first step is the spatial alignment of the target images, which is commonly defined as “registration, and the second is the fused display of the target images, which is defined as “fusion”. Mistakenly, different terminologies have been inter-changeably used in the literature to describe a single step process: such as superimposition, matching, integration, merging and correlation.

According to van den Elsen *et al* and Maintz *et al*,[23,24] the registration process was classified into intrinsic and extrinsic models. The intrinsic model depends on anatomical landmarks and segmented bodies or voxel values. The extrinsic model depends on fiducial markers that are either invasively screwed into the tissues or non-invasively attached to the surface skin. Screw-mounted fiducial markers have been considered a gold standard approach for many years to measure the accuracy of the registration process. However, the invasiveness of this approach limits its use to surgical procedures and *in-vitro* experiments. Anatomical landmarks in the intrinsic registration models are often conspicuous and easy to locate in the human head, however; registration of large tissues in complex regions requires detection of a large number of anatomical landmarks. User interaction is also required to identify the landmarks, which can implicate an operator-bias especially with inexperienced operators. Due to the high degree of similarity between same modality images, monomodal image registration is considered a much easier process than multimodality image registration. In multimodality image registration, such as MRI and CT or CBCT, identifying matched anatomical landmark is a challenging task. Another intrinsic approach is using voxel values (gray values) of the image to spatially align the center of gravity and principal orientation of two images. Using the full image content of gray values in a relative entropy histogram, a method known as “maximization of mutual information”, is a conceptually appealing technique due to its flexibility, easy implementation, automatic and fast use in multimodal image registration (Figure 2.2). However, accuracy concerns and sophisticated computational requirements/costs have delayed the clinical application of this registration technique.

For TMJ pathology, MRI or CBCT are the choice of diagnostic imaging depending on availability and the therapeutic indication. Despite the advancement in MR imaging quality, it has not entirely overcome the limitations of the low quality presentation of the complex osseous structure of the TMJ. CBCT is superior at identifying cortical bone contouring, remodeling, developmental abnormality and pathological changes. Both imaging techniques have their limitations and remain complementary to each other in the TMJ diagnostic field.

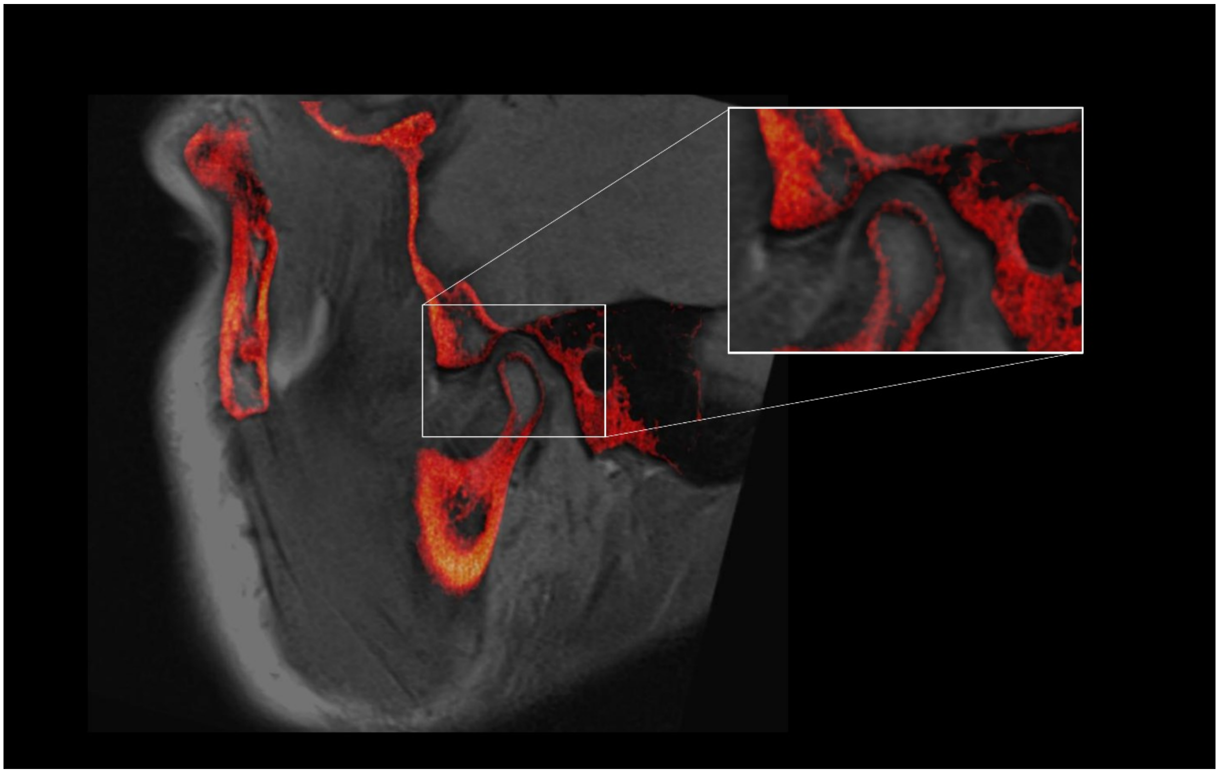


Figure 2.2: Sagittal view of registered MRI (grey color) and CBCT image (Red color) using maximum mutual information algorithm (intrinsic based registration). The image shows excellent superimposition of the anatomical tissues of the TMJ, despite the different receivers, FOV size, voxel size, voxel value, image-acquired orientation, slice thickness, image resolution and field inhomogeneity.

Accuracy of the MRI-CT/CBCT image registration:

Registration technique accuracy is a substantial issue when it comes to multimodality image registration. MRI-CT image registration, using maximum mutual information, have been proven accurate in many medical-imaging related studies.[25-28] The linear measurement error (target error) ranged between 0.4-1.6mm when registered images in the brain, skull and nasopharynx regions. Three studies have reported the accuracy of registration of MRI to CBCT images.[17,18] Pawiro *et al* used fixed fiducial markers, to a cadaver swine head as a gold standard, to measure the accuracy of mutual information based registration of MRI to C-arm CBCT.[17] The registration target error ranged between 0.62±3.19mm to 1.5±2.3mm. Tai *et al* used a complicated procedure, which involved multiple steps in five different computational software products, to register large FOV 3D MRI to CBCT image.[18] Although this registration technique was cumbersome and somewhat impractical for clinical use, the authors reported a small target error 0.29-0.71mm when measured against orthodontic dental models. Al-Saleh *et al* used fixed fiducial markers to 5 cadaver swine heads to measure the linear target error of MRI-CBCT image registration.[29] The authors' findings demonstrated a small linear target error (0.2±1.2mm) when compared to a laser scanner ground truth value. The accuracy of the multi-modality rigid registration has been proven accurate and accessible in the modern advanced imaging technology.

Review included articles:

Lin *et al* was the first to explore the 3D rendering of mandible from MRI and CT registered images.[22] One volunteer was scanned in MRI and CT scanner with 12 fiducial markers attached to the facial skin-surface. The centroids of the markers were identified to detect the center of gravity and spatial relation required for rigid registration. It was not clear how the centroids of the spherical markers were detected, or type of images that were utilized to detect the markers centroid. The authors did not describe the type of the surface coil used for MRI or the voxel size difference between the MRI and CT. Moreover, the registration algorithm/ methods, accuracy, or operator's bias to manually detect the markers' centroids were not reported. Extrinsic marker-based registration is rapid and conceptually straightforward, but lacks accuracy. Registration target errors, due to marker displacement (especially when attached to skin), patient position and movement, are not possible to control and substantially affect the registration function. The article's main objective was to draw the readers' attention to the feasibility of the MRI-CT registration process and its potential in TMJ anatomical screening. However, the report was simple and lacked details of technical and clinical reporting.

In a brief clinical report, Dai *et al* [19] highlighted the importance of merging the MRI and CT images to visualize TMJ tissues. The authors chose one sagittal slice of TMJ MRI and CT images from a previous study, as an example, to illustrate a hybrid image of TMJ via Photoshop® software. Since the image processing applied was not a real registration of two images, the authors indicated in their report that the method was not accurate, and it was merely an example of a future endeavor.

Al-Saleh *et al* published the first study that employed MRI and CBCT registered images to assess diagnostic reliability of TMJ pathology.[15] Three radiologists evaluated the quality of two techniques of image registration, extrinsic (fiducial marker-based) versus intrinsic (voxel value mutual information based) in 20 TMJ images. The authors reported poor quality and inaccurate extrinsic MRI-CBCT registration when using 5 skin surface attached markers. The poor alignment of the MRI and CBCT images was attributed to the displacement of the markers, and different patient positioning during imaging. Patients were at supine position during MRI and upright position during CBCT imaging. Matching surface markers seems to be insufficient nor reliable. In contrast, the mutual-information based registration was found to be accurate by all radiologists with high intra- and inter-examiner agreement. Moreover, TMJ osseous pathology and articular disc positon were assessed by all radiologists in 3-interval time. The study found that registered MRI-CBCT images have improved the reliability among radiologists in TMJ disc position evaluation. Although that study did not report the actual registration algorithm or the registration linear target error, it highlighted the importance of viewing well-defined osseous contours and articular disc tissue in one image.[15]

Fused MRI and CBCT images have better diagnostic value than the value of each image alone. Several challenges in multimodality image registration starting with, but not limited to, the different receivers, FOV, voxel size, voxel value, image-acquired orientation, slice thickness, image resolution, field inhomogeneity and image artifacts, were largely overcome with the recently introduced robust registration model (mutual information). Although mutual information based image registration is a popular technique in medical image processing, it has not yet been explored in the dental field except for two studies, the one by Al-Saleh *et al* [15] and another one for monomodality registration (i.e. two CBCT's) by Choi and Mah.[14] In addition, the study had a small sample size that could have biased the reported results.

Unlike the medical field, studies about the MRI-CT/CBCT image registration are sparse in the field of dentistry. Out of three studies included in this review,[15,19,22] only one study utilized the MRI-CBCT image registration for clinical investigation.[15] The need for well-designed studies in this area is clear.

Multimodality MRI-CBCT image registration has potential to meet clinical needs for simultaneous evaluation of soft and hard tissues at complex structures such as the TMJ, in the field of dentistry and craniofacial surgery. However, multimodal image registration technology is relatively young and there is little evidence regarding its clinical use in many areas in dentistry. Challenges, such as complexity and accuracy concerns for the different registration techniques including different imaging protocols have been improved over the past few years, but have not yet led to general clinical applicability. This review highlights the need for further work in the field of dental multimodality image fusion.

2.5 Future recommendations:

To explore the accuracy and clinical application of MRI-CBCT image registration in the field of craniofacial and TMJ. This review suggests the following:

1) Measure the accuracy of the MRI-CBCT mutual information algorithm using a gold standard tool independent of MRI or CBCT.
2) Test the usefulness of the fused MRI-CBCT in evaluating the TMJ among practitioners with different levels of expertise.
3) Explore objective tools to measure disc position or changes in relation to osseous structure using 3D volume rendering.

2.6 Conclusions:

There are very limited studies of MRI-CT/CBCT registration, with data insufficient to reach a conclusion regarding its accuracy or clinical use in the temporomandibular joints.

Mutual information based registration seems a promising technique, and exploring its accuracy and applications for TMJ analysis would be worthwhile in larger studies.

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Chapter 3: Assessing the Reliability of MRI-CBCT Image Registration To Visualize The Temporomandibular Joints *

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Preface

This research project, which is a part of this thesis, is an original work and received research ethics approval from the University of Alberta Research Ethics Board Project #Pro00032935, October 25, 2012.

In this project, I conceived, prepared the study design and coordination. I executed data acquisition, analysis, and interpretation, and finally drafted the manuscript. The participating radiologists, Drs. J. Jaremko and Z. Jibri (Department of Radiology and Diagnostic Imaging) and Dr. Alsufyani (Department of Dentistry) contributed in the present project by evaluating the obtained images quality and diagnosing the TMJ pathologies in three occasions. As well, they helped in drafting and approving the manuscript for submission. Dr. Lai (statistician) helped in confirming the performed the data statistical analysis. Dr. Major was the supervising/senior author and was involved in concept formation, manuscript drafting, critical revision of the intellectual content and final approval for manuscript submission.

3. Assessing the Reliability of MRI-CBCT Image Registration To Visualize The Temporomandibular Joints.

Abstract

Purpose: To evaluate image quality of two methods of registering MRI and CBCT images of the TMJ, particularly regarding TMJ articular disc-condyle relationship and osseous abnormality. **Methods:** MR and CBCT images for 10 patients were obtained and co-registered using two methods: intrinsic (anatomical landmarks) and extrinsic (markers) using Mirada XD software (Mirada® Medical, Oxford, UK). Three radiologists independently and blindly evaluated three types of images (MRI, CBCT and registered MRI-CBCT) at 2 times on two criterions: (1) quality of MRI-CBCT registrations (excellent, fair or poor) and (2) TMJ disc-condylar position and articular osseous abnormalities (osteophytes, erosions and subcortical cyst, surface flattening, sclerosis). **Results:** 75% of intrinsic registered images showed excellent quality, and 95% of the extrinsic registered images showed poor quality. Significant difference was found between the intrinsic and extrinsic registration (X^2= 108.5, P<0.01). The inter-observer variability of disc position in MRI (ICC= 0.50 at T1 0.56 at T2) was lower than the MRI-CBCT registered images (ICC= 0.80 [0.52-0.92] at T1, 0.84 [0.62-0.93] at T2). Erosions and subcortical cysts were noticed less frequently in the MRI-CBCT images compared to CBCT images.

Conclusions: Intrinsic registration proved superior to extrinsic registration. Although MRI-CBCT fused images were slightly more limited than CBCT alone to detect osseous abnormalities, use of the fused images improved the reliability among examiners in detecting disc position in relation to the condyle.

3.1 Introduction:

Cone-beam computerized tomography (CBCT) has become integral to the field of dentistry, specifically in practices of orthodontics, implant dentistry, and oral surgery.[1-4] Magnetic resonance imaging (MRI) is the current gold standard imaging tool to analyze the position and morphology of the temporomandibular joint (TMJ) articular disc position and morphology.[5] MRI is also useful to demonstrate condylar/disc translation on mouth opening, joint effusions and synovitis, as well as to a lesser extent osseous erosions and degenerative joint disease.[6] Concurrently, CBCT imaging has become the gold standard imaging tool for evaluation of TMJ bony changes. Pathological Changes such as condylar erosion, fractures, ankylosis, dislocation, and osteophytes are optimally viewed on CBCT.[1-4]

TMJ internal derangement is defined as the abnormal position of the articular disc in relation to the condylar head and articular eminence of the temporal bone.[7,8] At imaging, the disc is best seen on MRI and the bone is best depicted on CT. Therefore, to optimally assess for internal derangement, it is conceptually desirable to fuse MRI and CT images. Disc position is often inconsistently reported on MRI. A variety of methods have been reported in the literature attempting to define the disc position in relation to different articular osseous anatomy of the TMJ such as condylar outline, condylar head inclination, depth of glenoid fossa and articular eminence slope.[9-11]

The image's diagnostic value relies on two integral parts: the image's information content and the observer's correct interpretation. Approaches such as increased image resolution, observer calibration, standardized categorization and quantitative assessment methods have been introduced to enhance diagnostic value and reduce the decision making-errors when looking at TMJ articular disc position in an MRI.[9-11]

MRI-CBCT registered images are new to dentistry and this technique may accurately detect the anatomical changes in the maxillofacial region, TMJ and masticatory muscles. Data can be presented at equal resolution in any plane including the panoramic plane.

The relationship between the articular disc of the TMJ and mandibular condyle or glenoid fossa is often difficult to visualize with sole assessment of MRI particularly for the novice clinician. This finding is supported by the relatively low inter-examiner reliability for classification of TMJ internal derangement as previously reported in the literature.[12] Merging MRI and CT images result in a hybrid image that combine key features of both images, and allows better clinical interpretation of the TMJ characteristics and it stands to reason that registration of MRI and CBCT images will also be beneficial.[13]

Image registration is the alignment of two imaging data sets spatially and displays one fused image on a screen that contains both sources of information. The value of MRI and CT image registration has been investigated in the medical literature, and found to improve diagnosis, monitoring of disease progression and understanding of pathology involved in the brain and abdominal regions.[14-17] In general, two approaches can be taken to achieve image registration. The first is using skin surface fiducial markers provide three-dimensional points of reference to register and fuse different images. Fiducial markers, with radio-opaque hydrogel that appears in MR and CBCT images, are used in neurosurgery and radiotherapy intraoperative imaging, with a high level of image registration accuracy when the markers are firmly fixed to the patients.[18,19]

The second approach using multi-modality image registration with normalized mutual information (MI), which depends on correspondence analysis of statistical dependency of two images where one image can help predict the other, has been successfully applied on CT-MRI.[20]

The purpose of this study was, first, to evaluate the radiologists impression of quality of the two available methods of MRI-CBCT image registration (intrinsic; anatomical landmarks) versus (extrinsic: fiducial markers), and second, to evaluate the reliability of determining TMJ articular disc-condyle relationship and articular osseous abnormality using MRI-CBCT registered images compared to MRI or CT alone.

3.2 Materials and Methods:

Patients:

A total of 10 adult patients (20 TMJs) with history of TMJ disorders were recruited from the Temporomandibular Disorder/Orofacial Pain Clinic at the University of Alberta suspected of having a TMJ anatomic abnormality. The study was approved by the Human Research Ethics Board at the University of Alberta (Pro00032935) and informed consent was obtained from all participants. All patients had MR and CBCT images obtained at the same visit with skin surface attached fiducial markers (15mmX3.5mm) (IZI Medical, Maryland, USA). Self-adhesive skin-surface fiducial markers were placed in five different places in the face (1 at nasal ridge, 2 at zygomatic cheek bones, 2 at mandibular angles). Fiducial markers clearly appear in both MRI and CBCT and provide discrete three-dimensional points of reference to reconstruct and register images. Patients kept their mouth closed during imaging using centric occlusion bite stent polyvinylsiloxane material.

CBCT protocol:

Each CT scan was acquired in 360 degrees of rotation with proper subject upright positioning with Frankfort plane parallel to the floor, and was collimated to avoid radiosensitive structures (thyroid and orbits). Scans were performed using i-CAT scanner (Imaging Sciences International, Hatfield, USA) at a medium field of view setting, 16cm wide, 13cm height, scan time 26 seconds and 0.25 mm voxel size. This included the maxilla and mandible and both of the TMJ condyles.

MRI protocol:

MRI of the TMJ was performed in the supine position without sedation or intravenous contrast administration, by 1.5 Tesla scanner (Siemens, Munich, Germany) with a multi-channel head array coil. Small field of view (13cmX13cm) dedicated bilateral closed-mouth oblique sagittal sections were obtained perpendicular to the long axis of the condyle. Proton density-weighted images (PD) were obtained with slice thickness 3mm; inter-slice gap 0.3mm; repetition time/echo time 1800/11 ms; typically, 14 slices per side.

Image-registration:

MRI and CBCT DICOM files of the 20 TMJs were transferred to a desktop PC workstation. Mirada XD software (Mirada Medical, Oxford, UK) was used to perform multi-modality image registration for MRI and CBT data sets. Two methods of registration were performed using the software; 1) Automatic registration (intrinsic) and 2) marker-based automatic registration (extrinsic). In intrinsic registration, the two images were brought into a spatial alignment using the MI, and finally fused into a common display (Figure 3.1).[21]

The extrinsic registration instead depended on identification of the centers of the radio-opaque fiducial markers (torus-shaped with a 1.7mm central hole diameter) appearing in MRI and CBCT images. Using the 2D axial, coronal, and sagittal image sections, the operator would visually locate and mark the center in one image section and adjust/verify in the remaining two image sections. Both sets of registered images were then saved for assessment.

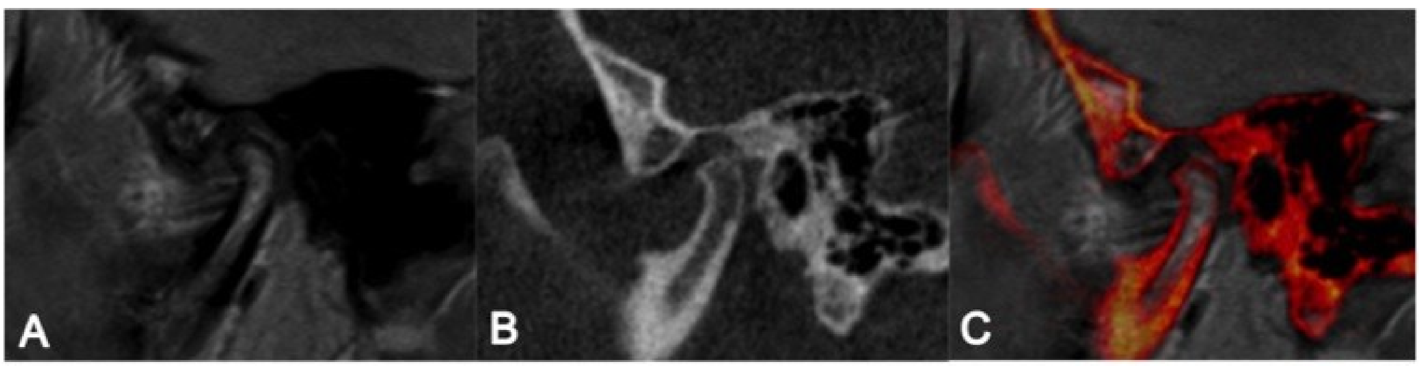

Figure 3.1: Sagittal image of the right TMJ of subject 9 showing (A) mild anterior disc displacement in the PD-MR image and (B) flattening of the antro-superior surface of the condylar head in the CBCT image. (C) Fused CBCT-MR image depicts the flattening noted in CBCT image (B) and differentiates condylar-temporal osseous contours from disc tissues noted in MR image (A).

Image assessment:

The MRI-CBCT registered images were synthesized by overlying the gray-scaled MRI over red color-coded bony structure of the CBCT image (Figure 1). Three radiologists (Z.J., J.J., N.A.), with 0, 5 and 8 years of experience in TMJ image analysis, subjectively evaluated the registered images independently and blindly in 2 steps. Step 1: examiners subjectively evaluated the quality of image registration (intrinsic versus extrinsic) and ranked them as Excellent: edges of TMJ articular surfaces (condylar head, glenoid fossa & articular eminence) overlap within one pixel; Fair: mild variation of the contours and edges of the articular surfaces, mimicking mild motion artifact; Poor: large variation of the contours and edges with minimal to no overlap between both images (Figures 3.2, 3.3, 3.4). Step 2: examiners evaluated the TMJ disc-condylar relationship and articular osseous abnormalities on MRI, CBCT and MRI-CBCT registered images. To evaluate reliability, two examiners repeated images evaluation twice in a 2-month interval, and the most experienced examiner (N.A.) repeated the evaluation 5 times in two-week intervals. The sagittal position of the articular disc was evaluated following the functional relationship of the disc intermediate zone to the condylar head surface to mild, moderate and full anterior displacement. The categorization guide for the anterior disc position categories in the closed-mouth position are represented in Figure 3.5. Osseous abnormalities (*hyperplasia, hypoplasia*), signs of remodeling (*surface flattening, sclerosis*) and degenerative changes (*subcortical erosion or cyst, osteophyte, foreign bodies*) of the articular surfaces were evaluated and reported.

Statistical analysis:

The image quality of the registered images was reported in an ordinal scale. A factorial design was devised to evaluate the quality of images (intrinsic versus extrinsic) across different contributing factors (e.g., time, examiners and registration type). Chi-square test results were reported and the level of significance was set at $p < 0.05$.

To determine reliability of evaluating the disc position across the 3 examiners and time, Intra-class Correlation Coefficients (ICC) were calculated, as the outcome measure was ordinal. To evaluate the reliability of evaluating osseous changes across the three examiners and time, Cohen's Kappa was computed, as the outcome measures were categorical.

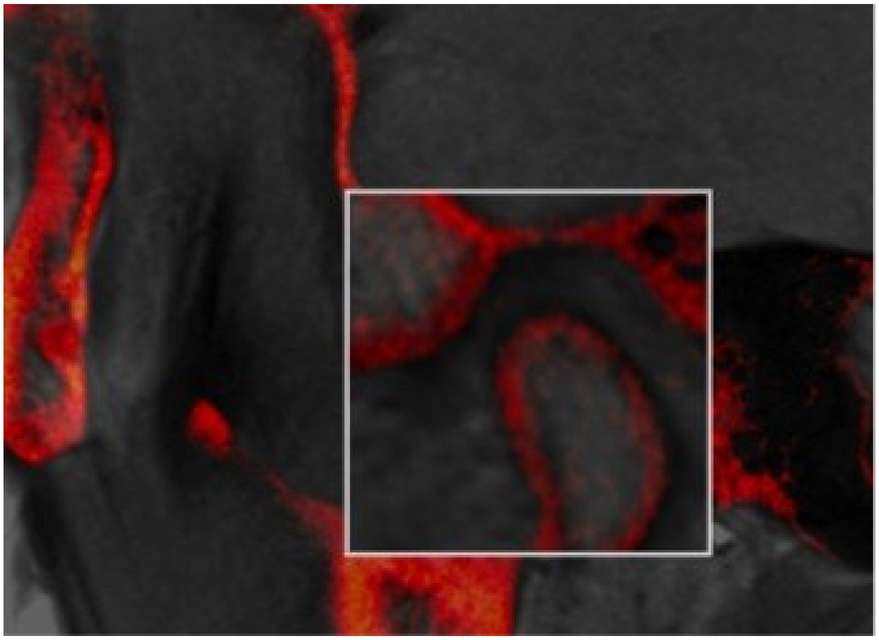

Figure 3.2: Sagittal image (MRI-CBCT intrinsic registration) of the right TMJ of subject 8 showing excellent edges of TMJ articular surfaces (condylar head, glenoid fossa & articular eminence) overlap within one pixel.

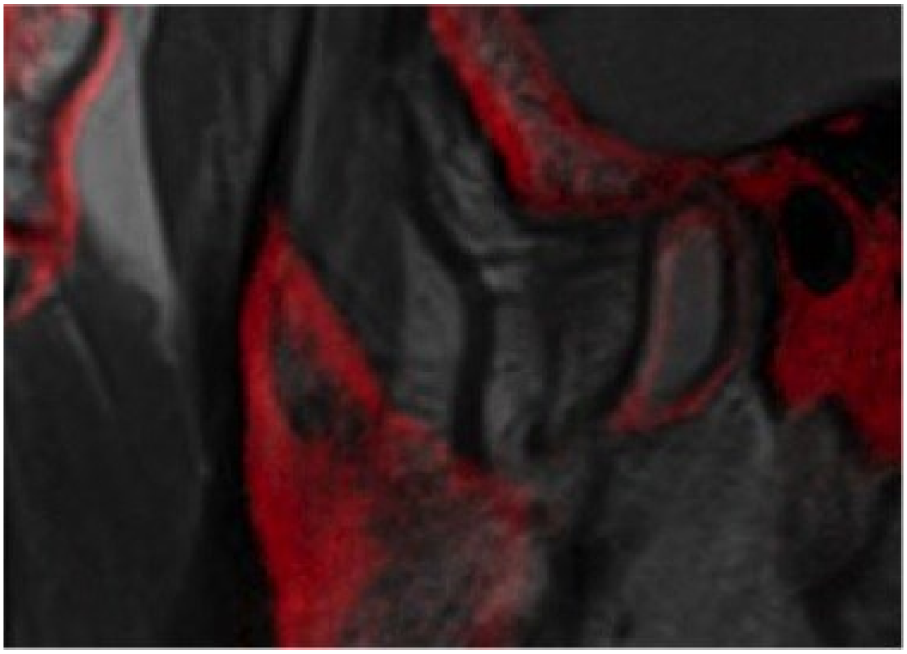

Figure 3.3: Sagittal image (MRI-CBCT extrinsic registration) of the right TMJ of subject 5 showing imperfect overlap contours and edges of the condyle, mimicking mild motion artifact. Registration quality was ranked as fair.

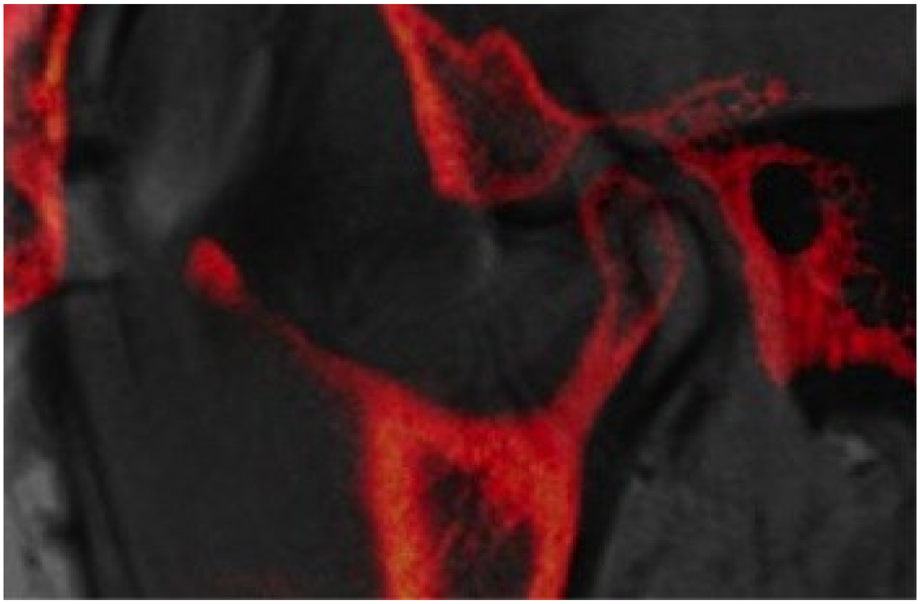

Figure 3.4: Sagittal image (MRI-CBCT extrinsic registration) of the right TMJ of subject 8 showing poor registration quality with large variation of the contours and edges of the condylar head, glenoid fossa & articular eminence with no overlap between both images.

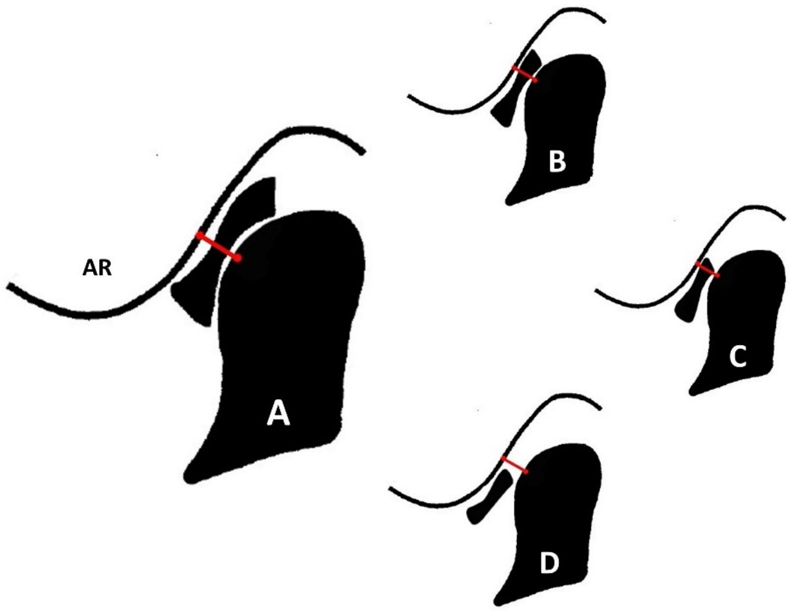

Figure 3.5: Illustration of the categories of the anterior disc displacement in closed-mouth position. (A) Normal disc position: the intermediate zone of the disc is interposed, in closest point, between the condylar head and posterior slope of the articular eminence (AR), with a “bow-tie” shape of the anterior and posterior bands of the disc. (B) Mild disc displacement: the intermediate zone of the disc is slightly anteriorly displaced. The posterior band of the disc opposed the condylar head. (C) Moderate disc displacement: the intermediate zone of the disc is completely displaced from between the joint osseous structures, or the posterior band of the of the disc located in the medial or lateral region of the joint. The condylar head is in contact with the junction between the disc posterior band and bilaminar zone. (D) Full displacement: the entire articular disc is anteriorly displaced relative to the posterior slope of the articular eminence and condylar head. The disc bilaminar zone is interposed between the osseous articular structures and occupied the narrowest joint space (represented by the red line).

2.3 Results:

Overall, 75% of the intrinsic registered MRI-CBCT images showed excellent image quality whereas only 5% of the extrinsic registered images showed excellent image quality. This difference in quality between the two registration methods was significant, X^2= 108.5 (*df=9*) and *P*<0.01. Moreover, the assessment of quality of images was not statistically different across examiners or over time (*P*<0.05). Due to the high quality of the “intrinsic” registered MRI-CBCT images, they were used for the TMJ assessment. The assessments of disc position of the evaluated images are reported in Tables 3.1 - 3.4. The reliability of disc position evaluation in MRI alone was low between examiners (ICC= 0.50 [0.04-0.78] at T1 and 0.56 [0.14-0.80] at T2) and high across time (T1- T2, ICC 0.80 to 0.97).

The reliability of disc position evaluation in MRI-CBCT registered images was high among examiners (ICC= 0.80 [0.52-0.92] at T1 0.84 [0.62-0.93] at T2] and high across time (ICC ranged between 0.91 and 0.98).

The reliability in reporting each osseous abnormality across the different examiners and time varied. Inter-examiner agreement on reporting osseous changes was fair to poor (*k*= 0.1-0.5). Substantial to excellent inter-examiner agreement was noticed between the second and third examiners for sclerosis and erosions (*k*= 0.6-0.9).

The average frequency of each osseous abnormality in different image modalities at T1 & T2 is summarized in Table 3.5. Loose intra-articular body was found in only one joint. One examiner reported hyperplasia in 2 TMJs of one patient and hypoplasia of 1 TMJ only. The frequency of reporting other abnormalities (*osteophytes, erosions and subcortical cyst, surface flattening, sclerosis*) was similar between MRI-CBCT images and CBCT images except for slight reduction in the frequency of reporting erosions and subcortical cysts in the MRI-CBCT images.

Table 3.1: Assessment of disc position in MRI at T1 and ICC value of the inter-examiner reliability.

T1		**Examiner 2**			
		Normal	*Mild*	*Moderate*	*Severe*
Examiner 1	*Normal*	5	2	1	3
	Mild	2	1	0	0
	Moderate	0	1	0	0
	Severe	0	4	0	1
T1		**Examiner 3**			
		Normal	*Mild*	*Moderate*	*Severe*
Examiner 1	*Normal*	1	5	2	3
	Mild	0	1	1	1
	Moderate	0	0	1	0
	Severe	0	0	0	5
T1		**Examiner 3**			
		Normal	*Mild*	*Moderate*	*Severe*
Examiner 2	*Normal*	1	3	3	0
	Mild	0	2	1	5
	Moderate	0	1	0	0
	Severe	0	0	0	4

Inter-examiner: ICC 0.5 [0.4 – 0.78]

Intra-examiner agreement: See T2 in Table 3.2.

Table 3.2: Assessment of disc position in MRI at T2 and ICC value of the inter-examiner reliability.

T2		Examiner 2			
		Normal	*Mild*	*Moderate*	*Severe*
Examiner 1	*Normal*	5	2	1	3
	Mild	2	1	0	0
	Moderate	0	1	0	0
	Severe	0	4	0	1
T2		**Examiner 3**			
		Normal	*Mild*	*Moderate*	*Severe*
Examiner 1	*Normal*	1	5	2	3
	Mild	0	1	1	1
	Moderate	0	0	1	0
	Severe	0	0	0	5
T2		**Examiner 3**			
		Normal	*Mild*	*Moderate*	*Severe*
Examiner 2	*Normal*	1	3	3	0
	Mild	0	2	1	5
	Moderate	0	1	0	0
	Severe	0	0	0	4

Inter-examiner agreement between 3 examiners: ICC 0.56[0.14 – 0.80]

Intra-examiner agreement:
Examiner 1 (2 times): ICC 0.88 [0.7 – 0.95]
Examiner 2 (2 times): ICC 0.8 [0.5 – 0.92]
Examiner 3 (5 times): ICC 0.97 [0.94 – 0.98]

Table 3.3: Assessment of disc position in MRI-CBCT at T1 and ICC value of the inter-examiner reliability.					
		Examiner 2			
		Normal	*Mild*	*Moderate*	*Severe*
Examiner 1	*Normal*	1	5	1	2
	Mild	0	3	1	1
	Moderate	0	0	0	0
	Severe	0	0	1	5
		Examiner 3			
		Normal	*Mild*	*Moderate*	*Severe*
Examiner 1	*Normal*	2	5	0	2
	Mild	1	2	0	2
	Moderate	0	0	0	0
	Severe	0	0	0	6
		Examiner 3			
		Normal	*Mild*	*Moderate*	*Severe*
Examiner 2	*Normal*	1	0	0	0
	Mild	2	6	0	0
	Moderate	0	1	0	2
	Severe	0	0	0	8
Inter-examiner agreement between 3 examiners: ICC 0.8 [0.52 – 0.92] Intra-examiner agreement: See T2 in Table 3.4.					

Table 3.4: Assessment of disc position in MRI-CBCT at T2 and ICC value of the inter-examiner reliability.					
		Examiner 2			
		Normal	*Mild*	*Moderate*	*Severe*
Examiner 1	*Normal*	1	5	1	2
	Mild	0	3	1	1
	Moderate	0	0	0	0
	Severe	0	0	1	5
		Examiner 3			
		Normal	*Mild*	*Moderate*	*Severe*
Examiner 1	*Normal*	2	5	0	2
	Mild	1	2	0	2
	Moderate	0	0	0	0
	Severe	0	0	0	6
		Examiner 3			
		Normal	*Mild*	*Moderate*	*Severe*
Examiner 2	*Normal*	1	0	0	0
	Mild	2	6	0	0
	Moderate	0	1	0	2
	Severe	0	0	0	8
Inter-examiner agreement between 3 examiners: 0.84 [0.62 – 0.93] Intra-examiner agreement: Examiner 1 (2 times): ICC 0.91 [0.8 – 0.97] Examiner 2 (2 times): ICC 0.96 [0.89 – 0.98] Examiner 3 (5 times): ICC 0.98 [0.97 – 0.99]					

Table 3.5: Frequency average (%) of osseous pathology of 20 TMJs as reported by examiners in CBCT and MRI-CBCT images.						
	Examiner 1		Examiner 2		Examiner 3	
	CBCT	MRI-CBCT	CBCT	MRI-CBCT	CBCT	MRI-CBCT
Hyperplasia	0	0	5	5	0	0
Hypoplasia	0	0	0	5	0	0
Osteophyte	65	65	100	100	90	65
Erosions or subcortical cyst	45	25	75	50	70	50
Surface flatting	25	30	80	75	75	75
Sclerosis	20	10	90	45	65	40
Foreign bodies	5	5	5	5	5	5

3.4 Discussion:

The process of image registration aims to find a correspondence of each point in a pair of images to spatially align them resulting in a common coordinate frame for both the images. We investigated two methods for performing rigid registration of MRI and CBCT image volumes; both methods were performed in commercially available imaging software (Mirada XD ver. 3.6, Mirada Medical Ltd, UK). The first method uses an automated Mutual Information (MI) based algorithm (intrinsic registration), and the second uses manually placed markers (extrinsic).

The automated intrinsic registration is completely automatic and hence eliminates operator bias by using an algorithm to maximize the image match.[14,22] This method does not require operator's interaction and can be accomplished within seconds.[14] Technically, the process works by automatically adjusting the rigid registration parameters (translation and rotation in 3D) to maximize the MI function, which is a measure of the statistical similarity between the two imaging volumes. During the process an estimate of the joint histogram is required to calculate the MI function and for this linear resampling of the moving image is used. The rigid registration parameters are iteratively refined to increase similarity between both images until optimal/final registration is reached.

The extrinsic registration requires an operator to manually click corresponding locations in the software. Specifically, the user locates the homologous markers in both MRI and CBCT images and specifies those as landmark locations within the software. Once all markers are located, the software can perform an automatic landmark registration which produces a rigid registration that minimizes the (mean-square) error between all the corresponding landmarks. This method allows some operator interaction to guide registration to maximize images overlap.

In both methods once the images are registered, the quality of image alignment is assessed using a fusion display which shows one image overlaid over the other. Technically, the software uses alpha-blending to create the fusion overlay and uses linear image interpolation to resample one image into the space of the other. A transparency tool can be used to adjust the blend between the two volumes where a user can adjust the intensity-blending ratio as desired[21].

Using color-coded bone tissues in the MRI and CBCT fused images to voxel-by-voxel overlap evaluation by human examiners.[23] Adding fiducial markers to the region of interest with uniformed appearance in the MRI and CBCT images is expected to reduce the potential error of the multimodality image registration. However, the rigid registration process does not compensate deformations due to motion artifact or change in patient's position. In this study, 5 fiducial markers were fixed to the participants' skin surface, which made them subject to dislocation during imaging. Moreover, the patients' different positions during MRI (supine) versus CBCT (upright) imaging added more error to the registration process. This error in the extrinsic registration explains the markers mismatch between the images, the large variation of the tissue contours and the low quality of the final registration reported by the examiners.

The high signal intensity and complex and unique shapes of the bony structures in the head area clearly provided a reliable foundation for well-defined intrinsic image registration. extrinsic accuracy is reportedly much higher in neurosurgical studies,[24] likely because markers in those studies are attached directly to bone such as the calvarium by screws, preventing the movements inevitable in use of markers taped to the skin as we did in this study. Results of our study suggest intrinsic registration was clearly superior to extrinsic registration.

MRI has been considered as the prime imaging modality to analyze the soft tissue changes in the TMJ. However, the accuracy of determining disc position and morphology is challenging and has been the subject of many studies.[11,12,25-27] Proper classification of the disc position improves the diagnostic interpretation of the imaging modality and allows comprehensive use of the provided information. This study used standardized classification of the disc position to improve the reliability of the examiners disc evaluation.[11]

The fiducial markers displacement during imaging procedure may have affected the MRI-CBCT image alignment and resulted in improper registration with substantial tissue misrepresentation in the final fused image. As a result, the superior quality of the intrinsic registered MRI-CBCT images over the extrinsic images rendered the latter inadequate for disc position assessment. Therefore, intrinsic registered images were chosen for further analysis and tissue assessment.

The reliability of disc position evaluation, across examiners and time, improved in MRI-CBCT fused images compared to MRI alone from 0.50 to 0.80 in T1 and from 0.56 to 0.84 in T2. This can be explained by the fact that disc position (as appeared in MRI) in relation to the condylar head and articular eminence (as appeared in CBCT) were better identified in the MRI-CBCT fused image.

Several measures were introduced over the years to improve the diagnostic accuracy of the disc position in MRI. For instance, imaging hardware and software upgrades, examiners calibration programs and quantification techniques were found to reduce examiners variability.[10,12] Tasaki *et al* reported almost perfect agreement (*k*=0.87) between two examiners in detecting disc position of 149 TMJs.[28] Orsini *et al* reported improvement of agreement among three examiners, to detect disc position in 160 TMJs, after calibration program from moderate (*k*=0.50) to substantial (*k*=0.68) agreement.[10] Nebbe *et al*[11] reported moderate to substantial agreement (*k*=0.49-0.61) for 70 TMJs, when standardized criteria for categorization were used in image analysis. Almost perfect agreement (*k*=0.91) among the four examiners was demonstrated at the disc displacement without reduction category. Compared with these studies, the relatively lower reliability as seen in this study may be attributed to the small number of cases and the variable experience levels of the radiologists involved.

CBCT has been reported to have excellent ability to evaluate osseous pathology of the TMJ.[29-32] CBCT showed high reliability to detect cortical erosions of the TMJ articular surfaces with 95% accuracy.[30] Alkhader *et al* reported osseous pathology of 106 TMJs MRI evaluated by 2 examiners and determined the sensitivity and specificity of MRI compared to the CBCT. The MRI mean sensitivity ranged between 30-82%, and the mean specificity ranged between 84–98%.[33] The inter-examiner agreement was fair (*k* =0.4-0.59) for all types of osseous pathology, and poor agreement (*k* <0.4) for the bone sclerosis. Different studies reported fluctuating MRI sensitivity (50-87%) and specificity (71-100%) values to detect the osseous pathology.[28,33,34] In this findings of this study were not in support of the findings in the literature, examiners showed poor to fair inter-examiner agreement in all types of osseous pathology. This range of reported values is attributed to the different imaging protocols, reference test and evaluation methods. The frequency reporting osseous changes in MRI-CBCT fused images was similar to CBCT images alone for most of osseous findings *osteophytes, erosions and subcortical cysts, surface flattening, sclerosis* (Table 5).

In this study, fused MRI-CBCT images are appropriate to detect changes in osseous morphology; however, CBCT alone may exceed fused MRI-CBCT in detecting minor abnormalities such as erosion. This is attributable to the overlying MR images masking small osseous changes in the MRI-CBCT fused images. Dynamic windowing and alteration of the relative transparency of the MRI and CBCT components of the fused images by the observer can minimize this effect.

The MRI-CBCT registered images provide a complementary imaging tool that utilizes best soft tissue morphology from MRI and well defined osseous tissue outline from CBCT.

This study had limitations, chiefly the small sample size and the variability of radiologists' interpretation experience. The wide range of experience of the radiologists assessing the TMJ's was in one sense a limitation, but in another sense a strength of the study because it demonstrates that MRI-CBCT fusion may improve performance for less experienced radiologists and perhaps compensate somewhat for lack of experience. This hypothesis could be tested more fully in later studies. This study was planned as a pilot project to determine whether the use of such tool enhances the diagnostic value of the TMJ soft tissue abnormalities in one combined image set. The MRI-CBCT fused image can provide diagnostically useful images for research purposes and may be especially helpful for novice practitioners to detect the disc position in relation to the bony condyle and articular eminence.

3.5 Conclusions:

Intrinsic registration proved superior to extrinsic registration. The diagnostic value of the MRI-CBCT images to detect osseous abnormality is comparable to CBCT alone except for small osseous changes such as erosions. The fused MRI-CBCT images improved the reliability among examiners of varying experience levels in classifying disc position in relation to the condyle.

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Chapter 4: Accuracy of Magnetic Resonance Imaging – Cone Beam Computed Tomography Rigid Registration of the Head: An *in-vitro* Study *

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Preface

This research project, which is a part of this thesis and is an original work (The Animal Research Ethics approval #AUP00000323).

This project was a collaborative project between the department of Dentistry and the Faculty of Computer Sciences, University of Alberta. I conceived, prepared the study design, executed data acquisition, analysis, and interpretation, and finally drafted the manuscript. Drs. Boulanger and Punithakumar (Computer sciences department) helped in the technical part of the project, represented in measuring the distances between the markers. Drs. Alsufyani, Jaremko, Major were involved in concept formation, manuscript drafting, critical revision of the intellectual content and final approval for manuscript submission.

4. Accuracy of MRI – cone beam CT rigid registration of the head: an *in-vitro* study.

Abstract:

Purpose: To evaluate the performance of cross-modality image registration procedure between magnetic resonance imaging (MRI) and cone-beam computed tomography (CBCT).

Methods: In-vitro diagnostic MRI and CBCT images of 5 cadaver swine heads were obtained prospectively. Five radiopaque fiducial markers were attached to each cadaver skull using resin screws. Automatic MRI-CBCT rigid registrations were performed. The specimens were then scanned using a three-dimensional (3D) laser scanner. The 3D coordinate points for the centroid of the attached fiducial markers from laser scan were identified and considered ground truth. The distances between marker centroids were measured in MRI, CBCT, and MRI-CBCT images. Accuracy was calculated using repeated measures of analysis of variance (ANOVA) and mean difference values. The registration method was repeated 10 times for each specimen in MRI to measure the average error.

Results: There was no significant difference ($p>0.05$) in mean distances of the markers between all images and the ground truth. The distances' mean difference between MRI, CBCT, and MRI-CBCT and the ground truth were 0.2 ± 1.1mm, 0.3 ± 1.0mm, 0.2 ± 1.2mm respectively. The detected method error ranged between (0.06mm and 0.1mm).

Conclusion: The cross-modality image registration algorithm is accurate for head MRI-CBCT registration.

4.1 Introduction

Complex pathology in diagnostic imaging often requires more than one imaging modality to adequately define its features. Computed tomography (CT) scan depicts bony anatomy while magnetic resonance imaging (MRI) shows soft tissue structures. It is desirable to align and display the images of the same body parts from different modalities, helping the observer gain insights into the anatomy and pathology and plan treatment. Image registration involves finding a transformation of the coordinate system between two or more sets of images to allow alignment of all features that appeared in the sets of images.[1] The value of multimodality image registration is well established in the medical field.[2-9] Application of image registration in computer-assisted surgery and robotic systems is extensive in neurology, oncology, and orthopedics. Image-guided procedures require matching information (e.g. position of anatomical structures) from images taken on different modalities and/or at different times. Depending on the body tissues imaged, a rigid versus non-rigid registration can be performed. Rigid registration only allows rotation and translation of the image without deforming it. Rigid registration is the most common application in the area of human head, when using MRI and CT images, because of the distinct structure of the skull bone. Within the registration process, intensity-based spatial image alignment is performed. This method technically depends on similarity metrics, such as the mutual information, between the volumes and picture elements of the registered images, using either anatomic features in the images or fixed fiducial markers. The technique has been used in medical imaging analysis since at least 1994.[10] Few studies in the literature reported the accuracy and measurement error of the 3D MRI and CT images.[11-15] The published studies involved different imaging protocols, imaging targets, registration techniques, and error measurement procedures.[11-15]

Coned beam CT (CBCT) has a smaller amount of radiation exposure and shorter examination time than conventional CT, and has become integral to the field of dentistry in the practice of orthodontics; implant dentistry, and oral surgery.[16-18] The linear measure accuracy of fusing MRI and medical CT has been reported in the literature.[11,13-15,19] However, only a limited number of studies discuss the applicability and accuracy of MRI and CBCT image registration.[13,20-22] MRI-CBCT head registration provides a complimentary image of hard and soft tissue structures in the maxillofacial region. This allows convenient and simultaneous viewing for diagnosis, measurement, treatment planning, and outcome assessment, of –for example - muscle, lymph nodes, and salivary glands best seen at MRI relative to the bony anatomy best depicted by the CBCT. When evaluating temporomandibular joints (TMJ), a natural application is objectively assessing the location of the articular disc best seen at MRI relative to the glenoid fossa and articular eminence most clearly depicted in CBCT. Measurement of growth or surgical changes in the hard and soft tissues of the TMJ in one fused image is a great opportunity for both the expert and novice.

The aim of this study is to measure the linear error of the fused MRI-CBCT images in comparison to pre-determined laser scanned inter-marker distances as the ground truth.

4.2 Materials and Methods:

Specimen Preparation

Five specimens (fresh cadaver adult swine heads) were supplied by the Surgical Medical Research Institute. Specimens were euthanized for other purposes than this study. Disc-shaped multi-modality fiducial markers (1.7mm diameter, 5mm thick, Beekley Corporation, Bristol, Connecticut, USA) were used, which appear bright and of consistent shape in both CBCT and MRI. Five markers were directly attached to the skull of each specimen: 2 markers at the frontal bone, 1 marker at nasal bone, and 2 markers at zygomatic bone (Refer to Figure 4.1 for an example). Resin screws were used for attaching the markers to the specimen because of their low intensity in the MRI and appeared radio-opaque in the CBCT images. . The screws were 2.5 cm long and custom-made to fit into the centroid of the fiducial markers, and manufactured at the dental laboratory at the School of Dentistry.

Image acquisition

Specimens were imaged in consecutive CBCT and MRI sessions, and then immediately measured by a high-precision (57 micrometers) laser scanner to detect 3D marker locations as the ground truth for comparison purposes. The laser scanner is a commercial unit used in manufacturing computer equipment to highly accurate tolerances and is calibrated to an expected the accuracy of 57 micrometers (0.057 mm, Kreon 3D scanner, Lemoges, France). We used the laser scanner measurements as the ground truth due to this accuracy which is far superior to the resolution of any imaging modalities including CBCT. The CBCT data were acquired with the swine cadaver specimen positioned as a human head would be positioned in i-CAT® CBCT scanner (Imaging Sciences International, Hatfield, PA, USA). CBCT images were acquired with a large field of view (FOV) setting (23cm wide, 17cm height), scan time 9 seconds and 0.3 x 0.3 x 0.3 mm, voxel size (120KVp, 5mA). We used a multi-channel 12-element head array coil in a 1.5 Tesla MRI (Seimens Syngo MRB17, Erlangen, Germany). Axial T1-weighted spoiled gradient echo 3D sequence was obtained with FOV 46cm wide, 36cm height, slice thickness 1mm, slice spacing 1.2mm, echo time 4.8sec and repetition time 13 msec and 1.0 x 1.0 x 1.0 mm voxel size.

Figure 4.1: Fresh Cadaver's swine head showing five fiducial markers attached in the zygomatic, frontal and nasal bones with resin screws.

Image registration and 3D reconstruction

CBCT and MRI volumes were registered using intensity-based image registration software (Mirada XD, Mirada Medical Ltd, Oxford, UK). The automated registration algorithm does not require a user-defined region of interests or manual landmarks, and entire images were used in the computation of the transformation function. The grey-level intensity values from CBCT and MR images may not correspond linearly, and therefore, a mutual information based function was used as the similarity measure. If the noise inherent in MR and CBCT images were Gaussian, the mutual information based similarity measure is less subjective to noise than other common measures such as sum of squared differences since it relies on the probability distributions of the intensity values rather than the values themselves.

During the registration process, we will consider the CBCT volume U to be fixed and the MRI volume V to be moving and goes through a transformation T. We state the problem of aligning image volumes as the optimization of a similarity measure based on mutual information:

$$\hat{T} = \arg\max_{T} \, S_{MI}(U, V, T)$$

where S_{MI} is the mutual information between volumes U and V after transformation T.

The mutual information S_{MI} is given by:

$$S_{MI} = \sum_{i=0}^{I_U} \sum_{j=0}^{I_V} p_{ij} \log \frac{p_{ij}}{p_i p_j}$$

Where p_{ij} is the joint probability that corresponding to voxels in U and transformed V have intensities i and j, respectively; p_i is the probability of intensity i appearing in volume U; and p_j is the probability of intensity j appearing in transformed volume V.

The above optimization problem can be solved using Powell's conjugate direction method[25]. Powell's approach has the advantage over gradient based optimization techniques that it does not require explicit computation of the gradient of the similarity measure. It consists of an iterative process which optimizes the mutual information one parameter at a time, until none of the parameters changes the value of the mutual information significantly any longer.

The transformation matrix $\hat{T}$ obtained using the registration algorithm was used in the reconstruction of both volumes and fiducial markers. Custom software, written in the open-source Python programming language with libraries from the Visualization Toolkit (VTK, Kitware, New York, USA), was used for volume transformation and reconstruction of the registered images. DICOM parameters such as image position and orientation were taken into account during the reconstruction of the registered CBCT and MR volumes (Figure 4.2, a)

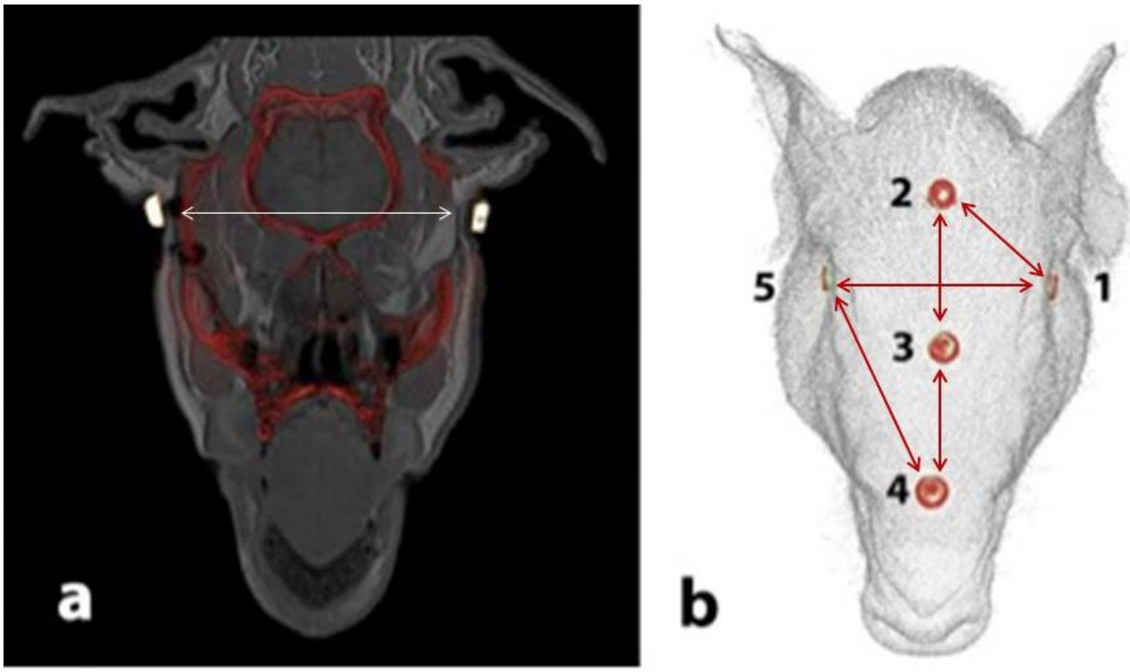

Figure 4.2: (a) Axial view of the MRI-CBCT fused image showing the fiducial markers at the zygomatic bones. The wire horizontal line represents the measured distance between point 1 and point 5; (b) Top view of the digitized cadaver's head using a laser scanner to detect centroid location of the numerically ordered fiducial markers. The arrows represent the measured distances between points. Distances were labeled as follows; A= distance between points 1-2; B= distance between points 2-3; C= distance between points 3-4; D= distance between 4-5; E= distance between points 5-1.

Centroid detection of the fiducial markers

Fiducial markers were identified in the laser-scanned specimens and the x, y, z coordinate positions of the marker centroids noted. The distances between the centroids of fiducial markers were then measured and considered as the ground truth, and used for comparison with distances from other imaging modalities (Refer to Figure 4.2, b for an example scan results from the laser scanner).

The centroid of the fiducial markers in 3D models of MRI, CBCT, and MRI-CBCT registered images were manually identified to generate x, y and z coordinate positions of the centroid locations. Euclidean distance between a pair of points P_1 = (x1, y1, z1) and P_2 = (x2, y2, z2) is calculated as:

$$d = \sqrt{(x1 - x2)^2 + (y1 - y2)^2 + (z1 - z2)^2}$$

After the markers' centroid points were detected, markers were numerically ordered (Figure 4.2) and distances were measured as follows: "A"= distance between points 1&2, "B"= distance between points 2&3=, "C"= distance between points 3&4, "D"= distance between points 4&5, "E"= distance between points 5&1.

Error estimation of the method

The intra-rater reliability of marking the fiducial marker centroids was evaluated. One specimen was randomly selected, and markers identified manually once per day for 10 days. The standard error of the mean inter-centroid distance was reported.

Statistical analysis:

Repeated measures analysis of variance (ANOVA) was performed to evaluate for significant differences between inter-marker distances.

Ethics approval:

The Animal Research Ethics approval #AUP00000323, Faculty of Medicine and Dentistry. Animal welfare assurance #A5070-01.

4.3 Results:

The marker-distance differences in MRI, CBCT, and MRI-CBCT in comparison to the laser-scanned ground truth were 0.2±1.1mm, 0.3±1.0mm, 0.2±1.2mm (mean ± standard deviation, SD), respectively (Table 4.1). The repeated measures ANOVA showed no significant difference ($P>0.05$) in the mean of marker-distances (A-E) between all images and the gold standard values.

Error of method: The intra-rater reliability is presented in Table 4.2; the minimum detected error was 0.06 mm and the maximum detected error was 0.1 mm.

Table 4.1: Pairwise Comparisons (Bonferroni) of the mean difference of the different imaging modalities compared and the gold standard data.						
Imaging modality		Mean Difference	Standard Error	Sig.	95% Confidence Interval for Difference	
					Lower Bound	Upper Bound
Gold standard	CBCT	0.30	1.00	0.76	-2.40	1.79
	MRI	0.20	1.10	0.85	-2.11	2.51
	MRI-CBCT	0.21	1.24	0.86	-2.38	2.80

Table 4.2: Mean, standard deviation and standard error results of measuring 10 times in one specimen.			
Distance	Mean	Standard Deviation	Standard Error
A (points 1 & 2)	100.32	0.43	0.07
B (points 2 & 3)	44.12	0.20	0.06
C (points 3 & 4)	38.01	0.24	0.07
D (points 4 & 5)	86.92	0.23	0.07
E (points 5 & 1)	129.86	0.48	0.15

4.4 Discussion

The value of multimodality image registration extends beyond common use in stereotactic neurosurgery to many clinically significant applications such as diagnostic and treatment outcome evaluations. CBCT is now the standard imaging procedure in many dental specialties, including but not limited to oral and maxillofacial surgery, orthodontics, and TMJ examination. MRI is also considered the gold standard to view TMJ articular disc, and can be utilized to detect soft tissues pathology and masticatory muscles conditions. Although the MRI and CT/CBCT registration has multiple clinical applications in the medical practice, very limited effort has been done to explore the benefits of such useful tool in the clinical practice of dentistry. For example, Al-Saleh *et al* [21] tested the reliability of using fused MRI-CBCT images to diagnose TMJ disc position in relation to the surrounding osseous articular structures among different examiners. Tai *et al* [20] introduced fused MRI-CBCT images to visualize face profile as a tool for orthodontic and orthognathic treatments evaluation. A study by Gaudino *et al* [23] showed that MRI can be useful to display the lamina dura and periodontal ligament when compared to CBCT images.

However, the clinical benefits of registration are dependent on its accuracy. Inaccuracy and complicated registration procedure can be challenging in multimodality image registration especially with routine TMJ/MRI protocol that includes small field of view and limited sectional images. Tai *et al*,[20] reported the accuracy of full head MRI and CBCT image registration using linear measurements of orthodontic cast models as reference measurements. The margin of linear error reported ranged between 0.29 and 0.71mm, which supports the findings of our study. However, in their study the authors reported a complex registration procedure that required 5 different software programs which is not practical for clinical or research use. Rigid registration using mutual-information provides a robust tool to fuse routine TMJ MRI with CBCT in easy, fast, and automatic steps without the burden for extra steps by the clinicians. Recently, the authors of this study reported the reliability of the evaluating TMJ internal derangement and osseous abnormality, using fully automatic MRI-CBCT registration.[21] The same image registration procedure was applied in this study to prove the concept is accurate.

Previous accuracy studies of in-vivo brain,[14,15] or skull base/nasopharynx,[19] MRI with CT image registration revealed measurement errors ranging from 0.41 to 1.6 mm. In these studies, the authors used anatomical landmarks or fiducial markers and explained increased error in some images due to the loss of resolution as this negatively impacts the intensity distribution and consequently mutual information between the images. In the present study, the registration was performed using Mutual Information algorithm; we the fiducial markers were only utilized to quantify the error in the registration process. Although it may have implicitly affected the registration, we did not use the fiducial markers explicitly to compute any of the registration parameters, i.e., only the overall image information was used to compute the mutual information and the subsequent image transformations. In a previous publication, Al-Saleh *et al* reported visual assessments of MRI-CBCT registered images and showed that image alignment obtained with a similar registration approach was accurate where no fiducial markers were used.[21]

Moor *et al* [11] used a head and neck phantom to measure the accuracy of mutual information based CT-MRI image co-registration in three coordinates (*x, y* and *z).* The authors reported the mean difference between the coordinates as 0.43±0.14 mm along the *x*-axis and 0.37±0.07mm along the *y*-axis.[11] The authors however did not use anatomical or fiducial landmarks and only measured the coordinates of the phantom's center. Pawiro *et al* employed a swine head cadaver with attached heterogenic fiducial markers (spherical steel markers for 2D x-ray, polytetrafluoroethylene marker for CT images, aluminum markers for CBCT, and olive oil markers for MR images) to create a gold standard data set.[24] The authors validated the markers position using anatomical landmarks to evaluate the accuracy of MRI, CT and CBCT images co-registration using mutual information. The reported registration error for the MRI (*T1*) and CBCT ranged between 0.62±319mm to 1.5±2.3mm. The large error was attributed to lower image contrast/resolution or intensity in-homogeneities in the aluminum markers affecting neighboring tissues.

The mean measurement error of CBCT/MRI registration in our study, 0.2±1.2mm, is similar to previous in-vitro studies and to the lower ranges reported in the in-vivo studies. Determining the accuracy of image registration is challenging in medical imaging and requires careful consideration of a "gold standard" reference independent of the imaging modalities tested. In this study, distances between rigidly attached fiducial markers were used as a measuring tool to detect marker displacement in different imaging modalities, used MRI and CBCT protocols common in dentistry, and used an independent gold-standard measurement using a highly accurate industrial laser scanner. Measuring the distances between markers provides an objective method to measure the accuracy of the registration between different imaging modalities.[25] However, it is a manual process that necessitates an operator measurement error. The operator's reliability was small (maximum error was 0.1mm) indicating high reproducibility/reliability. Despite the differences in the imaging sensors and voxel sizes between MRI and CBCT, the applied multi-modality image registration was robust and yielded numerically accurate and visually satisfying overlap. The mean differences of the markers' distance values of the MRI and CBCT images compared to the laser scanner image were 0.2 mm and 0.3mm respectively. The MRI-CBCT image registration showed the small value of the mean difference (0.2mm) from the laser scanner image.

This study had limitations. The sample size was necessarily small. Although cadaver pig head mimicked human head tissues, the movement factor during image scanning was absent in this study. Therefore, the measured accuracy may be overestimated. Also, the study measured the accuracy in image registration between MRI (PD) and CBCT. Other MRI weighted sequences such as (TI & T2) may have different results and can be evaluated in the future. Finally, we used fiducial markers to measure the registration accuracy quantitatively. However, the presence of markers in the images might have affected the registration algorithm since the entire image including the markers was used, when computing the mutual information between CBCT and MR images.

This study demonstrates a high level of accuracy using a well-known mutual information iterative algorithm offered by commercially available software.

This study shows that MRI-CBCT image registration is accurate when the structures being registered are fixed, rigid and easily segmented. The short processing and fully automatic rigid registration provides a complementary image, which we expect to be of great value in the in the field of dentistry and maxillofacial management. The findings of this study support the accuracy of using multimodality image registration to improve the readability of diagnostic imaging in the field of dentistry and maxillofacial region.

4.5 Conclusion:

A mutual information iterative algorithm provided an accurate and reproducible tool to register MRI and CBCT of the head in the tested sample. Future work entails testing its clinical use to evaluate growth changes and treatment outcomes in the field of dentistry with initial focus on the tissues of the temporomandibular joints.

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Chapter 5: MRI Alone Versus MRI-CBCT Registered Images to Evaluate Temporomandibular Joint Internal Derangement *

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5.1 Introduction
5.2 Material and methods
5.3 Results
5.4 Discussion
5.5 Conclusions
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Preface

This research project, which is a part of this thesis, is an original work and received research ethics approval from the University of Alberta Research Ethics Board Project #Pro00053614, March 2, 2015.

In this project, I conceived, prepared the study design, executed data acquisition, analysis, and interpretation, and finally drafted the manuscript. The participating radiologists, Dr. J. Jaremko (Department of Radiology and Diagnostic Imaging) and Dr. Alsufyani (Department of Dentistry) contributed in the present project by evaluating the obtained images quality and diagnosing the TMJ pathologies in two occasions, and helped in drafting and approving the manuscript for submission. Dr. Lai (statistician) helped in confirming the performed the data statistical analysis. Drs. Lagravere, Nebbe, Major were involved in concept formation, manuscript drafting, critical revision of the intellectual content and final approval for manuscript submission.

5. MRI Alone Versus MRI-CBCT Registered Images to Evaluate Temporomandibular Joint Internal Derangement

Abstract

Purpose: To evaluate the effect of the MRI-CBCT image registration on improving the inter- and intra-examiner reliability when evaluating temporomandibular joint (TMJ) internal derangement compared to MRI alone.

Methods: MRI and CBCT images of 25 patients (50 TMJs) were obtained and co-registered using mutual-information rigid image registration via Mirada XD software (Mirada Medical, Oxford, UK). Two experienced radiologists independently and blindly evaluated two types of images (MRI alone and MRI-CBCT registered images) at 2 times (T1 & T2 for TMJ internal derangement based on sagittal and coronal articular disc position in relation to the head of condyle and posterior slope of the articular eminence.

Results: The intra-examiner reliability in MRI alone (examiner 1 = ICC 0.85[0.74-0.92]; examiner 2 = ICC 0.91[0.84-0.95]) was lower than the MRI-CBCT registered images (examiner 1 = ICC 0.95 [0.91-0.97]; examiner 2 = ICC 0.97 [0.96-0.99]). The inter-examiner reliability of evaluating the internal derangement in MRI alone (ICC = 0.52 [0.18-0.73] at T1; 0.71 [0.45-0.84] at T2) was lower than the MRI-CBCT registered images (ICC= 0.97 [0.95-0.98] at T1; 0.98 [0.96-0.99] at T2).

Conclusions: The MRI-CBCT registered images improved the intra- and inter-examiner reliability to evaluate the internal derangement of TMJ.

5.1 Introduction:

In an anatomical sagittal view with maximal dental inter-cuspation, the intermediate zone of the articular disc is interposed between the head of the condyle and posterior slope of the eminence. This position of the disc (specifically the intermediate zone) was considered a better descriptor of a normal joint anatomy.[1] The intermediate zone of the articular disc is anatomically and histologically suited to accept and distribute forces of mastication that come to bear on the joint surfaces during rest and function. During function, the condylar head and articular disc travel down the posterior slope of the articular eminence to full range of motion at the height of the eminence. A condylar head that translates to a point anterior or posterior to the articular eminence can be indicative of a joint's hypermobility or hypomobility. Displacement of the intermediate zone of the articular disc relative to the functional load surfaces of the osseous components of the joint is therefore indicative of disturbed joint function. The TMJ internal derangement (ID) is defined as abnormal relationship of the articular disc to the condyle, where the posterior band of the disc is in an anterior position relative to the condylar head in the maximum intercuspation.[2-6]

Oblique sagittal joint imaging appears to be the most descriptive view for visualization of the internal joint structures. On oblique sagittal images, the position of the posterior band of the articular disc relative to the superior aspect of the head of the condyle (12 o'clock position) has been endorsed by many studies in the evaluation of internal derangement.[7-10] This description of disc position does not consider the functional relationship of the articular disc relative to the functional osseous components of the jaw joints (disc, condyle and posterior slope of the eminence). The high reported prevalence (approximately 22%) of asymptomatic internal derangement patients may be overstated due to inaccurate determination of disc position due to use of the twelve-o'clock position for assessment of normal disc position.[11]

Magnetic resonance imaging (MRI) is the current gold standard to analyze the position and morphology of the temporomandibular joint (TMJ) articular disc. A challenge in diagnosing and quantifying internal derangement may be attributed to inconsistent disc position classification in relation to the condylar head, imaging protocols, examiner's inexperience, and the suboptimal depiction of TMJ osseous structures in MRI.[12-16] Since the articular disc is best depicted on MRI and the condylar head and eminence are best seen on CBCT, conceptually, fusing MRI and CBCT together is considered a desirable tool to assess TMJ ID. The fused MRI-CBCT image combines the optimum imaging modalities to visualize both soft tissues and hard tissues in one display without affecting the quality or the nature of the original MRI and CBCT images. Al-Saleh *et al* explored different techniques to co-register MRI to CBCT images of the TMJ and assessed its potential to improve radiologists' reliability to diagnose TMJ soft and hard tissues pathology.[17-19]

The purpose of the present study is to evaluate whether the use of MRI-CBCT image registration improves the inter- and intra-examiners' reliability when evaluating TMJ ID compared to MRI alone.

5.2 Materials and Methods:

Patients:

A total of 25 adult patients (50 TMJs) with history of TMJ pain and noises on jaw movement or function, which was confirmed upon clinical examination by a TMD specialist at the Temporomandibular Disorder/Orofacial Pain Clinic at the University of Alberta, were recruited in the study.[5] The study was approved by the Human Research Ethics Board at the University of Alberta (Pro00032935). Informed consent was obtained from all study participants. All patients had MRI and CBCT images obtained at the same visit with the teeth in maximum intercuspation using polyvinylsiloxane occlusal bite stents.[18]

Imaging protocol:

The CBCT scans were obtained using Next Generation i-CAT® scanner (Imaging Sciences International, Hatfield, USA) at a medium field of view setting (16cm wide, 13cm height, scan time 26 sec. and 0.25mm voxel size) including maxilla and mandible and TMJ condyles. Imaging machine rotated 360 degrees with the subjects seated in the upright position with Frankfort plane parallel to the floor.

MR images of the TMJ were obtained with the subjects in the supine position, employing medium field of view (13cmX13cm) making use of a 1.5 Tesla scanner (Siemens, Munich, Germany) with use of a TMJ coil. No sedation or intravenous contrast administration was used. Dedicated bilateral closed mouth oblique sagittal sections were obtained perpendicular to the long axis of the condyle. Coronal sections were obtained as well. Proton density-weighted images (PD) were obtained with slice thickness 3mm; inter-slice gap 0.3mm; repetition time/echo time 1800/11 ms; typically, 14 slices per joint imaged.

Image preparation and assessment:

Digital Imaging and Communications in Medicine (DICOM) files of all MRI and CBCT images were transferred to a desktop PC workstation. Mirada XD software (Mirada Medical, Oxford, UK) was used to perform automatic multi-modality image rigid registration. The MRI-CBCT images were brought into a spatial alignment using the mutual information (statistical dependency of one image on the other where one image can help predict the other) at a finally fused image in a common display.[20] Registered images were displayed in a color-coded fashion. The overlapped structures from MRI appeared in gray-scale and structures from CBCT appeared in scarlet red color. Color gradient, contrast and transparency were modified and adjusted as necessary to reach the best display of the disc tissues relative to the condylar head and articular eminence. (Figure 5.1). Two examiners (N.A.-oral maxillofacial radiologist & J.J. medical radiologist), each with 7-8 years of experience in diagnostic imaging of the TMJ, subjectively evaluated the MRI-CBCT registered images independently and blind to subject presentation or subject information that would bias interpretation of disc position on two occasions, baseline (T1) and at separate time intervals of 4-8weeks after (T2). Examiners evaluated the right and left TMJs with different randomization sequence. The examiners scrolled through all sagittal sections of each TMJ, and evaluated the disc position from the MRI alone and from the MRI-CBCT registered images. Using the guide illustrated in Chapter 3, Figure 3.5, the location of the intermediate zone of the disc relative to the head of the condyle was classified as normal position, mild, moderate or full anterior displacement. Further, to allow for comparison to other studies in the literature the disc position entries were dichotomized to 2 groups: 1. Normal (if disc location was normal or mild disc displacement); 2. Anteriorly displaced (if disc was moderate or severe disc displacement).

Statistical analysis:

The inter- and intra-examiner reliability of the radiologists in classifying the disc position at different times was analyzed using the Intra-class Correlation Coefficients (ICC) as a result of ordinal outcomes. In addition, Cohen's Kappa was calculated to determine the level of agreement in the dichotomized disc positions (Normal versus Anteriorly displaced). Reported ICC and Cohen's Kappa values were interpreted following Landis and Koch[21] method to describe the reported level of consistency/agreement as follows: ICC: 0-0.2= poor; 0.3-0.4= fair; 0.5-0.6= moderate; 0.7-0.8= strong; >0.8= almost perfect. Kappa coefficient *(k)* ≤ 0= poor, 0.01–.02= slight, 0.21–0.4= fair, 0.41–0.6= moderate, 0.61–0.8= substantial, 0.81–1= almost perfect.

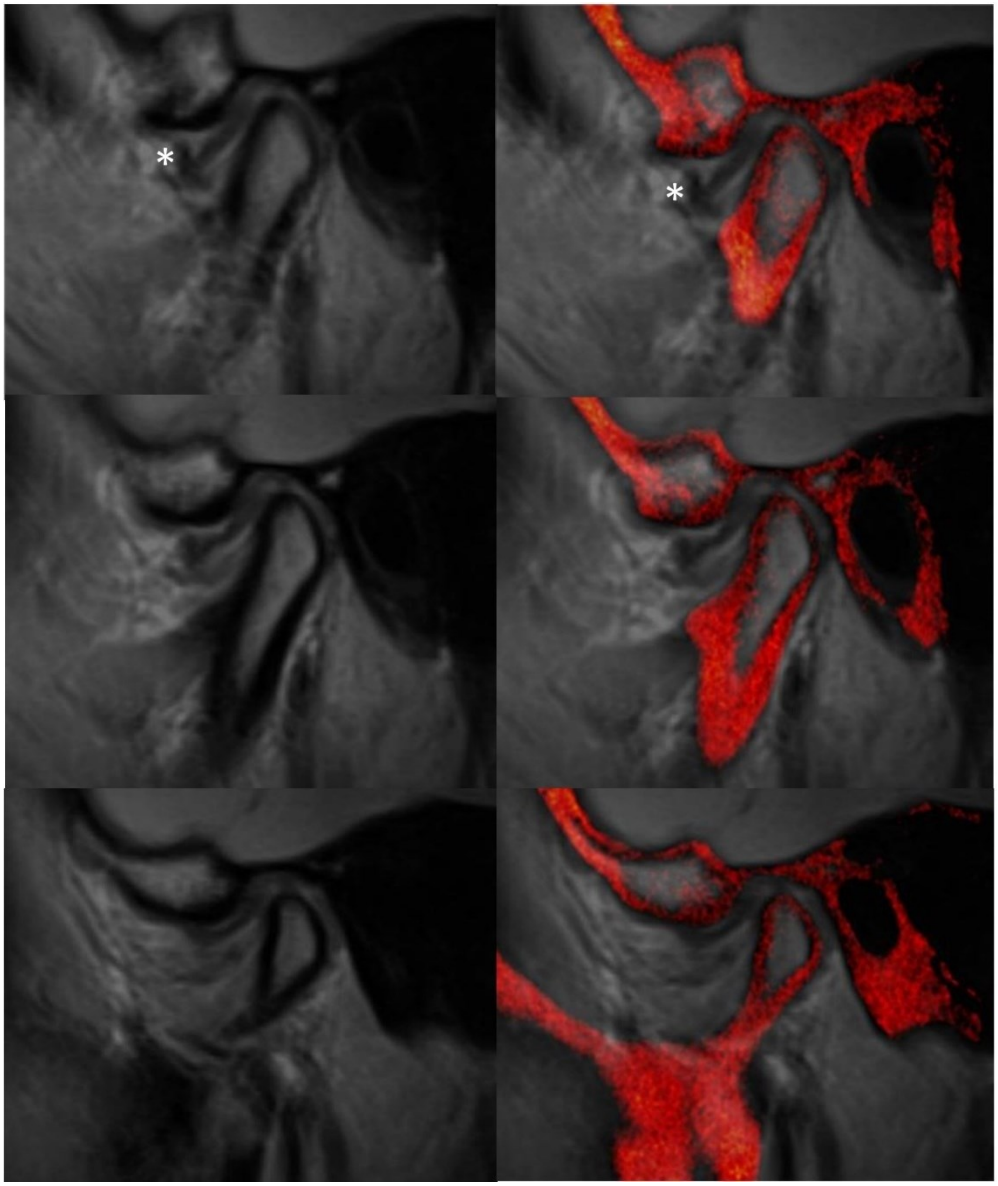

Figure 5.1: MRI-CBCT registration of TMJ. Two corresponding image panels of Sagittal PD-weighted MRI (left), and sagittal MRI-CBCT registered image sections (right), showing optimal registration depicted by normal tissue signals of the cortical bone and bone marrow of the condylar and temporal components of the joint. Note severely anterior displaced disc (white star*).

5.3 Results:

For 50 TMJs, the intra-examiners' reliability was almost perfect but lower in MRI (ICC=0.85[0.74-0.92]) than MRI-CBCT registered images (ICC=0.95[0.91-0.97]) across time for examiner 1. The intra-examiner reliability was almost perfect in both MRI alone (ICC= 0.91 [0.84-0.95]) and MRI-CBCT registered images (ICC 0.97[0.96-0.99]) across time for examiner 2. The articular disc position classification of the 50 TMJs by the 2 examiners at T1 and T2 are reported in (Table 5.1 and Table 5.2).

The inter-examiner reliability was moderate in MRI alone (ICC= 0.52 [0.81-0.73] at T1; ICC=0.71[0.45-0.84] at T2) almost perfect MRI-CBCT registered images (ICC 0.97[0.95-0.98] at T1; ICC=0.98[0.96-0.99] at T2).

When disc position classification was dichotomized to normal versus anteriorly displaced, examiner 1 showed moderate (k= 0.52) intra-examiner agreement in the MRI alone, and almost perfect (k= 0.91) agreement in the MRI-CBCT registered images. Examiner 2 showed substantial (k= 0.63) intra-examiner agreement in the MRI alone, and almost perfect (k= 0.92) agreement in the MRI-CBCT registered images.

The inter-examiner agreement, at T1, was fair (k= 0.29) among examiners in MRI alone and almost perfect (k= 0.96) in MRI-CBCT images. At T2, the inter-examiner agreement was moderate (k= 0.42) among examiners in MRI alone and almost perfect (k= 0.96) in MRI-CBCT images.

Table 5.1: Inter-examiner reliability in the assessment of disc position in MRI alone at baseline (T1) and after 4-8 weeks (T2)

T1		Examiner 2			
		Normal	*Mild*	*Moderate*	*Severe*
Examiner 1	*Normal*	1	3	2	1
	Mild	4	2	6	4
	Moderate	2	1	2	9
	Severe	0	1	5	7
T2		**Examiner 2**			
		Normal	*Mild*	*Moderate*	*Severe*
Examiner 1	*Normal*	2	7	1	1
	Mild	5	2	6	5
	Moderate	0	2	6	2
	Severe	0	0	1	10

Examiner 1: Intra-examiner ICC 0.85 [0.74-0.92]; Kappa 0.52.
Examiner 2: Intra-examiner ICC 0.91 [0.84-0.95]; Kappa 0.63.

T1: Inter-examiner ICC 0.52 [0.18-0.73]; Kappa 0.29.
T2: Inter-examiner ICC 0.71 [0.45-0.84]: Kappa 0.42.

Table 5.2: Inter-examiner reliability in the assessment of disc position in MRI-CBCT registered images at baseline (T1) and after 4-8 weeks (T2)

T1		**Examiner 2**			
		Normal	*Mild*	*Moderate*	*Severe*
Examiner 1	*Normal*	8	1	0	0
	Mild	2	9	1	0
	Moderate	0	0	8	2
	Severe	0	0	0	19
T2		**Examiner 2**			
		Normal	*Mild*	*Moderate*	*Severe*
Examiner 1	*Normal*	7	0	0	0
	Mild	2	13	1	0
	Moderate	0	0	5	2
	Severe	0	0	1	19

Examiner 1: Intra-examiner ICC 0.95 [0.91-0.97]; Kappa 0.91.
Examiner 2: Intra-examiner ICC 0.97 [0.96-0.99]; Kappa 0.92.

T1: Inter-examiner ICC 0.97 [0.95-0.98]; Kappa 0.96.
T2: Inter-examiner ICC 0.98 [0.96-0.99]; Kappa 0.96.

5.4 Discussion:

Multi-modality image registration is a robust, automatic and highly accurate technique, based on the mutual information theory, and is commonly used in the medical field.[22-25] Our research team aimed to explore, optimize, and evaluate initial reliability of registering MRI and CBCT images to evaluate changes in the TMJ.[17-19] In a previously published study, the mutual-information-based MRI-CBCT registration technique showed superior fused image quality compared to the marker-based technique.[18] Three radiologists evaluated the TMJ osseous pathology and disc displacement in MRI-CBCT registered images and noted improved inter-examiners' reliability in reporting disc derangement (MRI alone, ICC=0.5 at T1 and 0.56 at T2; MRI-CBCT registered images, ICC=0.80 at T1 and 0.84 at T2).[18] Although the findings were promising, they were treated with caution due to the small sample size (10 patients). The present study was conducted to confirm the positive influence of the MRI-CBCT image registration on the examiners' reliability when diagnosing TMJ internal derangement. The study confirmed that using MRI alone, experienced radiologists with clearly defined criteria of disc position classification (Chapter 3, Figure 3.2), were almost perfectly consistent across time (ICC 0.85-0.91), but moderately consistent when compared to each other (ICC 0.52-0.71). After dichotomizing the classifications of the disc position in the MRI alone, the agreement values were slightly diminished. Most of the disagreement was in the mild and moderate disc position classifications. In the dichotomized classifications, mild disc displacement was included in the normal disc group and moderate disc displacement was included in the displaced disc group which lead to greater disagreement (intra-examiner: k= 0.52-0.63; inter-examiner: k=0.29-0.42). With MRI-CBCT images, the findings demonstrated improvement in reliability over time and between the two radiologists (intra-examiner: ICC 0.95-0.97; k= 0.91-0.92; inter-examiner: ICC

0.97-0.98; *k*= 0.96). This improvement in inter-examiners' reliability can be attributed to improvement in definition and identification of anatomical structures displayed by the MRI-CBCT registered images. In other words, fused images reduced the disagreement gap within and between each examiner(s) such that the subjectivity of diagnosis is reduced and a more standardized diagnosis/classification is reached.

Examiners' consistency/agreement in detecting the articular disc displacement using MRI has been well-reported in the literature.[12-15,26-28] Some studies reported fair to moderate inter-examiners agreement with *k* values ranged from 0.4 to 0.6.[13,26,27] when examiners were calibrated and guided how to classify the disc position. Ahmad *et al* reported strong inter-examiner agreement (*k*= 0.8) when the 4 examiners underwent an extensive 2-day calibration program.[28] Although the calibration sessions seemed to result in encouraging agreement levels among examiners, they do not seem to be clinically practical when professionals from different specialties interpret the TMJ MRIs individually and independently. Widmalm *et al* and Butzke *et al* reported poor inter-examiner agreement (*k*= 0.1-0.2) when no calibration sessions were offered to examiners.[14,15] Their findings confirmed that highly experienced radiologists (oral & maxillofacial or medical) were subject to poor agreement, when diagnosing disc displacement without calibration sessions. Widmald *et al* suggest that the most reliable MRI interpretation requires a group of observers who are calibrated, experienced, and jointly discuss these images before confirming a diagnosis.[14] Unfortunately, this does not appear to be the standard of care in image interpretation as TMJ MRIs are usually interpreted in isolation by a single observer (radiologist or physician) in a hospital or imaging center often with little experience or specific education in TMJ disorders.[14] It thus appears that regardless of the superiority of MR imaging as a modality for identification of soft tissue structures of the jaw joint, the above noted limitations hamper ideal interpretation of joint anatomy, and provides an opportunity for improvement in joint imaging interpretation. It has been suggested that examiners' reliability in MRI interpretation improved when using the functional position of the intermediate zone of the articular disc and well defined criteria for classification of disc-condyle relation are employed.[1,12,13,29-31] Examiners' consistency/agreement in classifying disc position was found to improve when the new assessment method using MRI-CBCT image registration to visualize TMJ was recently introduced.[18]

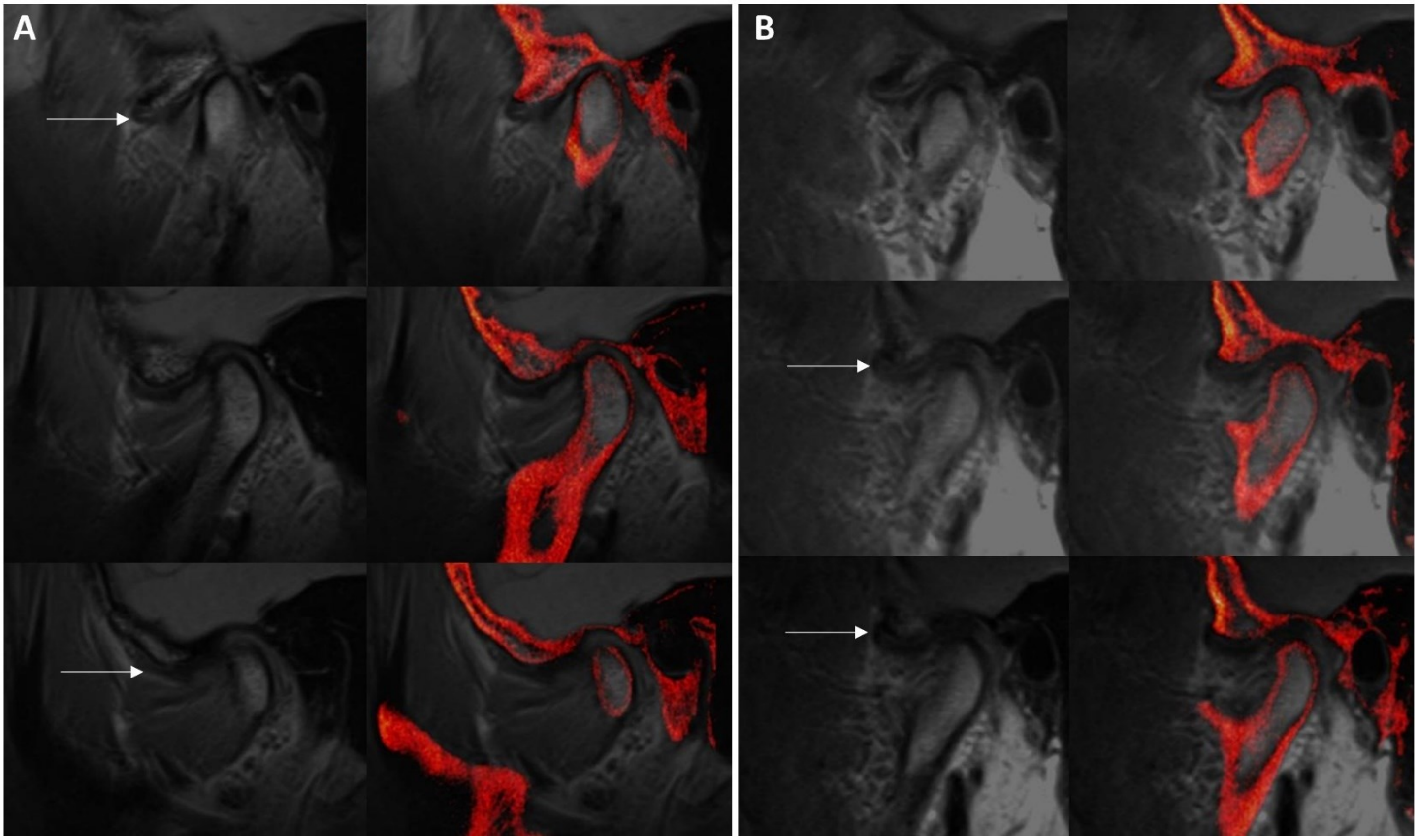

Figure 5.2: Improving TMJ disc detection using MRI-CBCT registration. Two corresponding image panels of Sagittal PD MRI and MRI-CBCT registered image sections of two TMJs of two different patients. The A and B images show joint space narrowing and disc thinning such that the disc can be mistaken for the outer cortical lining of the articular eminence (white arrows). The fused images better highlight cortical boundaries from actual disc tissue.

The rigid multi-modality image registration of MRI and CBCT image volumes was performed using commercially available imaging software (Mirada XD ver. 3.6, Mirada Medical Ltd, UK). The registration process finds a correspondence of each point in a pair of images via automated mutual information based algorithm. This algorithm calculates the statistical similarity between the voxels' values of the both images to construct a joint histogram. Iterative transformation in x,y,z dimensions and linear resampling of the MRI is used to maximize similarity toward final registration and matching with the CBCT image. [25,32] The final fused display shows one image overlaid the other, with the possibility to adjust the blend/transparency between the image volumes. The image registration itself provides no additional information on disc morphology and displacement. However, by clearly outlining the surrounding osseous structures (such as condylar outline, condylar head inclination, depth of glenoid fossa and articular eminence slope), it can enhance the diagnostic value and reduce the decision making-errors when evaluating the disc internal derangement.[18] The complementary nature of CBCT imaging and MR imaging in diagnosing osseous pathology and soft tissue alterations respectively, provides opportunities for fusing these images to improve examiner interpretation of joint anatomy. In PD-weighted and T1-weighted MRI, which are commonly used in MRI interpretation for TMJ, the articular disc has low signal intensity similar to that of the cortical bone of the condylar head, glenoid fossa and articular eminence. In some cases, where the joint space is reduced, the articular disc is in very close proximity to the cortical boundaries of the condylar head or posterior slope of the articular eminence (Figure 5.2). These tissues present with similar low signal and may easily be confused, resulting in error or inconsistency in the diagnoses of internal derangement. Moreover, in severe cases of TMJ degeneration, the size, shape of the articular disc may be altered, and increased bone marrow signal may impact the ability to identify the structures of the joint

(Figures 5.3 and 5.4). MRI-CBCT image registration offers the opportunity to reduce these common sources of diagnostic errors in TMJ-MRI interpretation. Although the MRI-CBCT image registration in the open-mouth position is technically possible, additional CBCT imaging for mouth open position does not appear feasible since it does not provide additional osseous information while exposing subjects to additional radiation exposure.

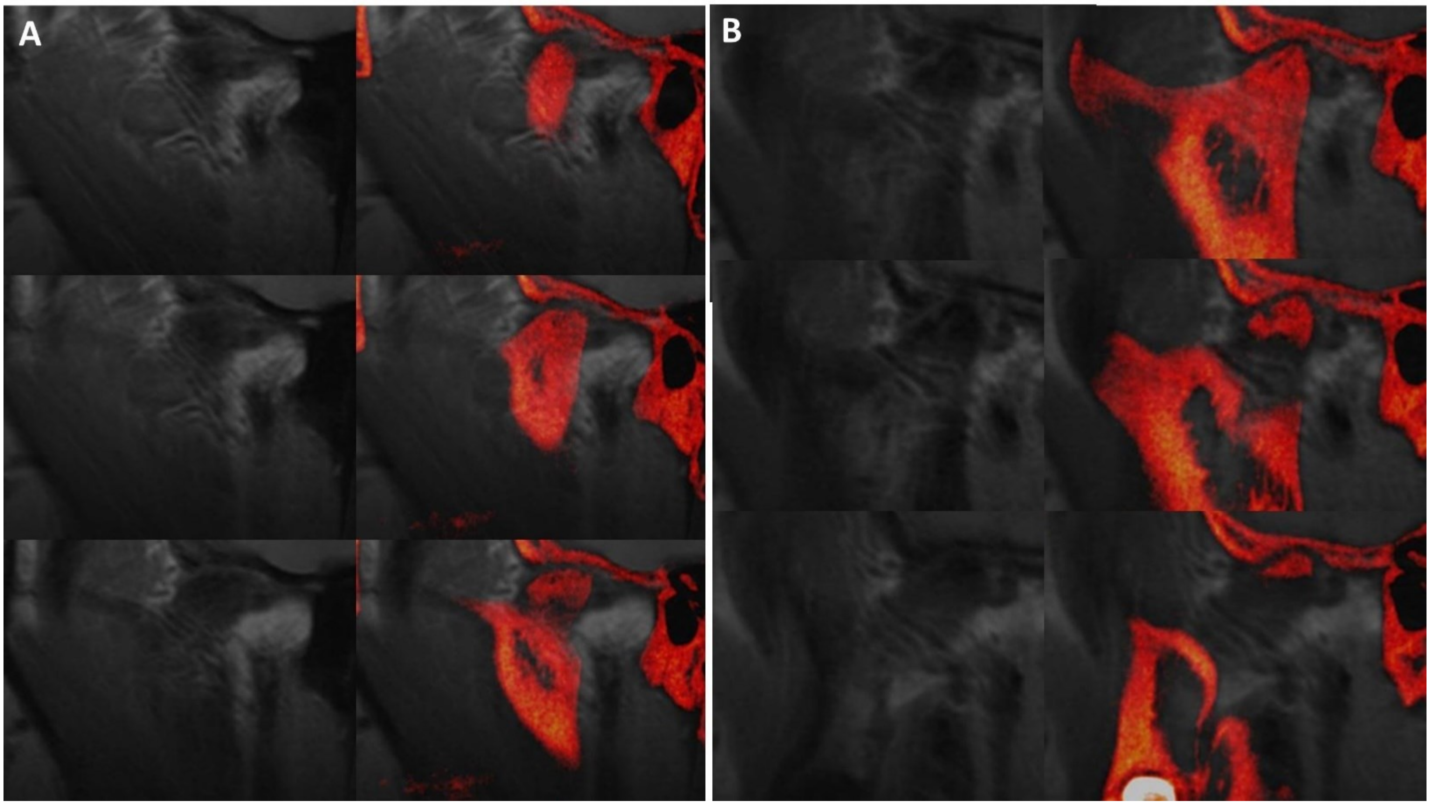

Figure 5.3: Improving detection of TMJ osseous structures using MRI-CBCT registration. Two corresponding image panels of Sagittal PD MRI and MRI-CBCT registered image sections of two TMJs of the same patient. The A and B images show lack of condylar head definition in MR image sections due to severe degenerative joint changes affecting bone marrow signal. The MRI-CBCT registered images clearly depicts exact shape and location of the severely sclerotic condyle and temporal components of the joint.

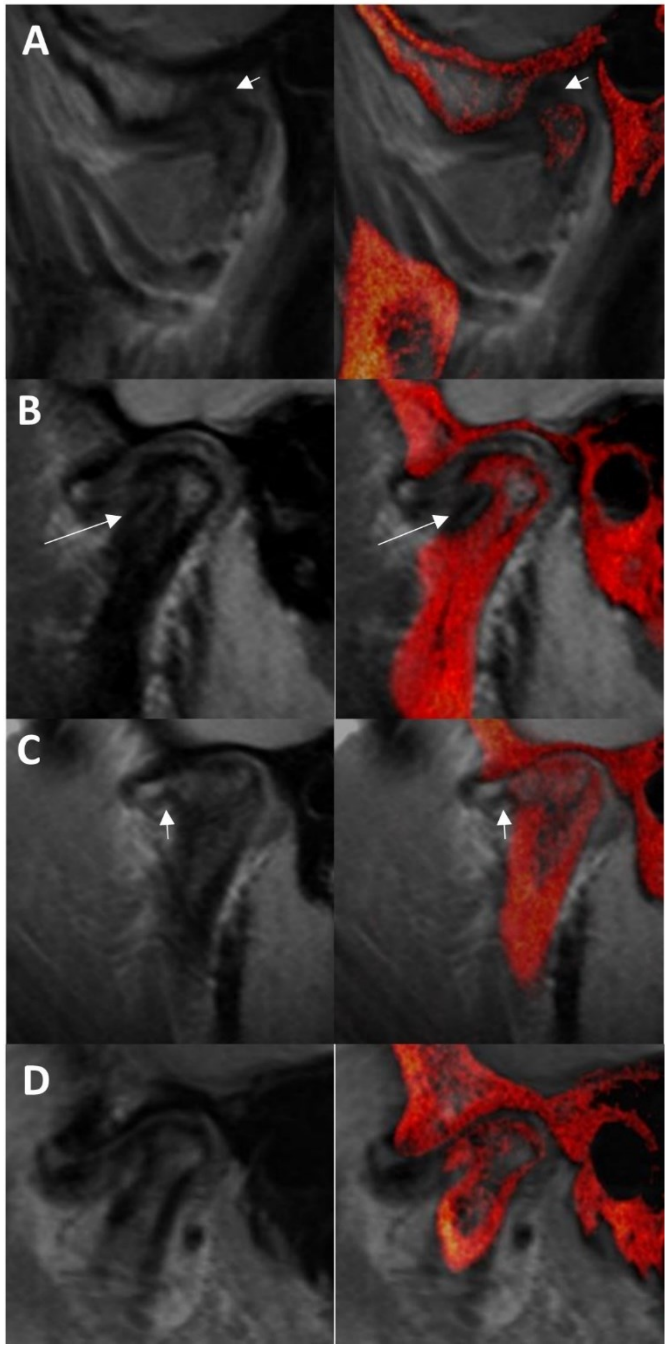

Figure 5.4: Improving TMJ soft and osseous tissue differentiation using MRI-CBCT registration. Two corresponding image panels of Sagittal PD MRI and MRI-CBCT registered image sections of one TMJ. In sections A and B, muscle fibers or retro-disc tissues (white arrows) can be mistaken as part of the condylar head. In sections, C and D, stretched disc tissue at the anterior aspect of the condylar head can resemble osteophyte formation. The fused images clearly depict disc tissue from osteophytes or normal osseous anatomy.

The small number of examiners is a limitation of the current study. We had an experienced dental radiologist and an experienced clinical radiologist. Given that the MRI-CBCT tool is likely of the most value in aiding novice users, further evaluation in a broad spectrum of examiners of different level of expertise is needed to further validate this tool. Images of different groups of patients with different TMJ conditions should be used to explore the advantages of MRI-CBCT registered images over MRI or CBCT only in TMJ diagnostic imaging.[19]

The advancement in image registration technology seems to contribute significantly to the improvement of two main challenging aspects in TMJ diagnostic imaging; examiners' knowledge, regardless their level of expertise, and enhanced definition of anatomical structures. MRI-CBCT registered images may also be an excellent teaching tool to reduce the TMJ anatomical complexity when studying MR images in dental school or medical school. Future effort should be made to apply this tool in tissue segmentation and volume rendering to visualize the TMJ tissue in three-dimensional model. This will allow accurate detection of medial and lateral rotations of the articular disc and the associated degenerative changes of the osseous surfaces involved.

5.5 Conclusion:

The MRI-CBCT registered images significantly improved the intra- and inter-examiners' reliability among experienced readers to evaluate internal derangement of TMJ compared to MRI alone.

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Chapter 6: Usefulness of MRI-CBCT Image Registration to Evaluate Temporomandibular Joint Internal Derangement by Novice Examiners *

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** Submitted to Oral Medicine, Oral Surgery, Oral Pathology & Oral Maxillo Radiology (2016).*

Preface

This research project, which is a part of this thesis, is an original work and received research ethics approval from the University of Alberta Research Ethics Board Project #Pro00053614, March 2, 2015.

In this project, I conceived, prepared the study design and coordination. I executed data acquisition, analysis, and interpretation, and finally drafted the manuscript. The participating radiologists, Dr. Alsufyani (Department of Dentistry) helped in selecting the appropriate images for TMJ tissue evaluation by the participants. Dr. Lai (statistician) helped in confirming the performed the data statistical analysis. Drs. Lagravere, Jaremko and Major were the supervising authors and were involved in concept formation, manuscript drafting, critical revision of the intellectual content and final approval for manuscript submission.

6. Usefulness of MRI-CBCT Image Registration to Evaluate Temporomandibular Joint Internal Derangement by Novice Examiners

Abstract

Purpose: To assess whether novice examiners can more reliably determine temporomandibular joint (TMJ) disc derangements using fused magnetic resonance and coned-beam computed tomography (MRI-CBCT) images compared to MRI alone.

Methods: Thirty dental students with minimal exposure to TMJ imaging received a 30-minute calibration session explaining TMJ diagnostic imaging, normal anatomy, and pathophysiology of the TMJ internal derangement. The students then evaluated the disc positions of 16 TMJs in two sets of images (MRI-alone and MRI-CBCT images) randomly and independently. The disc positions evaluated by two experienced radiologists were used for comparison.

Results: The internal consistency among all students improved from an unacceptable consistency (α = 0.40) with MRI alone to a good consistency (α = 0.84) with MRI-CBCT images. The agreement between students and the radiologists improved from a poor agreement with MRI alone (k mean=0.07±0.12) to a moderate agreement with MRI-CBCT images (k mean=0.55±0.25). This improvement in the agreement was significant (p<0.001).

Conclusions: Fusing MRI and CBCT images to visualize the TMJs in a single display significantly improved the examiners' reliability and accuracy of assessment of disc positions. The improvement of the novice readers in assessing the disc positions highlights the potential use of MRI-CBCT image fusion as an educational tool.

6.1 Introduction:

Diagnosing temporomandibular joint (TMJ) disc derangement is an area of great challenge and controversy. Magnetic resonance imaging (MRI) has been considered the "gold standard" imaging tool to visualize disc position and to evaluate TMJ internal disc derangement.[1] Choices of treatment, including surgical interventions as well as research endeavors involving the TMJ, are influenced by MRI findings. However, the routine two-dimensional MRIs have inherent limitations when it comes to TMJ imaging, such as artifacts, the suboptimal definition of osseous structure outlines and gaps between image sections.[2,3] Reliability of diagnostic interpretation of internal disc derangement is limited due to these issues. Widmalm et al.[4] evaluated the reliability of four senior (oral and maxillofacial facial) radiologists with significant experience in MRI interpretation for TMJs. The inter-examiner reliability for assessing disc displacement without reduction was poor (ICC=0.34). This issue of poor inter-examiner reliability has also been reported in other studies in the literature.[4-8] Calibration sessions, image evaluation techniques and image quality improvement techniques, have been used to reduce examiner variation in reporting disc displacement. [6,7,9,10]

In oral radiology, educators suggest that novices follow analytical-reasoning strategy (shape, size, location, borders and interaction with surrounding structures) to analyze the radiographic features of an abnormality to reach an accurate diagnosis.[1,11,12] Others suggest that novice clinicians should start with "backward-reasoning" where they can compare a radiographic image to another that was seen previously following a non-analytic reasoning.[13,14] Both approaches, however, are limited by the variations in the radiographic appearance of an abnormality and the clinician's limited experience.[1] It is believed that novice examiners or experts out of their domain tend to use a combination of backward-analysis (based on previous experience) and systematic reasoning to form a diagnostic interpretation.[14] Baghdady et al. investigated the role of basic science knowledge in improving the diagnostic accuracy of radiographic oral lesions in novice dental students.[12] Their study revealed that basic science knowledge helped the students understand the disease entities and their reaction with the surrounding tissues, rather than merely memorizing radiographic features. Of importance, radiographic interpretation is a process that includes visual exploration, the detection of findings, the recognition of patterns and diagnostic decisions.[15] Blesser and Ozonoff suggested that the ambiguity of the radiographic image to the novice may interfere with the complex process of image interpretation. Specifically, the "visual transformation of anatomy to the visual sensory eye system" would be affected because the novice would struggle with recognizing the anatomy or detecting pathological features.[16] [17] The success of an expert's interpretation is due to the ability to picture-match previously known pathologies, the ability to understand a 2D image of a 3D structure, and the ability to understand the physiology and pathophysiology of the lesions.[11,12,18,19]

Al-Saleh et al.[7] introduced a new approach for registering MRI and CBCT images. The fusion of the MRI and CBCT images provided a novel tool to evaluate the articular disc position between the head of the condyle and the articular eminence. Al-Saleh et al.[20] also explored the effect of using MRI-CBCT registered images in improving the intra- and inter-examiner reliability when evaluating TMJ internal derangement compared to using MRIs alone. Although MRI-CBCT fused images improved the disc position assessment by experts, the value of this tool for novice examiners is unknown. By providing a distinct outline of the osseous articular structures surrounding the soft tissues with a clear color contrast, the tool may aid novice users more than experts familiar with the complex contrast patterns seen in MRIs.

The primary purpose of this study was to assess whether novice examiners can assess TMJ articular disc derangements more reliably using fused MRI-CBCT images compared to MRIs alone. The secondary purpose was to explore the usefulness of this tool in educating dental students in the diagnosis of TMJ articular disc derangement.

6.2 Materials and Methods:

Included images:

We used a subset of the MRI and CBCT images of subjects with a history of TMJ disorders on clinical examination used in a previously published study.[20] We included images of adult patients from the Temporomandibular Disorder/Orofacial Pain Clinic at the University of Alberta. This study was approved by the University of Alberta Human Research Ethics Board (Pro00053614). The CBCT images were obtained using the Next Generation i-CAT® scanner (Imaging Sciences International, Hatfield, USA) at a medium field of view setting (16X13cm, exposure time 7 sec, 5 mA, 120 Kvp, and 0.25mm voxel size) including maxilla and mandible and TMJ condyles. The MR images were obtained in the supine position with a multi-channel 12-element head array coil in 1.5 Tesla scanner (Siemens Syngo MRB17, Erlangen, Germany), without sedation or intravenous contrast administration, at mouth-closed oblique sagittal Proton Density (PD)-weighted images with small FOV 13X13cm^2, slice thickness 3mm (14 slices per TMJ), inter-slice gap spacing 0.3mm, echo time 11msec and repetition time 1800 msec. The MRI-CBCT registration procedure was performed based on a non-guided intrinsic registration technique.[7] The mutual information-based algorithm for multimodality image co-registration was used to find the correspondence of each point in the MRI and CBCT images and spatially align them after assuming one common coordinate. The mutual information-based algorithm utilizes a joint entropy histogram spread to calculate the statistical dependence between the corresponding voxels in the MRI and CBCT images. After detecting the similarity between the two images, images are resampled using linear interpolation followed by iterative refinement to increase similarity between both images until final registration is reached.[21]

From the pool of MRI and CBCT TMJ images used in the previous study, only image sets in which both experts/radiologists agreed on the diagnosis on two separate occasions were included in this study. A total of 16 TMJ images from 11 patients were selected. Two sets of 16 TMJ sequences (MRI alone and MRI-CBCT) were prepared. The MRI-CBCT registered images were displayed with the overlapped structures from the MRIs appearing in a gray-scale color and the structures from the CBCT appeared in a scarlet-red color (Figure 1). The mid-sagittal section with the best and most representative view of the articular disc, condylar head, and glenoid fossa was selected from each TMJ for evaluation by the novice examiners. The location of the articular disc intermediate zone in relation to the condylar head was used to classify the disc position into two categories (normal and anteriorly displaced disc), following the guide illustrated in Figure 2. When they were not sure, students were asked to rate the disc position as “not clear”. The experts identified 4 TMJs with normal disc positions (25%) and 12 TMJs with full anteriorly displaced disc positions (75%).

Novice examiners:

Because the study involved the use of medical diagnostic imaging, the targeted participants had to have some knowledge of TMJ anatomy and related terminology with ideally minimal, if any, exposure to the interpretation of TMJ diagnostic imaging, particularly MRI and CBCT images. Therefore, senior dental students were approached to participate in the study. A total of 30 students (18 dental students and 12 orthodontic graduate students) satisfied the inclusion criteria and agreed to participate in the study.

Image evaluation:

Participating students received a 30-minute calibration session explaining the TMJ diagnostic imaging modalities (MRI and CBCT), characteristics of normal anatomy, and the pathophysiology of the TMJ articular disc derangement. The calibration session also involved 10 test examples of MRI and CBCT images of the TMJ and the different articular disc positions, for training and verification that the diagnostic process was well understood. The students were then directed to the diagnostic scoring phase. The two sets of images (MRI alone and MRI-CBCT fused images) were displayed, in random order to avoid learning-experience bias, on computer monitors housed in dark rooms. The students were not given any clinical information regarding the patients from which the images were obtained. They independently classified articular disc positions on separate scoring sheets as *normal, displaced,* or *not clear*. They were also asked to provide a commentary note at the end of their evaluation, explaining their experience in visualizing and classifying the disc positions in their own words.

Statistical analysis and sample size calculation:

The Cronbach's Alpha test was used to assess the internal consistency (reliability) of the students' disc classifications in the MRI alone and MRI-CBCT fused images.

To assess the accuracy of the students' disc classifications against the two expert radiologists, i.e. gold standard, in the MRI alone and the MRI-CBCT fused images, the students' classifications were dichotomised to *normal* and *abnormal/displaced* disc positions then the Cohen's Kappa was completed. The "*not clear"* scores were not included in the Kappa analysis for accuracy assessment. Finally, Welch's T-Test was performed to detect the statistical significance between the accuracy values (Cohen's Kappa) in both MRI alone and MRI-CBCT fused images.

The values of Cronbach's Alpha and Cohen's Kappa tests were interpreted as follows: Cronbach's Alpha (*alpha*) test, < 0.5= unacceptable, ≥ 0.5= poor, ≥ 0.6= Questionable, ≥ 0.7= Acceptable, ≥ 0.8= Good, ≥ 0.9= Excellent.[22] Kappa coefficient (k) ≤ 0= poor, 0.01–0.20= slight, 0.21–0.4= fair, 0.41–0.6= moderate, 0.61–0.8= substantial, 0.81–1= almost perfect. [23]

Using the goodness-of-fit formula provided by Donner and Eliasziw,[24] at α level of 5% and power level of 80%, and expected moderate agreement between students and expert radiologists at k = 0.5-0.6, the appropriate sample size was determined to be 22 to 32 examiners.

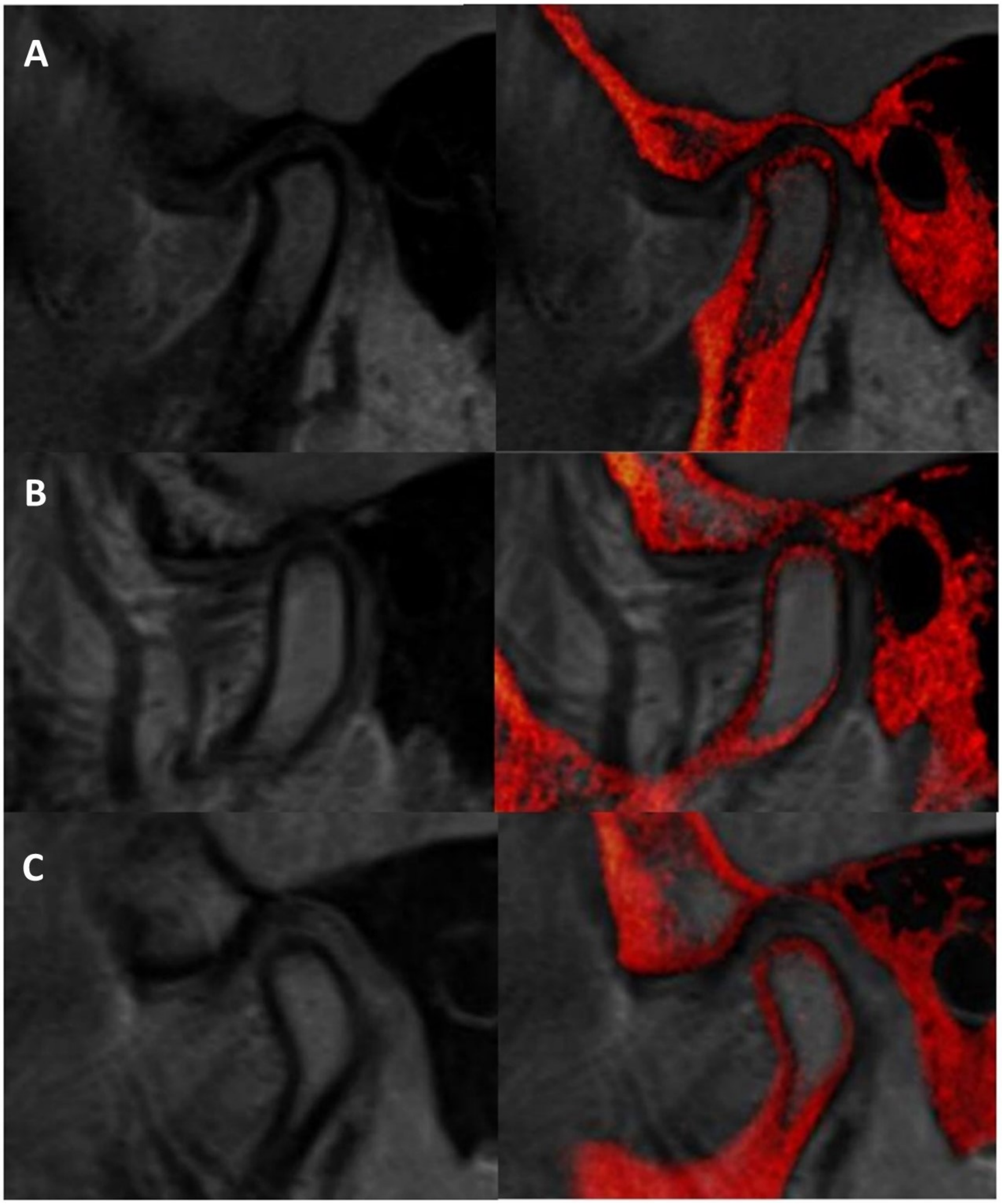

Figure 6.1: Mid-sagittal image sections of the TMJ, MRI in the left panel and MRI-CBCT fused on the right A and B showing anteriorly displaced disc, and C showing normal disc position. Note MRI-CBCT fused images better highlight boney contours and easily differentiate between disc and articular eminence presenting with similar tissue signals.

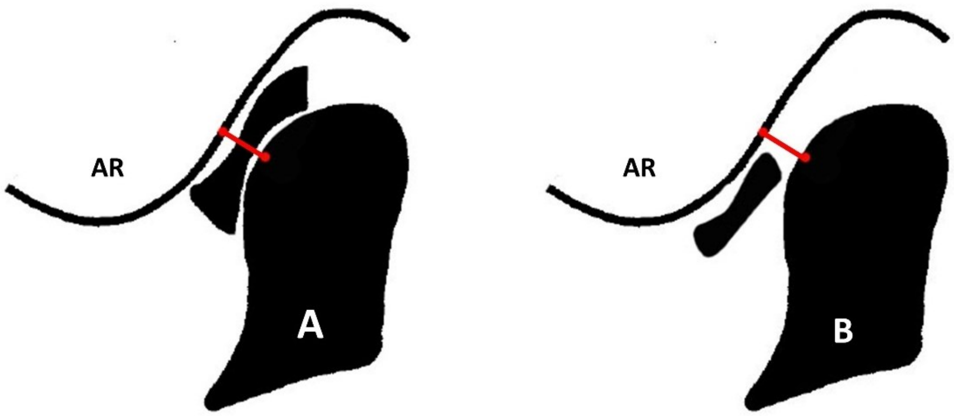

Figure 6.2: Illustration of the articular disc position classification in closed-mouth position. (A) Normal disc position: the intermediate zone of the disc is interposed, in closest point, between the condylar head and posterior slope of the articular eminence (AR), with a “bow-tie” shape of the anterior and posterior bands of the disc. (B) Displaced: the articular disc is anteriorly displaced relative to the posterior slope of the articular eminence and condylar head. The red line represents the disc bilaminar zone interposed between the osseous articular structures and occupied the narrowest joint space. *(Republished with permission of British Institute of Radiology, from Assessing the reliability of MRI-CBCT image registration to visualize temporomandibular joints. Al-Saleh MA, Jaremko JL, Alsufyani N, Jibri Z, Lai H, Major PW. 44(6):20140244. 2015)*

6.3 Results:

The internal consistency among all students was improved from an unacceptable consistency (Cronbach's α = 0.40) with the MRI alone to a good consistency (Cronbach's α = 0.84) with the MRI-CBCT images. The students' accuracy in disc position evaluations, i.e. agreement between students and the true values by the expert radiologists, was improved from a poor agreement with the MRIs alone (*mean* k =0.07 ± 0.12), to a moderate agreement with the MRI-CBCT fused images (*mean* k =0.55 ± 0.25). Welch's T-Test showed a statistically significant improvement (t $=-9.20$, *CI [-9.78, -8.83]*, $p <0.001$) in the students' accuracy vs. expert ratings in MRI-CBCT images vs. MRI alone.

Figure 6.3 shows the distribution of the k values of all 30 students when classifying articular disc position with MRI alone and MRI-CBCT images. Eight students showed poor agreements, which was even less than the chance agreements ($k < 0$).

The students had the option to report "*Not clear*" when they were not sure about the disc positions. "*Not clear*" was reported 176 (36.7%) times with the MRI alone, and 22 (4.6%) times with the MRI-CBCT images. The distribution of the students' scores is reported in Table 6.1. The commentary notes reported by the students following the image evaluations were also summarized into five categories and are reported in Table 6.2.

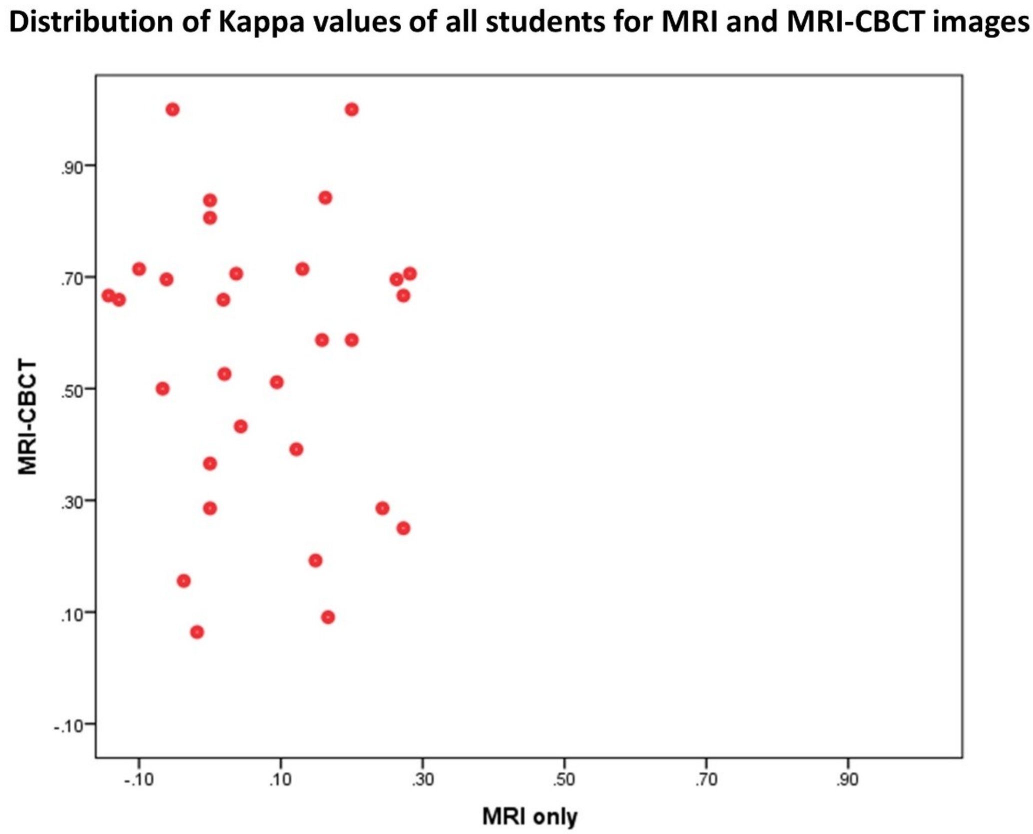

Figure 6.3: The scatter plot shows the distribution of *k* values of all 30 students when classifying articular disc position with MRI only and with MRI-CBCT images. With the MRI only, the minimum *k* value is -0.14, and the maximum value is 0.28. With MRI-CBCT images, the minimum value was 0.06 and the maximum value was 1.

Table 6.1: Classification of the disc position reported by the students in both MRI and CBCT-MRI images.					
Imaging modality		**MRI-CBCT images**			**Total**
		Normal	**Full displacement**	**Not clear**	
MRI	**Normal**	53	90	5	148 (30.8%)
	Full displacement	44	102	10	156 (32.5%)
	Not clear	64	105	7	176 (36.7%)
Total		161 (33.5%)	297(61.9%)	22 (4.6%)	480 (100.0%)
The evaluated 16 TMJs included 12 TMJs with anteriorly displaced discs (75%), and 4 TMJs with normal disc position (25%).					

Table 6.2: Summary of the commentary notes reported by the students regarding the MRI only and the MRI-CBCT images after the images evaluation process.	
Easy to identify anatomical structures in the MRI-CBCT images, especially the condyle, articular eminence and the space in between.	13 students
Easy to see cortex, condyle outline, and to distinguish between bone and soft tissues in the MRI-CBCT images.	9 students
Colors contrast improves visualization in the MRI-CBCT images.	10 students
Anatomy in MRI only is not clear.	3 students
"Difference was not very pronounced between the MRI-only and the MRI-CBCT images".	1 student

6.4 Discussion:

Errors in image interpretation such as recognition error (failed to see the abnormality) and decision error (wrong analysis of the abnormality) can result from challenging visual images, lack of training/experience, radiographic characteristics and locations of the abnormalities.[16] [11,25,26] Previous studies in this domain focused on improving the diagnostic reliability of the expert examiners since they are the ones who interpret MRI findings for TMJs.[6,7,9,10] The application of MRI-CBCT images has shown potential to improve the reliability of the assessment of disc positions as compared to MRIs.[7, 25]

Accurate and consistent interpretation of MRIs in the diagnosis of TMJ internal derangement is challenging to novice readers and radiologists who are experts in different imaging domains. Even radiologists who have considerable experience in TMJ interpretation demonstrated low reliability when diagnosing TMJ disc derangement on MRIs.[4] Widmalm et al. reported poor reliability (average k=0.08 [0.01-0.3]) when four experienced radiologists diagnosed disc displacement with reduction on MR images.[4] Thissuggests that the diagnosis of TMJ disc derangement by a single radiologist should not be accepted as a gold standard. Rather, a consensus of a group of specialists should be used for accurate diagnosis of this type of TMJ disorder.[4] Although, this may seem like an extreme measure and unreasonable in many circumstances and facilities, it reflects the need to improve the diagnostic assessment of TMJ disc derangement. Some measures suggested in other studies to improve the accuracy and reliability of TMJ disc derangement assessments include extensive examiner calibrations and the use of disc position quantification techniques.[6,7,9,10]

When diagnosing TMJ internal derangement from MRIs, the position of the low-intensity bow-tie shaped articular disc (interposing between the head of the condyle and the articular eminence), is the diagnostic key. The articular disc can be variably displaced from this functionally appropriate position representing internal derangement. The degree of disc displacement is evaluated based on the disc location relative to the condylar head. Since osseous structures are not clearly visualized in MRIs, overlapping the MRIs on the CBCT images provided a precise bone definition, which improved the diagnostic ability to visualize disc positions relative to the condyles.[7]

MRI-CBCT image registration relies on the mutual information theory, and it is an automatic, accurate and reliable process.[27] Multimodality image registration does not change the composite image properties. It preserves the image signal intensity, resolution, contrast, and quality. By clearly outlining the surrounding osseous structures, the MRI-CBCT image registration can improve the diagnostic value and reduce the decision-making errors when evaluating disc displacements.[7,20]

In the present study, the articular disc position in relation to the head of the condyle and posterior slope of the articular eminence was evaluated by two examiners (N.A. oral maxillofacial radiologist & J.J. medical radiologist), with 7-8 years of experience in diagnostic imaging of the TMJ. Articular disc positions were subjectively scored independently and blinded to subject information on two occasions, at separate time intervals of 4-8 weeks, in a previous study by the same authors.[20] Student reliability was poor with the MRIs alone when individually compared to the experts' readings (*k* mean=0.07±0.12). However, their reliability improved with the MRI-

CBCT images (*k* mean=0.55±0.25). The improvement was also identified in the students' inter-examiner reliability scores (α = 0.40 and α = 0.84 for MRI alone and MRI-CBCT images respectively).

The findings of this study are consistent with the findings from our previous study, which revealed substantial improvement in intra-examiner and inter-examiner reliability of two experienced clinical radiologists on two separate occasions.[20] Using MRIs alone, the intra-examiner agreement was moderate to substantial (*k*= 0.52-0.63), but fair to moderate when compared to each other (inter-examiner: *k*=0.29-0.42). With the MRI-CBCT images, the intra- and inter-examiner agreement were almost perfect (*k*= 0.91-0.92).[20]

Adding the colored outline of the condyle and articular eminence from the CBCT improved the visualization of the space where the articular disc is positioned and appeared to aid in the identification of the disc. Providing the novice students with a session that explained the TMJ anatomy and the TMJ internal derangement pathophysiology allowed them to understand the different disc positions. The use of MRI-CBCT images provided a tool to reinforce their understanding of internal derangement.

The students were given the chance to record "not clear" for the images where they were unsure of the anatomy or the disc location. Out of 960 decision scores by the students, 198 (20%) images were scored "not clear". Of the 198 "not clear" scores, 176 scores were for the MRI-alone images. This number was reduced dramatically in the MRI-CBCT images where only 22 were scored as "not clear". The poor reliability in determining the disc positions from MRIs was probably influenced by the lack of experience in anatomy detection and therefore lack of decision. The findings clearly illustrate the usefulness of the CBCT osseous outlines on the MRIs on the students' diagnostic decision-making. The option of not making a diagnostic decision (not clear) is often not offered in reliability study designs and is indicative of the difficulty faced by the novice clinicians when viewing with MRIs. This highlights the difficulty that novice readers often face when making a decision. The color contrast contributed to the diagnostic evaluation process. The color itself does not affect the visualization of the disc body; however, it demarcates the osseous tissues around the disc. This was supported by the students' commentary notes about how the fusion of the MRI-CBCT images enhanced the visualization quality of the different tissues. Other commentary notes highlighted the importance of the anatomy outlines in the fused images.

MRI-CBCT image registration has contributed to the TMJ diagnostic interpretation in two aspects; 1) Improving the anatomical definition of the articular osseous tissues and, by doing so, improving reliability and ease of decision-making. This allowed examiners with minimal or no experience to successfully diagnose TMJ disc derangements in a relatively consistent pattern; 2) It has the potential to be used as a radiology training tool to improve the competency of dental undergraduate and graduate students and possibly radiology residents in evaluating TMJ disc position from MRIs alone. Additional research is needed to explore benefits for TMJ clinicians and radiology residents at different levels of training and expertise.

The registration procedure used in the present study could also be adapted to the open jaw position. However, ensuring that the mandible is in the same position relative to the cranial base is identical during acquisition of the CBCT and MRI would be challenging. Furthermore, open mouth CBCT images are not routinely taken and the additional radiation exposure may not be warranted.

The small number of included images and the single spectrum of examiners with the same level of experience are limitations of the current study. A web-based evaluation tool can be used in the future to facilitate evaluation of a larger number of images by a wider spectrum of novice examiners with different levels of experience, such as medical students, diagnostic radiology residents and TMJ disorders specialists.

6.4 Conclusions:

Fusing MRI and CBCT images to visualize TMJ soft tissues and bone in a single display significantly improved the reliability and accuracy of assessment of articular disc positions by novice readers compared to making the same assessment using MRIs alone. This improvement highlighted the potential use of MRI-CBCT image registration as an educational tool, for medical/dental students and radiology residents.

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Chapter 7: Changes in Temporomandibular Joint Morphology in Class II Patients Treated with Fixed Mandibular Repositioning and Evaluated Through Three-Dimensional Imaging: A Systematic Review *

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Preface

This systematic review, which is a part of this thesis, is an original work. In this review, I conceived, prepared the study design and coordination. I ran the electronic search in the library electronic data bases, collected the information, summarized and critically appraised the findings and finally drafted the manuscript. The participating co-authors, Dr. N. Alsufyani (Department of Dentistry) contributed in the present review by evaluating the included articles. Drs. Flores-Mir, Nebbe and Major were involved in concept formation, manuscript drafting, critical revision of the intellectual content and final approval for manuscript submission.

7. Changes in Temporomandibular Joint Morphology in Class II Patients Treated with Fixed Mandibular Repositioning and Evaluated Through Three-Dimensional Imaging: A Systematic Review

Abstract

Objectives: to estimate the effects of skeletal Class II malocclusion treatment using fixed mandibular repositioning appliances on the position and morphology of the temporomandibular joint (TMJ).

Methods: Two independent reviewers performed comprehensive electronic searches of MEDLINE, EMBASE, EBM reviews and Scopus (until May 5, 2015). The references of the identified articles were also manually searched. All studies investigating morphological changes of the TMJ articular disc, condyle and glenoid fossa with 3D imaging following non-surgical fixed mandibular repositioning appliances in growing individuals with Class II malocclusions were included in the analysis.

Results: Out of 269 articles initially reviewed, only 12 articles used MRI and 2 articles used CT or CBCT images. Treatment effect on condyle and glenoid fossa was discussed in 8 articles. Treatment effect on TMJ articular disc position and morphology was discussed in 7 articles. All articles showed a high risk of bias due to deficient methodology: inadequate consideration of confounding variables, blinding of image assessment, selection or absence of control group and outcome measurement.

Conclusion: Reported changes in osseous remodeling, condylar and disc position were contradictory. The selected articles failed to establish conclusive evidence of the exact nature of TMJ tissue response to fixed mandibular repositioning appliances

7.1 Introduction

Mandibular retrusion is considered the most common characteristic of Class II malocclusion in children and adolescents.[1] Mandibular repositioning appliances have been reported to successfully correct Class II malocclusions.[2-6] However, it is uncertain whether these appliances have beneficial or harmful effect on the articular tissues of the temporomandibular joint (TMJ).[7,8] It has been suggested that fixed repositioning appliances apply near constant forces to the TMJ, and may cause remodeling of the articular condyle and glenoid fossa, repositioning of the condyle, and rotation of the mandibular body,[5] which may lead to permanent damage to the TMJ structure(s). However, one previous systematic review revealed weaknesses of the literature and lack of evidence for disk changes and/or condylar or glenoid fossa remodeling.[9]

Many methods have been used in the literature to evaluate the TMJ tissues. Although magnetic resonance imaging (MRI) is a sensitive and valid tool to analyze the morphology of TMJ articular disc, joint effusions, and synovitis,[10,11] the reported assessment of articular disc position has been of a subjective nature. Subjective assessment of stages of disc displacement has relatively poor inter-examiner reliability.[12] Moreover, MRI has limited value when it comes to accurately depicting TMJ osseous abnormalities.[13] Computed tomography (CT) is the gold standard for imaging bone. Cone-beam CT (CBCT) has much lower radiation exposure than multi-detector CT,[14] and is now used widely in orthodontic practice for the assessment of TMJ bone remodeling.[15,16]

Although these different methods have been reviewed previously, an updated systematic review is necessary due to several reasons:

- The previous systematic review identified controversies that were not resolved.

- The previous systematic review is outdated, and several additional related articles have been published.
- The previous systematic review focused exclusively on one type of fixed functional appliance.

The purpose of this review is to evaluate the fixed mandibular reposition appliance's effects on TMJ morphology and position (condyle, glenoid fossa, and articular disc) in skeletal Class II malocclusion treatment.

7.2 Materials & Methods

Search strategy

Four databases, (MEDLINE, EMBASE, All EBM Reviews, and Scopus) were systematically searched in all languages (until May 5, 2015). Keywords used in the search were *orthodontic appliances, functional/activator appliances, Crossbow or Forsus or Jasper Jumper or Herbst or MARA or Functional Mandibular Advancer, temporomandibular joint, TMJ, temporomandibular joint disc, jaw joint, mandibular joint, computed tomography, cone-beam computed tomography, magnetic resonance imaging.* A librarian specializing in health sciences databases was sought to identify the best selection of both truncated and MESH terms. An example of search terminology used in Medline is summarized in Table 7.1 Specific words used and how they were combined per database can be found in Appendix B. In addition, bibliographies of the identified articles were manually searched.

Inclusion criteria

Study design: Clinical trials, cohort studies, case-control studies, cross-sectional studies, prospective and retrospective studies that investigated the TMJ morphologic and positional changes after non-surgical Class II malocclusion treatment using fixed appliances were included. Case series/reports (unless consecutively treated), commentaries, editorials, letters were excluded.

Participants: Inclusion was restricted to children and adolescent patients with skeletal Class II malocclusion treated with fixed mandibular anterior repositioning appliance.

Outcome measures: Any changes of the TMJ articular tissues, assessed by 3D imaging modalities (MRI, CT, CBCT) were included.

Selection process: All abstracts identified during the database search were screened thoroughly by two independent reviewers (M.A. & N.A.). Potentially relevant abstracts were then selected for full article independent evaluation by the same two reviewers. Any selection discrepancy was solved through discussion between the two reviewers.

Collected data

Study design, population, appliance type, treatment duration, imaging modality, and measured outcomes for all included articles were summarized in Table 7.2. Outcomes that represent the change in condyle morphology/position, remodeling of glenoid fossa and disc morphology/position were reported and analyzed.

Critical appraisal

To evaluate the articles for risk of bias, a recently developed quality assessment tool "Risk of Bias Assessment Tool for Non-Randomized Studies (RoBANS)" was used.[17] Kim *et al*. confirmed the inter-rater reliability, feasibility, concurrent, construct, and face validities of this RoBANs tool. RoBANS was deemed suitable for the articles included in this review that assess before-and-after intervention outcomes.[17] The same reviewers independently evaluated the included articles for risk of bias.

Table 7.1: Midline database search results.

	Keywords	Number of articles
1	Orthodontic functional appliance, Activator, Crossbow, Jasper Jumper, MARA, Herbst, Mandibular forward positioning,	190,000
2	Computed tomography, CT, x-ray, Cone-beam computed tomography, CBCT	289,586
3	Magnetic resonance imaging, MRI	278,522
4	Temporomandibular joint, TMJ internal derangement, TMD	22,650
8	(1) AND (2) AND (3) AND (4)	140

Table 7.2: Characteristics of the included studies.

	Study Design	Population	Treatment type	Imaging	Measured outcome
Ruf and Pancherz 1998.[5]	Prospective cohort study.	15 patients (11 M, 4 F) received treatments; mean age (13.5 years). - No control.	Herbst appliance; Treatment duration (5-10 months).	- MRI, 4 times (before, at start, during & after treatment).	- Evaluated condyle and glenoid fossa remodeling following increased signal intensity in MR images. - Evaluated condyle position using Joint Space Index (JSI).[38]
Ruf and Pancherz 1999.[20]	Prospective cohort study.	39 patients (15 M, 22 F) received treatments; 25 adolescents (mean age 12.8 years), and 14 adults (mean age 16.5 years). - No control.	Herbst appliance; Treatment duration (adolescents 7.1 months; adults 8.5).	- MRI, 4 times (before, at start, during & after treatment). - Lateral Ceph., 2 times (before & right before the end of treatment).	- Evaluated condyle, glenoid fossa and ramus remodeling following increased signal intensity in MR images. - Measured distances in lateral Ceph. to evaluate condyle and glenoid fossa remodeling.
Pancherz et al. 1999.[18]	Prospective cohort study.	15 patients (10 M, 5 F) received treatments; mean age (13.7 years). - No control.	Herbst appliance; Treatment duration (6 -11 months).	- MRI (before, in 6 weeks, 13 weeks and right after treatment (7month)).	- Evaluated articular disc position and subjectively classified position using "disc position index".[41] Three slices (medial, central and lateral) of closed and open mouth MR image were analyzed.
Ruf and Pancherz 2000.[35]	Prospective cohort study.	62 patients (27 M, 35 F) received treatments; mean age (14.4 years). - No control.	Herbst appliance; Treatment duration (7.2 months).	- MRI (before, right after treatment and one year after treatment).	- Evaluated condyle and glenoid fossa remodeling following signal intensity in MR images. - Evaluated condyle position using JSI. - Evaluated articular disc position using (12 o'clock position,[42] disc posterior band angle[43,44] & intermediate zone position[41]).
Kinzinger et al. 2006.[26]	Prospective cohort study.	20 patients (11 M, 9 F) received treatments; age (16 -25 years). - No control	Functional Mandibular Advancer (n=17); Herbst (n=3). Treatment duration (6-9 months)	- MRI, 4 times (before, at start, during & after treatment).	- Evaluated condyle position using JSI.
Kinzinger et al. 2006.[27]					- Evaluated articular disc position using 12 o'clock position and intermediate zone position. Three slices (medial, central and lateral) of closed and open mouth MR

Kinzinger et al. 2006.[36]		15 patients (8 M, 7 F) received treatments; age (12 -16 years). - No control	Functional Mandibular Advancer; Treatment duration (6-9 months)		image were analyzed.
Kinzinger et al. 2007.[28]		20 patients (10 M, 10 F) received treatments; age (6 - 16 years). - No control			- Evaluated condyle position using JSI. - Evaluated condyle shape in axial, sagittal and coronal sections.
Aidar et al. 2006[21]	Prospective cohort study.	20 patients (7 M, 13 F) received treatments; mean age (12 years). - No control.	Herbst appliance; Treatment duration (12 months)	- MRI, 3 times (before, during & after treatment).	- Evaluated articular disc position using the angle between the disc posterior band, condyle and articular eminence. Three slices (medial, central and lateral) of closed and open mouth MR image were analyzed.
Aidar et al. 2009[22]		32 patients (16 M, 16 F) received treatments; mean age (12 years). - No control.			- Evaluated articular disc position using 12 o'clock position and intermediate zone position. Three slices (medial, central and lateral) of closed and open mouth MR image were analyzed.
Aidar et al. 2010[23]				- MRI, 4 times (before, during, after Phase I, after Phase 2).	
Aidar et al. 2013[24]					- Evaluated the condylar morphology changes in the sagittal view and classified as normal (rounded with soft and intact cortex), remodeled (flattening) and degenerative (cavities, erosions, osteophytes or resorption).
Arici et al. 2008[25]	Prospective clinical trial.	30 patients (13 M, 17 F) received treatments; mean age (12 years). - Control: 30 patients (9 M, 21 F) received no treatment; mean age (12 years).	Forsus nitinol flat-spring (n=30); Treatment duration (6-9 months).	- CT, 2 times (before & after treatment).	- Evaluated the volume of the condyle and glenoid fossa. - Evaluated the joint space using the circular space around the condyle in axial view.

LeCornu et al. 2013[29]	Case-control study	7 patients received treatments; mean age (13 years). - Control: records of 7 patients received class II elastics treatment; mean age (13.4 years).	Herbst appliance; Treatment duration (13 months). Control group treatment duration (18.4months).	- CBCT, 2 times (before, after treatment).	- Evaluated the condylar head, glenoid fossa remodeling using color-mapped image super-imposition technique, scaled from -3mm to +3mm to represent bone remodeling.

7.3 Results

Database search

The electronic database search yielded a total of 269 articles. The primary review resulted in 30 potential articles that were further considered for inclusion. Based on a full-text review 17 articles were selected.[18-34] Two articles were identified by manual search as well.[35,36] The article selection process is presented in Figure 7.1. Finally, 14 papers fulfilled the inclusion criteria of our review.[18-29,35,36] The remaining 5 articles from this final selection stage were excluded for the following reasons:

1) The MRI evaluation of the TMJ condition was performed after treatment. Data were compared with norms in the literature.[30,33]

2) The TMJ condition was evaluated using 2D imaging tools (such as transpharyngeal radiographs, conventional tomography, transcranial oblique radiographs or lateral cephalograms).[32,34,37]

Characteristics of the included articles

Included studies consisted of cohort groups of adolescent patients with class II malocclusions. Twelve articles reported the changes in TMJ articular tissues as demonstrated in MRI.[18-24,26-28,35,36] One article[25] used CT scan images to evaluate the volume of the condyle and glenoid fossa while another[29] used co-registered serial CBCT images to assess TMJ osseous structures changes.

Synthesis of results

Results of the included studies were summarized in Table 7.3. Due to the heterogeneous nature of the finally selected studies a meta-analysis was not attainable.

Quality assessment

The 14 included articles were assessed and scored according to guidelines of RoBANS. [17] Assessments results are shown in Table 7.4. All included articles were considered to have high risk of bias. Multiple forms of bias were evident such as missing control group, ignoring gender effect as a co-factor, inadequate measurement tools and data analysis. Ten articles did not conduct blinding during image analysis.[18-20,25-29,35] Four articles report descriptive analysis without proper statistical analysis.[21-24] One article [17] reported results in graphics, which led to missing or unclear data.[18] One article [20] reported incomplete data.[21] Scoring agreement between reviewers was 89% agreement, and kappa score of 0.8 both considered the substantial agreement.[38]

Figure 7.1: PRISMA 2009 Flow diagram

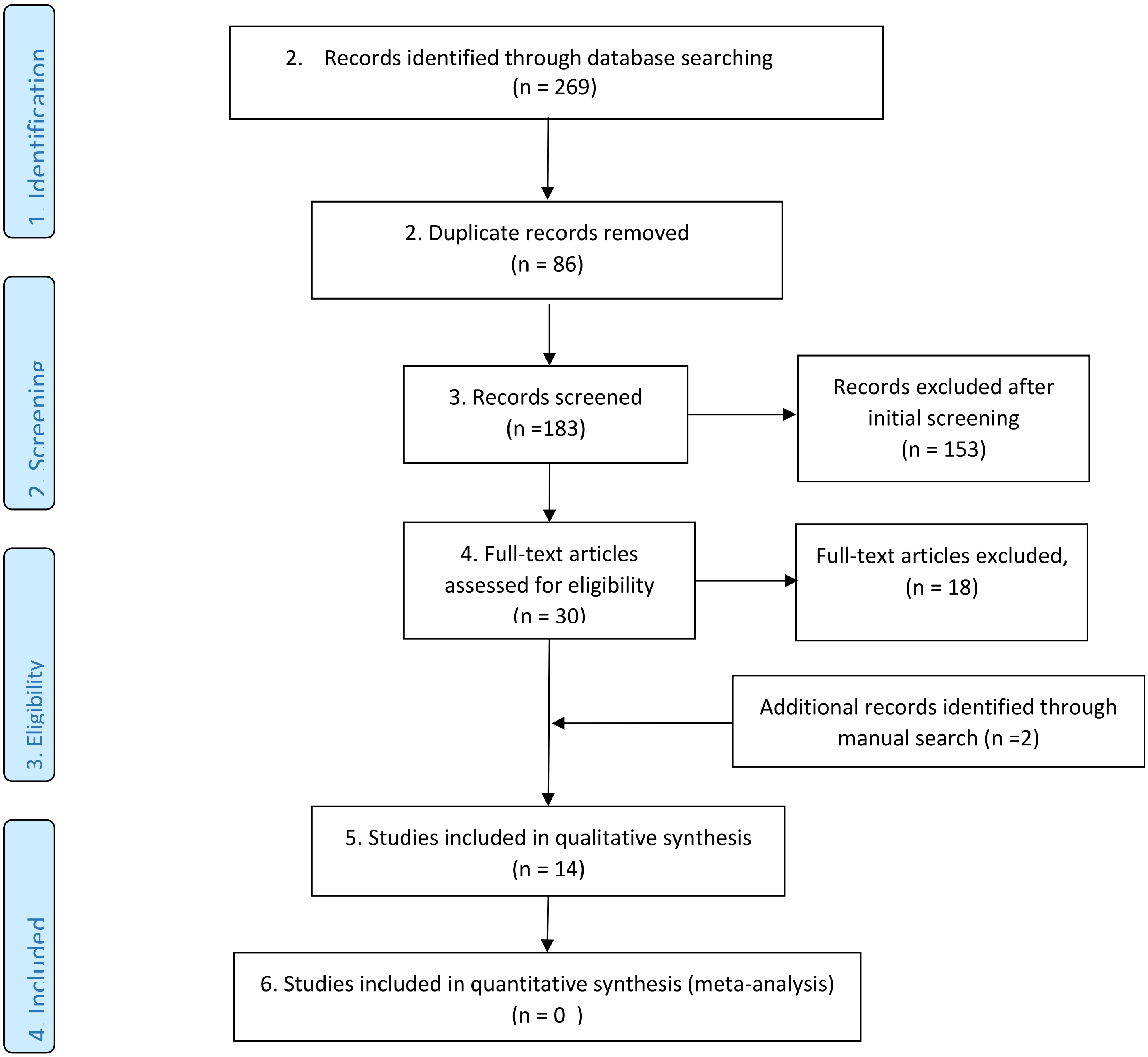

Table 7.3: Summary of the included articles results.	
Ruf and Pancherz 1998.[5]	*Osseous remodeling:* - Remodeling of post-glenoid process in (73% TMJs) at 6-12 weeks. - Remodeling of postero-superior surface of the condyle in (96% TMJs) at 6-12 weeks. *Condyle position:* - Acceptable anterior and posterior joint spaces change that was not affected by Herbst treatment.
Ruf and Pancherz 1999.[20]	*Osseous remodeling:* - Remodeling of postero-superior surface of the condyle in adolescents and young adults in (92-96% TMJs) at 6-12 weeks. - Remodeling of posterior ramus in (7% TMJs) at 6-12 weeks. - Remodeling of glenoid fossa in (72-78% TMJs) at 6-12 weeks. - Higher signal intensity was noticed in adults after appliance replacement (~7months).
Pancherz et al. 1999.[18]	*Articular disc position:* - Before treatment, an average protrusive disc position was reported. During treatment, over 50% of TMJs showed retrusive disc position. After treatment, discs were at retrusive position in comparison to their initial position. There was large individual variation in disc position index scores.
Ruf and Pancherz 2000.[35]	*Osseous remodeling:* - Before treatment, osteoarthritic changes were noticed in (17 TMJs), with associated disc displacement in (10 TMJs). - After treatment, osteoarthritic changes were seen in 7 TMJs. - One year after treatment, osteoarthritic changes were seen in 4 joints with associated disc displacement. *Condyle position:* - Condyles were at slightly anterior position in the fossa before and 1 year after treatment. - Condyles were at more anterior position during the period of appliance treatment and returned to their original position after appliance removal. *Articular disc position:* - General disagreement of the 3 systems to evaluate the disc position in the same individuals was reported in the study. - Using “disc posterior band angle”, articular discs were at more retrusive position during treatment, and returned to their original position after appliance removal. - Using “intermediate zone position”, articular discs were at more retrusive position during treatment than its original position.
Kinzinger et al. 2006.[26]	*Condyle position:* - During early treatment, condyles were significantly anteriorly displaced and gradually reduced to a central position within the fossa after appliance removal.
Kinzinger et al. 2006.[27]	*Articular disc position:* - Before treatment, 40% of TMJs had anterior disc displacement. Fifteen percent of TMJs with displaced discs improved to the normal physiological position after treatment. - The *posterior band angle* analysis, all normal joints remained at the same physiological position after treatment. Using the

	analysis of variance (ANOVA), joints with disc displacement were significantly improved (*P*=0.03) from 28.5°±12.7° before treatment to 18.1°±13.3° toward physiological position after treatment. - The *intermediate zone position* analysis revealed that mean values of disc anterior displacement were significantly improved (*P*=0.04) from 1.47±0.89mm before treatment to 0.88±0.76mm toward physiological position after treatment.
Kinzinger et al. 2006.[36]	*Articular disc position:* - Before treatment, 37% of TMJs had anterior disc displacement. - The *posterior band angle* analysis, all normal joints remained at the same physiological position after treatment. Using the analysis of variance (ANOVA), joints with disc displacement were significantly improved (*P*=0.01) from 32.2°±9.8° before treatment to 19.1°±11.2° toward physiological position after treatment. - The *intermediate zone position* analysis revealed that mean values of disc anterior displacement were significantly improved (*P*=0.01) from 1.67±0.67mm before treatment to 0.86±0.74mm toward physiological position after treatment.
Kinzinger et al. 2007.[28]	*Condyle position:* - Neither anterior nor posterior joint spaces of all TMJs showed significant changes after treatment in comparison to the baseline findings. *Condyle shape:* - The value of the dimensions' rations indicated no changes in condyles morphology during or after treatment.
Aidar et al. 2006[21]	*Articular disc position:* - According to subjective assessment, all TMJs showed normal disc position before treatment, posteriorly displaced discs during treatment and normal disc position post treatment. - According to objective measurement, the central slice showed that discs were posteriorly positioned by a mean difference of 2.5° (*P*>0.01) at the completion of treatment. No differences were detected in the medial or lateral slices.
Aidar et al. 2009[22]	*Articular disc position:* - 65% of TMJs had normal position before and after treatment. - 35% of TMJs had anterior disc displacement before treatment and improved to a normal position after treatment. - 14% of TMJs had partially reducing discs in open-mouth position before treatment, which became completely reducing after treatment. - Disc morphology was improved in 14% of TMJs from no-biconcave to biconcave morphology in open-mouth position.
Aidar et al. 2010[23]	*Articular disc position:* - 10% of TMJs that had normal disc position after appliance removal, suffered anterior disc displacement after phase II treatment. - 8% of TMJs had lost biconcavity shape of the articular disc after phase II treatment.
Aidar et al. 2013[24]	*Osseous remodeling:* - 3% TMJs changed from normal to remodeled. - 5% of TMJs changed from remodeled to normal. - 2% changed from degenerative to remodeled.

Arici et al. 2008 [25]	*Volume of articular tissues and condylar space:* - Volume of condyle and glenoid fossa continues to increase in the same rate in both test and control groups. - Anterior joint space volume increased in the test group by 38%, and in the control group by 20%. - Posterior joint space volume decreased in the test group by 9%, and increased in the control group by 2%.
LeCornu et al. 2013 [29]	*Osseous remodeling:* - Bone resorption was noticed at the anterior surface (1.4mm - 1.7mm) and bone deposition at the posterior surface (0.6mm - 0.8mm) of the glenoid fossa in the Herbst group. - Class II elastics group showed bone deposition at the anterior surface (-1.3mm - -1.5mm) and bone resorption at the posterior surface (-1.2mm - -1.4mm) of the glenoid fossa. - The condylar head was anteriorly displaced in the Herbst group by about 2.5 - 2.9 mm more than the comparison group.

Table 7.4: The risk-of-bias Assessment Tool (RoBANS) for the included articles.														
	Ruf & Pancherz 1998 [5]	*Ruf & Pancherz 1999* [20]	*Pancherz et al. 1999* [18]	*Ruf & Pancherz 2000* [35]	*Kinzinger et al. 2006* [26]	*Kinzinger et al. 2006* [27]	*Kinzinger et al. 2006* [36]	*Kinzinger et al. 2007* [28]	*Aidar et al. 2006* [21]	*Aidar et al. 2009* [22]	*Aidar et al. 2010* [23]	*Aidar et al. 2013* [24]	*Arici et al. 2008* [25]	*LeCornu et al. 2013* [29]
The selection of Participants: *Selection Biases caused by the in adequate selection of participants.*	High	High	High	High	High	High	High	High	High	High	High	High	Low	High
Confounding variables: *Selection Biases caused by the in adequate confirmation and consideration of confounding variables.*	High	High	High	High	High	High	High	High	High	High	High	High	High	High
Measurement of exposure: *Performance biases caused by inadequate measurement of exposure.*	High	High	High	High	High	High	High	High	High	High	High	High	High	Low
Blinding of outcome assessments: *Detection biases caused by the inadequate blinding of outcome assessments.*	High	High	High	High	High	High	High	High	Low	Low	Low	Low	High	Unclear
Incomplete outcome data: *Attrition biases caused by the inadequate handling of incomplete outcome data.*	Low	Low	High	Low	High	Low	Low	Low	High	Low	Low	Low	Low	Low
Selective outcome reporting: *Reporting biases caused by selective reporting outcome.*	Low	Low	High	Low	High	Low	Low	Low	High	Low	Low	Low	Low	Low
Overall risk of bias	High	High	High	High	High	High	High	High	High	High	High	High	High	High

7.4 Discussion

Since 2003, many articles have discussed the effect of different mandibular repositioning appliances on TMJ. The findings in these articles were critically analyzed to shed the light on the evidence presented by the included articles. Popowich *et al.* in 2003,[9] analyzed the available evidence on the effect of Herbst appliance on TMJ in 5 articles. The included articles reported condylar and gelnoid fossa remodeling and disc position using MRI, CT and tomography. Despite the methodological and assessment limitations of the reported articles, MRI data failed to provide conclusive evidence about condylar position relative to the glenoid fossa. This systematic review highlights the weaknesses of the reviewed articles and the apparent lack of condylar and glenoid fossa remodeling, or disc position changes.

Osseous remodeling and condyle position:

The articles published by Ruf and Pancherz [19,20] were based on subjective MRI assessment of remodeling of the glenoid fossa and condyle surface without evidence of blinding, report of calibration or reliability. The authors evaluated high signal intensity changes due to the hydrated subcortical layer in adolescents as an indicator to the bone remodeling, which has not been validated. Although MRI is considered as the most precise imaging technique to visualize the articular disc,[39] it has poor identification of the osseous tissue margins and limited value when it comes to describing TMJ osseous abnormalities.[13] Furthermore, these articles did not have an untreated control. Articles used a quantitative method to measure condyle position within the fossa. The condylar position was reported to be highly variable with a tendency of anterior positioning in some cases. However due to “large individual variation”, the authors reported an acceptable joint space change that was not affected by Herbst treatment.

It appears that the Kinzinger *et al.* [26-28,36] articles, which evaluated condyle position changes using MRI, were essentially the same treatment sample without a control group. Furthermore, there was no report of examiner blinding. The reproducibility study, which was based on an assessment of just 4 cases, done twice, showed significant method error. In addition, the plane orientation during imaging acquisition at multiple times produces an inevitable error that was not reported.

The 2013 Aidar *et al.* article also used MRI to assess bone change.[24] Again there was no control group. Evaluator calibration process, blinding and inter-observer agreement were reported: excellent (Kappa = 0.87). Accepting the limitation that there was no control group in this study, there was some evidence of insignificant condylar remodeling in some cases.

The CT images provide 3D reconstruction of the TMJ with high diagnostic quality, accurate and reliable linear measurements that allow evaluation of joint space changes.[40-42] The volumetric approach used by Arici *et al.* 2008,[25] has not been validated and provides conflicting evidence with the more widely accepted approaches. The authors did not report standardization of joint or mouth positioning during the scan or adjustment of the head orientation of the volumetric data after image acquisition. The lack of standardization has a significant impact on where the "central slice" would be located and selected. Consequently, the 3 selected slices may not be reproducible nor do they adequately highlight or quantify the actual remolding of the condyle and glenoid fossa or the change in joint space. A note is made of the relatively high radiation dose of Helical CT used in their imaging protocol: CBCT would have been an alternative with less radiation dose. Despite including untreated control group, the authors also failed to address other methodological flaws such as randomization and blinding to avoid the significant risk of bias in the reported findings.

The LeCornu *et al.* study in 2013,[29] provided the most appropriate method for assessing bone remodeling using CBCT superimposition of serial images. Unfortunately, they had a small sample size, and there was no randomization between the Herbst (test) and Class II elastics (comparison) groups. CBCT imaging machines and time intervals were different between the two groups. The images were low-resolution (0.5mm voxel size), and reliability was not reported. There was some evidence of greater anterior positioning of the fossa with Herbst treatment compared to Class II elastic wear. The Herbst patients showed resorption at the anterior wall of the glenoid fossa and deposition at its posterior wall by 3 mm and 2 mm, respectively, compared to control subjects.

Temporomandibular disc position:

Pancherz *et al.* in 1999 [18] used subjective analysis to determine the disc position using the "*disc position index*". The study concluded that Herbst appliance treatment placed the articular disc in a normal functional position even when it was initially anteriorly displaced. Data was reported using line charts that made exact data extraction impossible. Also, it was not clear whether the disc position index was a reliable tool to quantify disc displacement, especially with the significant variation in disc morphology between subjects. Although error of measurements was reported, the error margin of the assessment tool itself was not reported. Ruf and Pancherz in 2000 [35] reported results of 62 patients that were included in the previous article.[18] The authors analyzed the disc position using 3 assessment tools that were not proven to be valid or reliable. The authors categorized the disc to have "displacement tendency" if indicated by one tool only, and "completely displaced" if indicated by 2 assessment tools. There was a lack of agreement between the tools resulting in variations in categorizing disc position. Moreover, disc position was found to "vary largely in different image slices and at different times of examination". In one assessment tool (*intermediate zone assessment)*, the disc position was in a retrusive position post-treatment compared to its initial position by 0.3mm. However, the reported method error was larger than the detected difference (0.2-0.6mm). In addition to the lack of control/comparison group and blinding, and failing to rule out gender differences at baseline, the authors applied multiple t-tests to analyze multiple variables and outcomes thus increasing type I error. In our opinion, the studies designed by Pancherz *et al*. were unnecessarily complicated with several methodological flaws that warrant caution when interpreting their results.[18,35]

Kinzinger *et al.* in 2006 objectively assessed the disc position in one central slice image using 2 assessments tools.[27,36] Findings were in agreement with the ones reported by Ruf and Pancherz.[18,35] It was not clear whether the same subjects were used in the 2 studies. Taking into consideration the method error and the fact that one central slice does not reflect the disc position change; a significant bias in the findings can be implied. Ideally, disc position should be considered in all image slices or in 3D to account for possible mediolateral rotation/displacement. The method error of the tools was reported. However, it is unclear if these tools were valid or reliable. The findings showed that the disc was retruded to more physiologically correct position compared to its initial position by a mean difference of 0.6mm in the first article,[27] and 0.8mm in the second article.[36] These differences were even smaller than what was reported as an error of the assessment tool itself, which was 0.98 mm. The study did not consider the gender of participants, blinding of image assessment and the different appliance types as a confounder. The findings of these 2 articles should be interpreted with caution.

Aidar *et al.* in 2006 evaluated the disc position in 20 patients using coronal and parasagittal MRIs at three times.[21] It was noted that findings of coronal images were not reported in the article. Authors performed non-parametric Wilcoxon signed-rank test to analyze the data of each slice at different times. Another robust statistical test should have been performed instead of multiple Wilcoxon signed-rank tests, to avoid type I error. The images were assessed 3 times by double-blinded calibrated evaluators. However, too many unnecessary variables were considered with limited sample size to support adequate statistical analyses. Also, the central slice evaluation revealed a difference in disc position after treatment by 2.5°. Considering the 1.5° method error reported in the study, the small difference in the central slice should not be considered clinically significant. In 2009,[22] it was not clear if the authors had included patients from their previous study. The study was further complicated by introducing more variables pertaining to disc position categories (12 categories based on the displacement severity in mouth-closed position, and to 5 categories based on reduction during mouth opening), and 2 new categories of disc morphology. Further weakening the study, the authors provided descriptive data only, likely because multiple variables existed with a small sample size that failed to support any robust statistical test. In 2010, [23] further MR imaging was carried out to evaluate the disc position after full orthodontic treatment was completed. The article provided similar descriptive data that were not statistically analyzed and resulted in inconclusive results.

This systematic review followed a thorough procedure to screen the available literature in 4 common databases and critically analyzed the included articles. PRISMA reporting guidelines (check list and Flowchart) were followed to ensure detailed appraisal for the reviewed articles. The level of evidence regarding the change in disc position and disc morphology with mandibular anterior positioning appliances is low. Using a validated tool to objectively evaluate the disc position change is essential. Nebbe *et al* described a valid technique to measure changes in disc location relative to the functional load-bearing intermediate zone of the articular disc.[43] The midpoint of the intermediate zone was measured relative to 2 anatomical reference lines (Frankfort horizontal line and articular eminence plane).

7.5 Limitations of the included articles and future recommendations

Significant methodological limitations were identified in all the included articles. The high risk of bias in considering gender as confounding variable, blinding, untreated control, and incomplete outcome reporting deemed the findings questionable.

A well-designed study is required to establish articular tissue reactions to the mandibular anterior appliances to treat Class II malocclusion in the adolescent population. Suggestions for future research design are:

4) Although ethically questionable if not properly planned, a randomized clinical trial with un-treated control is the ideal design to detect the causal effect on TMJ accurately.
5) A larger sample size to empower the collected data analysis and support the clinical significance of the reported findings.

6) Use 3-D volumetric CBCT images before and after treatment with a standardized imaging protocol to overcome the shortcomings of the 2D images in evaluating the osseous changes of the TMJ. A valid and reliable superimposition technique should be conducted to quantify the osseous remolding.[44]

7) Despite the MRI implicit soft tissue contrast and high resolution, it is paramount to adequately evaluate the disc position in relation to the condyle and glenoid fossa using a valid and reliable tool adequately. Ideally, the articular disc should be segmented to avoid losing critical data and enhance the accuracy of the assessment process.

8) A double-blinded experienced examiner should conduct the image analysis to reduce method error and improve the assessment reliability.

9) Appropriate data analysis that considers age and gender should be performed to assess the evidence of the collected findings.

7.6 Conclusions:

Current literature that investigated the short-term effect of fixed functional appliances on actively growing patients showed critical design problems, and analytical flaws that prevented drawing any definite conclusions about conducted treatments.

The articles failed to establish evidence of the TMJ tissue reaction to the forces applied by the mandibular anterior positioning appliances.

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Chapter 8: MRI Alone Versus MRI-CBCT Registered Images to Evaluate Temporomandibular Joint Internal Derangement in Adolescents: A Pilot Study. *

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** Submitted to the Angle Orthodontists Journal*

Preface

This research project, which is a part of this thesis, is an original work and received research ethics approval from the University of Alberta Research Ethics Board Project #Pro00045191, March 11, 2015.

In this project, I conceived, prepared the study design, executed data acquisition, analysis, and interpretation, and finally drafted the manuscript. The participating radiologists, Dr. J. Jaremko (Department of Radiology and Diagnostic Imaging) and Dr. Alsufyani (Department of Dentistry) contributed in the present project by evaluating the obtained images quality and diagnosing the TMJ pathologies in two occasions. Dr. Major were involved in concept formation, manuscript drafting, critical revision of the intellectual content and final approval for the manuscript.

8. MRI Alone Versus MRI-CBCT Registered Images to Evaluate Temporomandibular Joint Internal Derangement in Adolescents: A Pilot Study.

Abstract

Purpose: To determine whether the use of magnetic resonance imaging (MRI) and cone-beam computed tomography (CBCT) image registration improves intra- and inter-examiner reliability when evaluating the temporomandibular joint (TMJ) disc position compared to MRI alone in adolescents. **Methods:** MRI and CBCT images of 10 adolescent patients (20 TMJs), who sought orthodontic treatment, were obtained and co-registered using multi-modality intensity-based registration via Mirada XD® software (Mirada Medical, Oxford, UK). Two radiologists blindly and independently evaluated the TMJ disc position in two sets of images (MRI-CBCT registered images and MRI alone) on 2 occasions, 8 weeks apart. The TMJ articular disc position was classified based on the sagittal disc position in relation to the head of condyle and posterior slope of the articular eminence at maximum dental occlusion. **Results:** In MRI alone, the inter-examiner reliability was strong at T1 (ICC= 0.72 [0.3-0.89]) and T2 (ICC=0.68 [0.21-0.87]). In MRI-CBCT images, the inter-examiner reliability was strong at T1 (ICC= 0.75 [0.39-0.9]) and moderate at T2 (ICC=0.48 [-0.3-0.79]). For examiner 1, the intra-examiner reliability was strong with MRI alone (ICC= 0.74 [0.35-0.89]) and with MRI-CBCT images (ICC=0.71 [0.28-0.88]). For examiner 2, the intra-examiner reliability was perfect (ICC= 0.88 [0.7-0.95]) with MRI alone and moderate (ICC=0.43 [0.4-0.77]) with MRI-CBCT images. **Conclusions:** The MRI-CBCT registered images did not improve the intra- and inter-examiner reliability among experienced readers to evaluate the TMJ internal disc derangement when compared to MRI alone.

8.1 Introduction:

TMJ internal disc derangement refers to an abnormal disc-condyle relationship, with the disc usually displaced in an anterior or medial position relative to the condylar head at maximum dental occlusion.[1-5] In a normal joint, the intermediate zone of the articular disc is interposed between the posterior slope of the eminence and condylar head, and distributes forces applied to the joint surfaces during function. Internal disc derangement disturbs the congruity between the functional components of the TMJ, which may potentially have an effect on normal condylar development in the adolescents. The rate of disc displacement in asymptomatic adolescents was reported to range from 24% -29 % of girls and 50% of boys, and the frequency of normal joints was found to increase with age increasing.[6] Altered condylar morphology can lead to altered craniofacial morphology in actively growing patients.[7-9] However, the association between internal disc derangement and degenerative changes of the condyle has been a source of controversy in the literature.[10,11] Although general agreement on the association between the disc displacement and condylar osteoarthritis is evident; disc displacement is more often considered a sign rather than a cause of osteoarthritis.[12,13]

Proper diagnosis of internal disc derangement allows for a more accurate management planning. MRI is considered the gold standard to assess the integrity of the disc-condyle relationship and to confirm the severity of the internal disc derangement.[14,15] However, the inter-examiners' reliability in detecting the disc position had variant values in different studies in the literature.[16-20] It was reported that examiners performance could be affected by their experience in TMJ diagnostic imaging, calibration processes, and quantitative assessment methods.[19-22]

Multi-modality image registration extracts two images of different sources and spatially aligns them in a common coordinate system. This process of image fusion maps the coordinates of each point in one imaging modality to a corresponding point on the other reference modality. The resulting fused MRI-CBCT image combines key features of both modalities and allows better interpretation of the disc-condyle relationship.[23] The MRI-CBCT registration process was considered to be an accurate computational process and was found to significantly improve the inter- and intra-examiners' reliability in detecting disc position in an adult population.[24,25]

The purpose of the present pilot study is to evaluate whether the use of MRI-CBCT image registration improves intra- and inter-examiner reliability when evaluating TMJ disc position compared to MRI alone in adolescents TMJ.

8.2 Materials and Methods:

Patients:

In the present pilot study, a total of 10 adolescents (20 TMJs), six females and four males with an age range from 12 to 18 years, who sought comprehensive orthodontic treatment at the Orthodontic Graduate Clinic at the University of Alberta were recruited. The participating patients were part of an ongoing clinical trial, and the included images were used for a preliminary analysis in the present study. The study was approved by the Human Research Ethics Board at the University of Alberta (Pro00045191). Informed consent was obtained from all study participants. All participants had MRI and CBCT images obtained at the same visit with the teeth in maximum intercuspation using polyvinylsiloxane occlusal bite stents.[25]

Imaging protocol:

The CBCT images were acquired at a low resolution medium field of view setting (16cm wide, 13cm height, scan time 9 sec., 5 mA, 120 Kvp, and 0.3mm voxel size). The images included both jaws and TMJ condyles. The imaging machine, Next Generation i-CAT® scanner (Imaging Sciences International, Hatfield, USA), rotated 360 degrees with the patients at the upright position with Frankfort plane parallel to the floor.

MRI scans were performed with patients in the supine position. Images were obtained at a medium field of view (13cmX13cm), without intravenous contrast administration or sedation, employing a TMJ coil in a 1.5 Tesla scanner (Siemens, Munich, Germany). Bilateral corrected-oblique sagittal sections of the proton density-weighted images (PD) were obtained with a slice thickness of 3 mm; 10% inter-slice gap; repetition time and echo time TR/TE 1800/11 ms.

Image preparation and assessment:

The MRI and CBCT images in the form of Digital Imaging and Communications in Medicine (*DICOM*) files were imported to the Mirada XD software (Mirada Medical, Oxford, UK) for automatic image co-registration. The MRI and CBCT images were co-registered using the mutual information technique and final fused images were displayed in a color-coded fashion.[26] The overlapped anatomical structures from CBCT appeared scarlet red color and the MRI appeared in gray-scale. The best display possible of the articular disc and the surrounding osseous structures, in the fused image, was obtained by modifying the color gradient, contrast, and transparency.

The right and left TMJs were evaluated with different randomization sequence by two examiners with 5-8 years of experience in diagnostic imaging of the TMJ (J.J. medical radiologist and N.A.-oral maxillofacial radiologist). The articular disc positions were subjectively evaluated from two sets of images (MRI-CBCT versus MRI alone) independently and blindly to subject information on two occasions, baseline (T1) and 8 weeks later (T2). For each TMJ, the examiners scrolled through all sagittal sections and evaluated the disc position according to the intermediate zone of the disc relative to the condylar head, as illustrated in Chapter 3, Figure 3.5. Disc positions were classified to normal position, mild, moderate or full anterior displacement. Further classification was performed by dichotomizing the disc positions into 2 groups: Normal (when the disc is normal or mildly displaced) and anteriorly displaced (when the disc is moderately or severely displaced) to allow for comparison to other studies in the literature.

Statistical analysis:

Intra-class Correlation Coefficients (ICC) were computed to evaluate the intra- and inter-examiners' reliability in classifying the disc position on different occasions of the two sets of images. Further, Cohen's Kappa test was performed to determine the level of agreement in the dichotomized classification of the disc position (normal or anteriorly displaced). Landis and Koch[27] interpretation of the ICC and Cohen's Kappa values was employed to determine the level of consistency and agreement of the examiners: ICC: 0-0.2= poor; 0.3-0.4= fair; 0.5-0.6= moderate; 0.7-0.8= strong; >0.8= almost perfect. Kappa coefficient (*k)* ≤ 0= poor, 0.01–.02= slight, 0.21–0.4= fair, 0.41–0.6= moderate, 0.61–0.8= substantial, 0.81–1= almost perfect

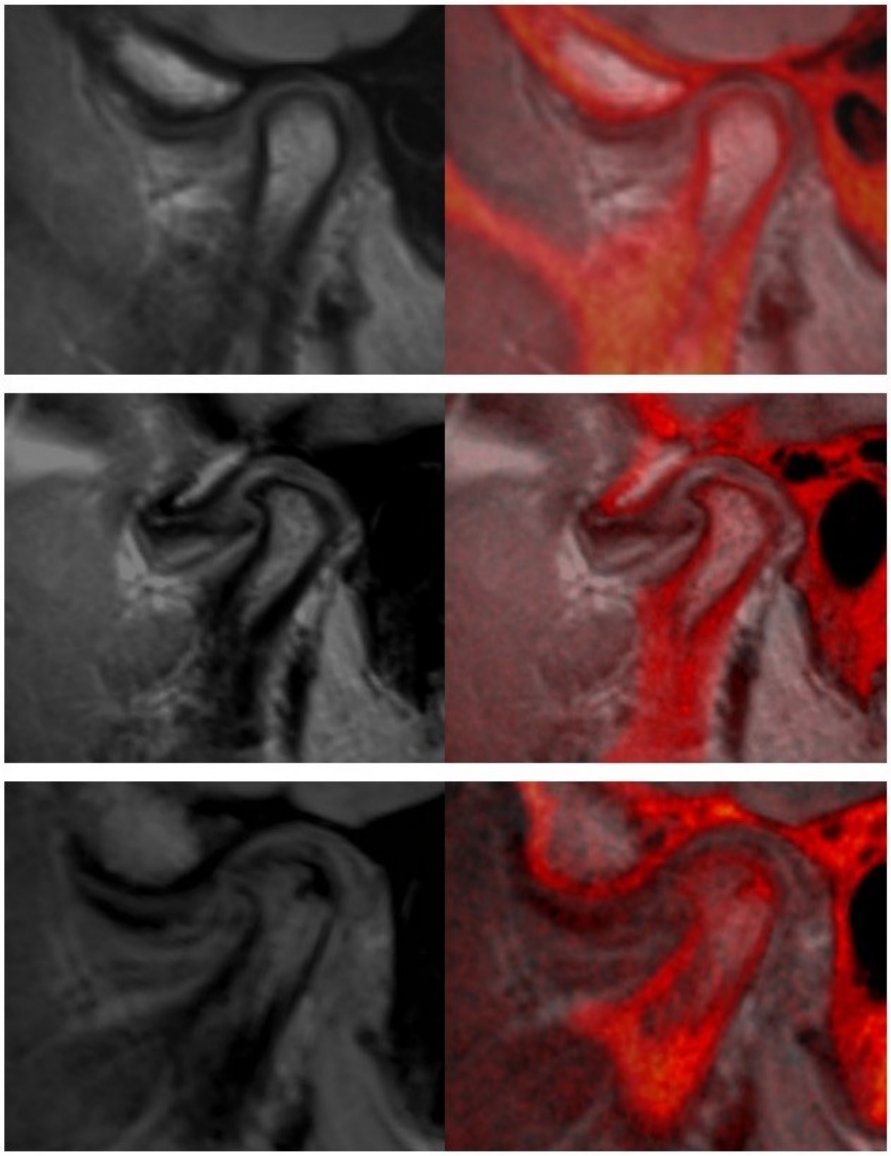

Figure 8.1: Co-registered MRI and low-resolution CBCT. Two corresponding image panels of oblique sagittal PD-weighted MRI (left), and sagittal MRI-CBCT co-registered image sections (right), showing the superimposed noise, marked in red hues, and suboptimal tissue depiction compared to MRI-alone.

8.3 Results:

The classification of articular disc position of the 20 TMJs at T1 and T2 by the two examiners are reported in Tables 8.1 and 8.2. An example of the examined MRI-CBCT co-registered images is presented in Figure 8.1.

In MRI alone, the inter-examiners' reliability was strong at T1 (ICC= 0.72 [0.3-0.89]) and T2 (ICC=0.68 [0.21-0.87]). In MRI-CBCT co-registered images, the inter-examiners' reliability was strong at T1 (ICC= 0.75 [0.39-0.9]) and moderate at T2 (ICC=0.48 [-0.3-0.79]). When disc position classification was dichotomized to normal or anteriorly displaced, the inter-examiner agreement showed substantial agreement at both T1 (k= 0.69) and T2 (k= 0.68) with the MRI alone, and variant agreement with the MRI-CBCT images, substantial at T1 (k= 0.63) and poor at T2 (k= 0.16).

For examiner 1, the intra-examiner reliability was similarly strong with MRI alone (ICC= 0.74 [0.35-0.89]) and with MRI-CBCT co-registered images (ICC=0.71 [0.28-0.88]). After dichotomizing disc position, the intra-examiner agreement was similarly moderate with MRI alone (k= 0.58) and with MRI-CBCT co-registered images (k= 0.62). For examiner 2, the intra-examiner reliability varied from almost perfect (ICC= 0.88 [0.7-0.95]) with MRI alone to moderate (ICC=0.43 [0.4-0.77]) with MRI-CBCT co-registered images. After dichotomizing disc position, the intra-examiner agreement was reduced to substantial (k= 0.79) with MRI alone and poor (k= 0.2) with the MRI-CBCT co-registered images.

<table>
<tr><th colspan="6">Table 8.1: Inter-examiner reliability in the assessment of disc position in MRI alone at baseline (T1) and after 4-8 weeks (T2)</th></tr>
<tr><th colspan="2" rowspan="2">T1</th><th colspan="4">Examiner 2</th></tr>
<tr><td>Normal</td><td>Mild</td><td>Moderate</td><td>Severe</td></tr>
<tr><td rowspan="4">Examiner 1</td><td>Normal</td><td>2</td><td>3</td><td>1</td><td>0</td></tr>
<tr><td>Mild</td><td>4</td><td>1</td><td>1</td><td>0</td></tr>
<tr><td>Moderate</td><td>1</td><td>0</td><td>0</td><td>2</td></tr>
<tr><td>Severe</td><td>0</td><td>0</td><td>4</td><td>1</td></tr>
<tr><th colspan="2" rowspan="2">T2</th><th colspan="4">Examiner 2</th></tr>
<tr><td>Normal</td><td>Mild</td><td>Moderate</td><td>Severe</td></tr>
<tr><td rowspan="4">Examiner 1</td><td>Normal</td><td>1</td><td>4</td><td>0</td><td>0</td></tr>
<tr><td>Mild</td><td>6</td><td>0</td><td>0</td><td>1</td></tr>
<tr><td>Moderate</td><td>1</td><td>0</td><td>1</td><td>2</td></tr>
<tr><td>Severe</td><td>0</td><td>1</td><td>1</td><td>2</td></tr>
<tr><td colspan="6">Examiner 1: Intra-examiner ICC 0.74 [0.35-89]; Kappa 0.58
Examiner 2: Intra-examiner ICC 0.88 [0.70-0.95]; Kappa 0.79

T1: Inter-examiner ICC 0.72 [0.30-0.89]; Kappa 0.69
T2: Inter-examiner ICC 0.68 [0.21-0.87]: Kappa 0.68</td></tr>
</table>

Table 8.2: Inter-examiner reliability in the assessment of disc position in MRI-CBCT registered images at baseline (T1) and after 4-8 weeks (T2)

T1		Examiner 2			
		Normal	*Mild*	*Moderate*	*Severe*
Examiner 1	*Normal*	6	4	1	0
	Mild	3	0	0	0
	Moderate	0	1	0	2
	Severe	0	1	1	1
T2		**Examiner 2**			
		Normal	*Mild*	*Moderate*	*Severe*
Examiner 1	*Normal*	2	1	1	0
	Mild	5	1	3	2
	Moderate	1	0	0	2
	Severe	0	1	0	1

Examiner 1: Intra-examiner ICC 0.71 [0.28-0.88]; Kappa 0.62
Examiner 2: Intra-examiner ICC 0.43 [-0.4-0.77]; Kappa 0.2

T1: Inter-examiner ICC 0.75 [0.39-0.90]; Kappa 0.63
T2: Inter-examiner ICC 0.48 [-0.3-0.79]; Kappa 0.16

8.4 Discussion:

The MRI-CBCT co-registered images provide a corresponding hybrid image of the soft and hard tissues of the TMJ. Multimodality image co-registration is a process that begins by determining the coordinates of each point in the MRI to its corresponding point on CBCT based on the intensities per one voxel.[28] The CBCT is selected as a reference image because it usually has a higher contrast of the depicted anatomical structures compared to the MRI. MRI is defined as a transferred image that is resampled point-by-point to match the geometry of the CBCT.[29,30] Once one common coordinate for the both images is assumed, the images are spatially aligned. The fast initial preliminary images overlap is refined using a joint histogram that is formed by both images intensities.[31] The histogram appears the sharpest when the two images are completely and perfectly aligned. In the case that the CBCT "reference image" has a low resolution or low signal-to-noise ratio, finding a sharp joint histogram and perfect co-registration are not easily attainable. The final fused MRI-CBCT image is displayed with a transparency tool that allows adjustment of the intensity-blending ratio as desired.[29-31]

The MRI-CBCT co-registration was previously demonstrated to be an accurate technique,[24] with an excellent quality resultant diagnostic images (Figure 8.2), which helped to improve the examiners' reliability to assess the TMJ disc position in adults.[25,47] In the present study, consistencies in evaluating disc position among examiners and across time were comparable in both MRI alone and MRI-CBCT co-registered images. The inter-examiner reliability was higher with the MRI alone compared to the MRI-CBCT co-registered images in T1 and T2. The intra-examiners' reliability was equally high with MRI alone as well as the MRI-CBCT co-registered images for examiner 1. However, examiner 2 showed a reduction in reliability from almost perfect with MRI alone to moderate with MRI-CBCT co-registered images. After dichotomizing the classifications of the disc position, the agreement values remained almost the same in both imaging modalities except for examiner 2 with the MRI-CBCT co-registered images. Examiner 2 showed more disagreement in classifying mild vs. moderate disc position with MRI-CBCT co-registered images, consequently reducing the intra-examiner agreement (*k*= 0.2) and the inter-examiner agreement (*k*= 0.16).

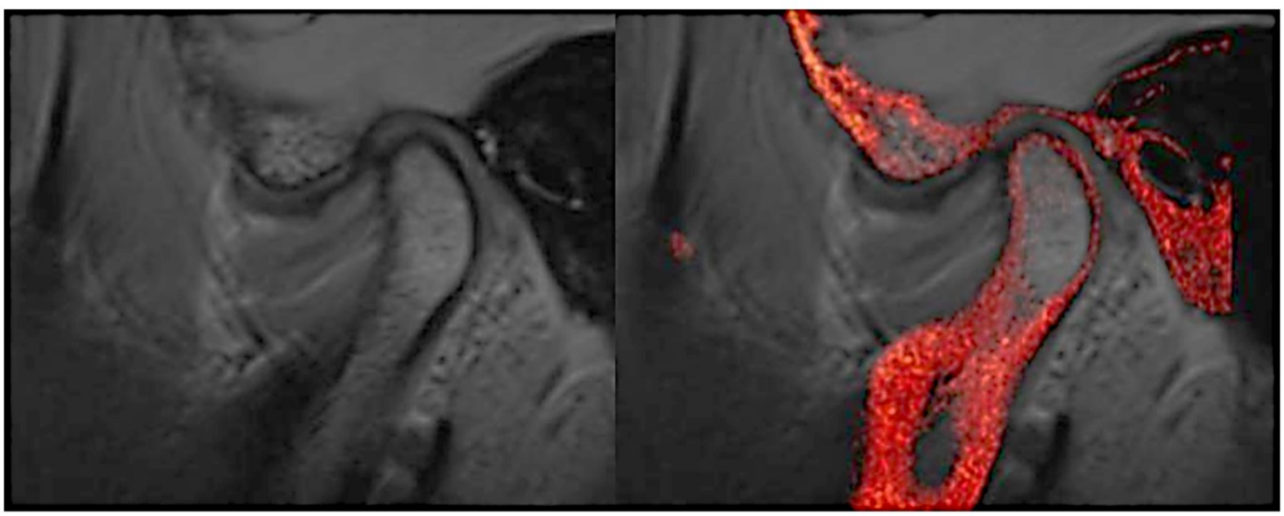

Figure 8.2: Co-registered MRI and high-resolution CBCT. Two corresponding images of oblique sagittal PD-weighted MRI (left), and sagittal MRI-CBCT co-registered image section (right), showing optimized co-registration and improved tissue depiction over MRI-alone.

The examiners' reliability values with the MRI alone, in the present study, were in agreement with the consistency values reported in a previous study (intra-examiner: ICC 0.85-0.91; *k*= 0.52-0.63; inter-examiner: ICC 0.52-0.71; *k*= 0.29-42).[47] However, the consistency values with the MRI-CBCT images, in the present study, were less than the values reported in a previous study (intra-examiner: ICC 0.95-0.97; *k*= 0.91-0.92; inter-examiner: ICC 0.97-0.98; *k*= 0.96).[47] The MRI-CBCT co-registered images seemed to reduce variations in the examiners' subjectivity and introduced a more standardized diagnosis or classification of the disc position.[25,47] However, in the present study, the findings revealed that MRI-CBCT co-registered images did not improve the examiners' reliability. The unimproved examiners' reliability can be attributed to the low signal-to-noise ratio, and occasionally the poor identification of anatomical structures displayed by the overlapped MRI and CBCT co-registered images (Figure 8.1). In this case, the fused images did not help to reduce the inconsistency gap between and within each examiner(s).

In previous studies with co-registered MRI and CBCT images of adult patients, the CBCT protocol used high resolution setting with longer radiation exposure time compared to the lower resolution images obtained for the adolescent patients in the present study.[25,47] In the present study, the CBCT radiation exposure time was 4 seconds with 5 mA, 120 Kvp, and 0.3 mm voxel size, whereas in the previously published studies a longer exposure time 7 seconds was performed with 5 mA, 120 Kvp, and 0.25 mm voxel size.[25,47] The longer exposure time allowed higher resolution of the CBCT images with a high signal-to-noise ratio; and therefore, allowed better alpha-blending intensity between the MRI and CBCT in the finally displayed image (Figure 8.2).

The value of the high-resolution CBCT TMJ images for the adolescents was emphasized in viewing fractured and displaced condyles, trauma and developmental abnormalities.[13] Also, three-dimensional high-resolution CBCT superimposition was found reliable in quantifying delicate surface changes of the TMJ articular surfaces.[32,33] Juvenile idiopathic arthritis (JIA) in adolescents younger than 16 years old was reported to potentially cause facial deformities with associated condylar surface flattening and erosions.[34,35] Junior *et al* found that 83% of the patients with JIA had TMJ osseous alterations detected on a small FOV high-resolution CBCT.[36] Koos *et al* classified the JIA based on the number and severity of the joint osseous alterations using high-resolution CBCT and contrast–enhanced MRI.[37] However, young children do not necessarily have a continuous and compact cortex outline of the TMJ, which making it difficult to detect degenerative changes from low-resolution CBCT images.

Radiation dose optimization has been encouraged by introducing the ALARA principle "as low as reasonably achievable" as a health care measure for patient's protection.[38] Despite the multiple guidelines available, no specific information about the radiation doses recommended for different applications in dentistry.[39-42] A general guideline encouraged reducing the radiation dose levels to as low as diagnostically acceptable "ALADA principle".[43] There is minimal evidence whether reducing the exposure parameters (Kvp, mA or scanning time) will impact the image quality and the diagnostic accuracy.[44] However, low-quality images can be diagnostically unacceptable in the case of subtle degenerative changes of the TMJ osseous surface, especially in children.[45] Yadav *et al* scanned adult dry skulls with 2 acquisition protocols (17 seconds exposure time with 5 mA, 80 Kvp) and (9 seconds exposure time with 5 mA, 80 Kvp) to evaluate the diagnostic accuracy of artificial small (1-2 mm in diameter) and large (1.5-3 mm in diameter) osseous lesions.[45] Their study revealed that the average detection of the small lesions was significantly lower (sensitivity 66%) than for the large lesions (sensitivity 75%).[45] Lennon *et al* reported similar accuracy (sensitivity 98-99%) in detecting artificial periapical lesions (diameter ~1mm) with 9 versus 17 seconds exposure time (4 mA; 90kvp).[46] Similar diagnostic accuracy has been previously reported in two studies evaluating external root resorption (diameter 0.5-1mm) with 9 versus 17 seconds exposure times (3 mA; 90kvp).[47,48]

It was suggested that specific exposure parameters should be modified according to specific diagnostic tasks on specific machines' models.[44] Therefore, the findings and recommendations made by different studies should be limited to the diagnostic tasks and the models of the machines employed in each investigation.[44] Ludlow and Walker recommended that practitioners should customize the acquisition protocols according to the investigated tissues, diagnostic question, clinical factors and patients' age and size.[49] In the present study, the acquisition protocol may be sufficient for orthodontic assessment of craniofacial morphology. However, the low-resolution acquisition protocol used in this adolescent study was insufficient to result in high-quality MRI-CBCT co-registered images.

The present study had several limitations. The present study was intended as a pilot study, therefore the small number of the obtained images and the participating examiners may have reduced the strength of the present study conclusions. The low signal-to-noise ratio of the CBCT images compromised the registration quality and negated the previously demonstrated value of the MRI-CBCT tool in improving examiners' reliability to diagnose disc positions. Conceptually, images of higher exposure parameters but small field of view should be considered when TMJ osseous changes are to be diagnosed and evaluated over time and may prove beneficial for fusion with MRI in adolescents.

5.5 Conclusion:

The MRI-CBCT registered images did not improve the intra- and inter-examiners' reliability among experienced readers to evaluate the TMJ internal disc position in adolescents when compared to MRI alone. The low signal-to-noise ratio of the CBCT images obtained for the adolescents affected the quality of the resultant fused MRI-CBCT image.

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Chapter 9: Morphological and Functional Changes of the Temporomandibular Joint and Stomatognathic System After Transmandibular Surgeries in Oral and Oropharyngeal Cancers: A Systematic Review *

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Preface

This systematic review, which is a part of this thesis, is an original work. In this review, I conceived, prepared the study design and coordination. I ran the electronic search in the library electronic data bases, collected the information, summarized and critically appraised the findings and finally drafted the manuscript. The participating co-authors, Dr. N. Thie (Department of Dentistry) and Dr. S. Armigo-Olivo contributed in the present review by evaluating the included articles. Drs. P. Boulanger, H. Seikaly, J. Wolfaardt and Major were involved in concept formation, manuscript drafting, critical revision of the intellectual content and final approval for manuscript submission.

9. Morphological and Functional Changes of the Temporomandibular Joint and Stomatognathic System After Transmandibular Surgeries in Oral and Oropharyngeal Cancers: A Systematic Review

Abstract

Objective: To critically analyze available evidence regarding the effects of transmandibular surgeries on morphological and functional changes of the TMJ and stomatognathic system. **Data sources:** Electronic search of MEDLINE, EMBASE, EBM reviews, Ovid HealthStar, Scopus, and hand searches. **Inclusion criteria:** Any paper investigating the TMJ morphological changes and/or functional outcomes following transmandibular surgeries. **Results and synthesis methods**: Two hundred seventy-one papers were obtained through the electronic database scan, and 6 papers via hand search. Twelve full papers were initially selected as potentially meeting eligibility for this review; however, only 5 papers finally fulfilled the study inclusion criteria and were analyzed for their methodology. All papers used clinical records and/or patient reports to evaluate TMJ pain, motion, dental occlusion, mouth opening, and deflection during opening as outcome measures. Only 4 papers conducted clinical examination after surgery, with associated patients' interviews and reports. The quality of all included papers was considered poor with high risk of bias according to the RTI item bank quality of assessment. **Conclusion:** Based on the limited available evidence for this systematic review and a high risk of bias of the analyzed papers, no firm conclusions can be established regarding the effects of transmandibular surgery on morphological and functional changes of the TMJ and stomatognathic system.

9.1 Introduction

Oral cavity and oropharyngeal cancers are one of the most common cancers in the head and neck region.[1] Treatment of the upper aero-digestive tract cancers can involve surgical intervention and/or chemo-radiotherapy based on the type and stage of cancer. The mandible is the skeletal frame that supports the muscles of mastication and is important in speech, chewing and swallowing functions. In addition, the mandible is fundamental to the cosmetic appearance of the lower third of the face. Surgical manipulation of the mandible, and particularly the TMJ, during cancer tissue removal has been reported to have implications on mastication, swallowing and cosmetic appearance.[2]

Access to oral cavity and oropharyngeal tumors can be achieved with different surgical approaches, which demonstrate different levels of invasiveness. Trans-oral surgery, has no mandibular involvement, and can be considered the least invasive method when it comes to oral functions.[3] Transmandibular surgery to treat oral cavity and oropharyngeal tumors can be either mandibulotomy (split mandible) to gain an access to tumor tissue, or mandibulectomy (mandibular resection) in the case of osseous tumor involvement. Mandibulotomy was first introduced in 1836 and the oncologic value of the transmandibular approaches has been well established in the surgical literature.[4]

The type and technique of surgical intervention affects mandibular and TMJ functions post-surgery.[5] It has been reported that patients undergoing mandibulotomy or mandibulectomy, have impaired speech and TMJ functions compared to patients who do not.[6] Although mandibulotomy is known to provide suitable access to most regions of the upper aerodigestive tract, some authors believe that its complications outweigh the surgical benefits.[7] Common complications include: plate exposure or failure, soft tissue missing, orocutaneous fistula, mandibular fracture, osteoradionecrosis, and malunion or misaligned bony union. Interruption of mandibular continuity results in functional disturbance and extent of defect varies according to the tumor location, extension, severity, stage, soft and hard tissues involved.[8] Free-flap reconstruction of the mandible provides various degrees of success in rehabilitating oral function, and restoring the lower face contour.[9,10] During the last two decades many treatment options have become available in the area of head and neck surgery. The matter of which surgery or reconstructive technique is providing the best functional and cosmetic treatment outcome has been debated in the literature.[11-14] Changes in the TMJ internal morphology, functions and mandibular movements after transmandibular surgery appear to have been poorly investigated.

The purpose of the present systematic review was to critically and systematically analyze the available literature regarding the effects of different transmandibular surgeries on morphological and functional changes of the TMJ and stomatognathic system. The PICO question was as follows: The purpose of the present systematic review was to critically and systematically analyze the available literature regarding "the effects of different transmandibular surgeries (i.e. mandibulotomy and mandibulectomy) on morphological and functional changes of the TMJ and stomatognathic system in patients with Oral and Oropharyngeal Cancers.

9.2 Materials & Methods

Search strategy

MEDLINE (1948 to June Week 1 2011), EMBASE (1980 to 2011 Week 23), EBM Reviews-Cochrane DSR, ACP Journal Club, and DARE (1980 through 2nd Quarter 2011), Ovid HealthStar (1966 to May 2011) and Scopus (1965 through June 16, 2011) were systematically searched in all languages. Key words used in the search were *mandibulotomy, osteotomy, mandibular osteotomy, mandibular swing, mandibular surgery, oropharyngeal surgery, otorhinolaryngologic surgical procedures, oral surgical procedures, maxillofacial surgery, surgery, oral, temporomandibular joint, TMJ, mandibular condyle, neoplasms, cancer, tumor, malignant, carcinoma, squamous cell, pharynx, oropharynx, oropharyngeal, mouth, oral, palate, parotid, tonsillitis, tongue, cheek, mouth mucosa, gum, gingiva.* Key words were also searched in a selection of both truncated and MESH terms, with the help of librarian who specializes in health sciences databases. Additionally, the literature search was complemented by manually searching the bibliographies of the identified papers.

Criteria for considering papers for this review

Type of study design: Any type of study design (e.g. clinical trials (CTs), cohort studies, case-control studies, cross-sectional studies, prospective and retrospective studies) investigating the functional or morphologic changes of the TMJ after transmandibular surgery (mandibulotomy and mandibulectomy) in patients with oral cavity or oropharyngeal cancers was included. Case reports with fewer than 10 cases; case series, editorial and opinion letters and literature reviews were not included.

Type of participants: Inclusion in this review was restricted to papers with participants meeting the following criteria: a) humans; b) no limitations on age and gender; c) patients with oral and oropharyngeal cancer treated with transmandibular surgeries; d) patients with TMJ trauma or infectious or rheumatic diseases. Neurological problems requiring surgery were not included.

Type of outcome measures: Any morphological, physiological or biomechanical changes of the TMJ and associated structures (degenerative joint disease, disk displacement and perforation, change in condylar position, capsular ligaments, effusion and inflammation) were included. Functional limitations of the stomatognathic system (e.g. trismus, limited mouth movement, loss of mandibular rotations, joint pain, alterations in swallowing and speech) were considered.

Method for considering papers for this review

The published abstracts or titles (in case of unavailable abstracts) that appeared in the database search were screened thoroughly by two independent reviewers (M.A. & N.T). The two reviewers selected papers that appeared to be potentially relevant for full paper evaluation. In case of vague abstracts or disagreement between reviewers' selections, full papers were selected for consideration. Full-text papers were obtained and analyzed by two independent reviewers (M.A. & S.A.) according to the inclusion criteria. Accordingly, each criterion was rated on a yes or no basis. Papers with doubtful criteria underwent re-evaluation by the 2 reviewers (M.A. & S.A.), and if no consensus was reached a third reviewer (N.T.) was involved to reach consensus by discussion.

Critical Appraisal

The final selected papers were involved in a critical appraisal process to determine their risk of bias and methodological quality. Viswanathan and Berkmann[15] developed an RTI (Research Triangle Institute) item bank based on 1,492 questions included in earlier instruments and organized by the quality domains identified by Deeks et al[16] Items were refined through face validity, cognitive, content validity, and inter-rater reliability testing. This process gave rise to 29 items/questions for evaluating the risk of bias and precision of observational studies of interventions or exposures. According to the authors, this RTI item bank could capture most of the domains of this type of research, is easy to use, can be adapted to different designs, and has guidelines for scoring.

Due to the observational nature of the selected papers in the present review, the Deeks et al[16] tool to determine risk of bias was applied. Each study was given a score and graded as low, moderate or high methodological quality/risk of bias based on the number of critical appraisal items met. The cut-off score was determined, based on previous systematic reviews and meta-analyses,[17,18] as follows; 0- 0.40 low quality/high risk of bias, 0.41- 0.70, moderate methodological quality/moderate risk of bias, and 0.71- 1.0 high methodological quality/low risk of bias.

Two reviewers (M.A. & S.A.) independently completed the critical appraisal, and the results were compared. At this stage, kappa and % of agreement was calculated using STATA version 10 (College Station, TX, USA) in order to determine the agreement between the reviewers for grading on article.

OMERACT quality outcome measures

The OMERACT [19] process was adopted in this review to establish the validity of each TMJ-related clinical outcome.

9.3 Results

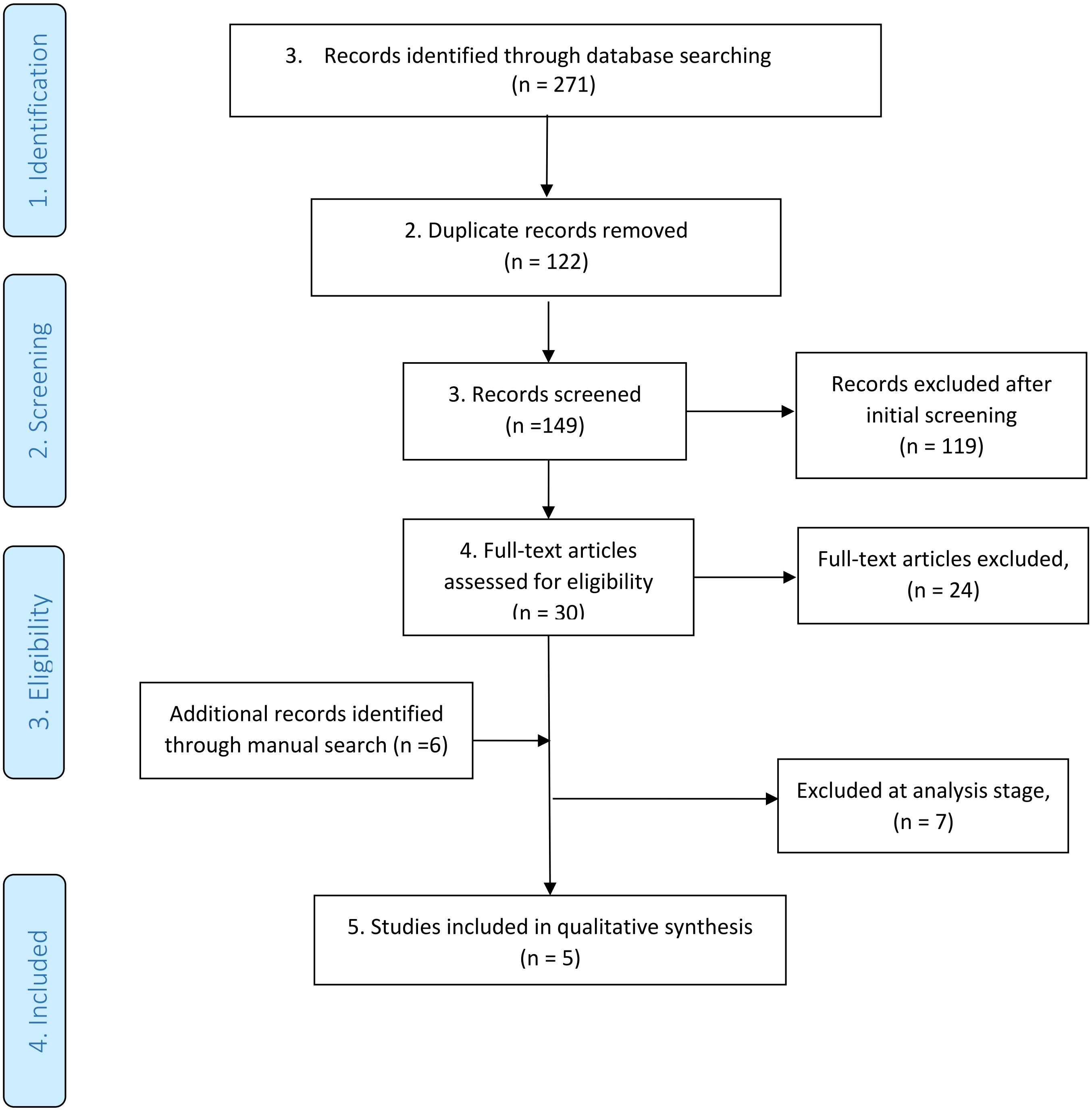
The electronic database search yielded a total of 271 papers. The primary review of titles and abstracts from databases search resulted in 30 potential abstracts/titles that were considered for inclusion. Based on the full-text review of the 30 papers, only 6 papers were selected.[20-25] The papers selection process is presented in Figure 10.1. Six papers were identified by manual search as well.[2,13,14,26-28] Finally, only five papers fulfilled the inclusion criteria of our review.[20-23,26] The other 7 papers were excluded for the following reasons: [2,13,14,24,25,27,28]

3) The TMJ outcome data (e.g. pain, clicking, movement, mouth opening, deflection and deviation) were not provided.[13,14,27,28]

4) The study purpose was to determine the TMJ functional outcome following orthognathic surgical treatment, and did not include any tumor related work.[25]

5) The study did not attempt to measure any TMJ and stomatognathic system functions. [2,24]

Figure 9.1: PRISMA 2009 Flow diagram



Characteristics of included papers

Information on the study patient's demographics, study design, tumor type, surgery type, adjuvant treatment, method and time of data collection of the selected papers are outlined in Table 10.1. The five included papers mainly investigated the TMJ and oral functions outcome following different models of tumor resections.[20-23,26] All selected papers were published between 1990 and 2002 by different authors in different research centers. Included papers consist of cohort patients with different oral cavity and head and neck tumors. Tumor histological types were reported in three papers only.[20,21,23] All papers reported outcome based on clinical records or operative log data, three papers executed clinical examination,[20-22] and three papers undertook patients' interviews.[21,23,26] Gellrich et al[23] and Riddle et al[21] reported the outcomes measures by means of standardized rehabilitation questionnaire. In total, four papers reported post-operative pain impairment including TMJ pain;[20-23] two papers reported limited mouth and TMJ movements due to muscle tenderness;[20,21] four papers evaluated interincisal opening, mouth deflection dental rehabilitation and occlusion;[20-22,26] and three papers reported speech and swallowing impairment, lip sensation, scar formation and cosmetic complaints.[21-23]

TMJ Pain

Christopoulos et al[20]found that the patients who underwent mandibulectomy experienced more TMJ pain than patients who underwent mandibulotomy. Riddle et al[21] reported symptoms of local pain and discomfort after mandibulotomy surgical intervention on a yes and no basis without comparing them to the control group. Only 6% of the evaluated patients reported persistent pain at the mandibulotomy site and 32% patients reported TMJ pain associated with chewing or speaking. Bertrand et al[22] reported the TMJ pain on the basis of frequency of occurrence. TMJ pain was considered as a post-operative complication that affected 30% of the study's patients. A standardized rehabilitation questionnaire also showed oral function impairment is caused by pain before and after surgery and at a 6-month follow-up appointment.[23] Patients with a higher incidence of pain before treatment showed significantly higher oral function impairment during and after treatment. Only 20% of patients reported TMJ impairment due to the painful experience of disease and treatment.

In summary, all of the analyzed papers found that TMJ pain could be identified after the surgical intervention, and gradually subsided with time. Based on one study that compared the mandibulectomy with mandibulotomy results, postoperative TMJ pain was found to be higher in the mandibulectomy group but this difference was not significant.[20]

Masticatory muscle tenderness, TMJ motion, interincisal opening and mouth deflection

Only two papers evaluated the TMJ-related muscular condition of patients after surgery.[20,21] Christopoulos et al[20] reported that 4% of patients were diagnosed with muscular tenderness after mandibulotomy. Riddle et al[21] reported 41% patients had muscular tenderness at least at one site of the temporalis and masseter muscles origins and insertions as a sign of trismus, which resulted in pain and discomfort during TMJ movements.

Four papers objectively measured the TMJ border movements and deflections.[20-22,26] Urken *et al* measured the interincisal opening of two groups of patients who underwent mandibulectomy in comparison to two control groups.[26] The paper detected significant clinical differences between the patients who underwent mandibulectomy and the healthy control groups. Interincisal opening average of the mandibulectomy patients was 29-39 mm, and 47 mm for the controls. Christopoulos *et al* found no significant difference in mouth opening between patients who underwent mandibulotomy (average 40 mm) and patients who underwent mandibulectomy (average 50 mm).[20] Mouth deflection of 3.3 mm and 9.5 mm was detected during mouth opening in patients who underwent mandibulotomy and mandibulectomy respectively. Riddle *et al* reported that 30% patients self reported diminished range of motion on opening the mouth as compared with their preoperative motion.[21] Patients who self-reported diminished opening had an average mouth opening of 41 mm, whereas patients without a sense of decreased range of motion showed an average opening of 44 mm.

Bertrand *et al* classified the TMJ lateral movement and the interincisal distance (ID) into three levels according to the severity of the restriction: Normal: slight difference in lateral motion and ID > 40 mm; Moderate: significant difference in lateral motion and ID > 30 mm; Severe: no lateral motion, ID < 25 mm (pure rotation).[22] Seventy-three percent of patients had severe mouth opening limitation due to postoperative radiotherapy.

Dental occlusion and rehabilitation

Four included papers reported the outcome of the post-operative prosthesis in terms of existence and retention.[20-22,26] Urken *et al* compared the retention of dental prostheses in patients who underwent mandibulectomy with reconstruction versus no reconstruction.[26] Patients were instructed to perform a series of mandibular movements, and the prosthetic stability and retention were evaluated. The authors reported that regardless the surgery type; none of the patients (7 with complete denture and 6 with partial dentures) was able to function with the prosthesis in place. Christopoulos *et al* reported that 48% of patients had a dental prosthesis after surgery. Over 97% of the patients were found to have adequate occlusion, however no information on their functional performance was provided.[20,26] Riddle *et al* reported that 77% of the mandibulotomy patients noticed a shift of their occlusion with their new post-operative prostheses.[21] Bertrand *et al* reported premature contact of teeth on the mandibulotomy side in 3% of patients.[22] At the 6-month recall evaluation, a periodontal infection with a 5 mm deep pocket was detected on teeth adjacent to the osteotomy line in 2 out of 64 cases.

Speech, chewing and swallowing

Three of the included papers reported the functional impairment of speech and swallowing.[20,23,26] Urken *et al* objectively evaluated the speech and swallowing. Patients who underwent mandibulectomy were asked to answer a series of questions.[26] Language pathologists rated patients' speech intelligibility based on a 7-point scale where a score of 7 represented normal speech. Mean score of reconstructed patients was 5.66 (±1.1), whereas the unreconstructed patients score was 4.8 (±1.6). Patients were asked to compare their post-surgical masticatory ability to their memory of the 1-year pre-disease state. Almost all reconstructed patients reported their enjoyment of eating was equal to their pre-disease state. Patients were instructed to bite forcefully against a force transducer to measure the bite force. Reconstructed patients had significantly greater average bite force (18 kg versus 2.3 kg). The chewing stroke was assessed with a video recording of the chewing motion. Reconstructed patients demonstrated a full free range of masticatory movements, whereas unreconstructed patients demonstrated chewing strokes with side-to-side grinding motions. The authors reported no significant differences in detectable abnormalities in the swallowing mechanism between reconstructed and unreconstructed patients.

Christopoulos *et al* compared dysphagia and diet consistency between patients who underwent different surgeries (mandibulotomy & mandibulectomy).[20] They reported that patients who underwent mandibulectomy had more common dysphagia, and 57% of mandibulectomy patients reported having soft diets versus only 43% of mandibulotomy patients. Gellrich *et al* found that the highest impairment reported was in chewing, and swallowing and tongue mobility functions shortly after surgery in all surveyed patients.[23]

Lip sensation, scar formation and cosmetics

Three included papers evaluated lip sensation and cosmetics.[21,22,26] Urken *et al* reported that patients who underwent mandibulectomy without reconstruction downgraded their esthetic ratings due to asymmetry of the lower third of the face.[26] In mandibulotomy cases, Riddle *et al* reported that 45% complained of a tingling sensation and a decrease in sensitivity of the lower lip.[21] Bertrand *et al* reported that 52% had lower lip sensation disturbances, 18% were objectively categorized as nerve injury.[22] Cosmetic complaints were encountered in only 9% of patients, which was related to a “string effect” during cervical extension movements.

9.4 Quality Assessment

The five included papers were assessed and scored following RTI item bank quality assessment guidelines, and the OMERAC quality outcome measurement.[20-23,26] Results of the assessment are reported in Tables 10.2 and 10.3. The agreement between reviewers in scoring the 5 papers with the item bank was 93.5% agreement and a kappa score of 0.88, which are both considered "very good agreement" as per Byrt.[29]

All papers were rated as poor quality/ high risk of bias. Several biases were evident such as selection, information, performance, attrition, and reporting bias among others, in addition to threats to precision.[30] In addition, papers failed to clearly provide details regarding inclusion/exclusion of the population under investigation, which increases the risk of selection bias even more. Three included papers did not have a comparison group and analysis was mainly descriptive with no statistical testing or prior hypotheses.[21-23] Based on the OMERACT assessment the validity, reliability, and feasibility of most of the outcomes measures were considered questionable.

Table 9.1: Sample demographics, study design, tumor type, surgery type, adjuvant treatment, method and timing of data collection of the selected papers.					
	Urken M. et al 1990[36]	**Christopoulos E. et al 1992[20]**	**Riddle S. et al 1997[21]**	**Bertrand J. et al 2000[22]**	**Gellrich N. et al 2002[23]**
Study design	Clinical trial (Prospective)	Retrospective study	Retrospective study	Retrospective study	Retrospective
How information was obtained	•Patient self-reporting. •Clinical examination.	•Clinical records. •Clinical examination.	•Patients self-reporting. •Clinical records. •Clinical examination.	•Clinical records. •Clinical examination.	•Patients self-reporting. •Clinical records.
Population Characteristics Mean age	•Sample size: 35 patients. •Age average G1: 51 years. G2: 52 years. G3: not reported. G4: 30 years.	•Sample size: 84 patients. •Age 61 years.	•Sample size: 93 patients. •Age 63 years.	•Sample size: 64 patients. •Age 48 years.	•Sample size: 1652 patients. •Age 59.5 years.
Tumor type	•Oral cancer (no details).	•Squamous cell carcinoma. •Adenoid cystic carcinoma. •Adenocarcinoma. •Primary bone tumor.	•Squamous cell carcinoma. •Pleomorphic adenoma. •Adenoid cystic carcinoma. •Sarcoma. •Glomus vagale. •Schwanoma.	•5 benign & 59 malignant. (15 tumors in oral cavity, 39 tumors in oropharynx, 2 in hypophrarynx, 5 in paraphraryngeal region)	•Squamous cell carcinoma of oral cavity. (mouth floor 31.7%; tongue 23.8%)
Surgery type	•Mandibulectomy with reconstruction (iliac crest flap). •Mandibulectomy without reconstruction. (hemitongue flab or pictoralis flap).	•Mandibulotomy. •Mandibulectomy.	•Mandibulotomy. (straight-line design).	•Mandibulotomy. (24 straight-line designs & 37 wedge-shaped designs).	•Oral surgery. (no details)

Adjuvant treatment	•Radiotherapy. (9 patients)	•Radiotherapy. (3%-9% of patients)	•Not reported.	•Radiotherapy. (5 pre-operative, 43 post-operative) •Chemotherapy. (2 post-operative)	•Radiotherapy. (362 patients) •Chemotherapy. (53 patients) •Chemo-radiotherapy. (107 patients)
Evaluation time after surgery	•G1: 4 to14 months. •G2: 6 months to 14 years.	•Mandibulotomy: 1 to 120 months, (average 24 months). •Mandibulectomy: •6 -150 months, (average 48 months).	•12 months.	•6 months.	•≥ 6 months.
Drop outs	•Not reported.	•31 patients were missed for the follow up appointment.	•37 died. •23 were unable to reach. •2 pediatric patients were excluded due to mandibular growth influence.	•3 patients were missed for the follow up appointment.	•132 patients (8%) were missed for the clinical examination.
Complications reported	•Soft tissue and neurologic defects (no details).	•Surgical complications (infection, fistula, malunion, nonunion, loss of graft, removal of fixation, and postoperative bleeding)	•Patient self-reporting (local post-operative pain, numbness, discomfort, persistent pain at the mandibulotomy site, trismus, malocclusion and cosmetic appearance).	•Infection of the osteotomy site or nonunion.	•Not reported
Measured outcomes	•Oral competence. •Dental rehabilitation. •Interincisal opening. •Bite force.	•Trismus. •TMJ pain. •Mouth deflection during opening &	•TMJ Pain and motion. •Temporalis & masseter muscle tenderness. •Occlusion.	•TMJ pain. •TMJ motion. •Occlusion. •Periodontal	•Time between symptoms and 1st visit to physician. •Impairment relating to disease symptoms such as

	•Speech. •Mastication. •Deglutition. •Chewing stroke. •Chewing performance. •Well-being. •Length of hospitalization. •Cosmetics.	closing. •Occlusion. •Interincisal opening. •Use of Prosthesis. •Presence of Dysphagia. •Type of diet.	•Interincisal opening. •Lip sensation. •Scar visibility and natural contour.	disease. •Lip sensation. •Cosmetic complaint.	(pain, speech, swallowing, chewing, tongue mobility, mouth opening, mandible mobility, neck-shoulder-arm mobility, taste, smell ability, appearance, physical strength, apatite, breathing, swallowing, dryness of mouth, bad breath, stomach trouble). •Medication. •Physical therapy. •Surgery decision judgment.

Table 9.2: Quality Assessment with RTI (Research Triangle Institute) item bank.

Methods Domain: Category	Item	Urken M. et al 1990[36]	Christopoulos E. et al 1992[20]	Riddle S. et al 1997[21]	Bertrand J. et al 2000[22]	*Gellrich N. et al 2002[23]*
Selection bias/confounding: - Sample definition & selection	1. Is the study design prospective, retrospective, or mixed?	Prospective	Retrospective	Retrospective	Retrospective	*Retrospective*
	2. Are critical inclusion/exclusion criteria clearly stated (does not require the reader to infer)?	Partially	Partially	Partially	Partially	*Yes*
	3. Are the inclusion/exclusion criteria measured using valid and reliable measures?	Cannot determine	Cannot determine	Cannot determine	Cannot determine	*Cannot determine*
	4. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups/arms of the study?	Yes	Yes	NA	NA	*NA*
	5. Was the strategy for recruiting participants into the study the same across study groups/arms of the study?	Cannot determine	Yes	NA	NA	*NA*
	6. Was the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?	Unclear	Unclear	NA	NA	*NA*
Performance bias: - Interventions exposure	7. What is the level of detail in describing the intervention or exposure?	Medium	Medium	Medium	Medium	*Medium/low*
Reporting bias: - Outcomes	8. Are the important outcomes pre-specified by the researchers? Do not consider harms in answering this question unless they should have been pre-specified.	Yes	Yes	Yes	Yes	*Yes*

Selection bias/confounding: - Creation of treatment group	9. Is the selection of the comparison group appropriate, after considering feasibility and ethical considerations?	Cannot determine	Yes	NA	NA	*NA*
	10. Any attempt to balance the allocation between the groups (e.g., through stratification, matching, propensity scores).	No or Cannot determine	No or Cannot determine	NA	NA	*NA*
	11. Did researchers isolate the impact from a concurrent intervention or an unintended exposure that might bias results, e.g., through multivariate analysis, stratification, or subgroup analysis?	No or Don't know: Concurrent intervention or unintended exposure is not described	Yes	No or Don't know: Concurrent intervention or unintended exposure is not described	No or Don't know: Concurrent intervention or unintended exposure is not described	*No or Don't know: Concurrent intervention or unintended exposure is not described*
	12. Did execution of the study vary from the intervention protocol proposed by the investigators and therefore compromise the conclusions of the study?	Cannot determine	Cannot determine	Cannot determine	Cannot determine	*Cannot determine*
Detection bias	Blinding 13. Were the outcome assessors blinded to the intervention or exposure status of participants?	Unclear	Unclear	Unclear	Unclear	*Unclear*
Information bias	Soundness of information 14. Are interventions/exposures assessed using valid and reliable measures, implemented consistently across all study participants?	Unclear	Cannot determine or measurement approach not reported	Cannot determine or measurement approach not reported	Cannot determine or measurement approach not reported	*Cannot determine or measurement approach not reported*
	15. Are outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Cannot determine or measurement approach not reported	Cannot determine or measurement approach not reported	Cannot determine or measurement approach not reported	Cannot determine or measurement approach not reported	*Cannot determine or measurement approach not reported*
Attrition bias:	16. Is the length of follow-up the same	Cannot	Cannot	NA	NA	*Yes/No*

- Follow up	for all groups?	determine	determine			
	17. Is the length of time following the intervention/exposure sufficient to support the evaluation of primary outcomes and harms?	Yes	Cannot determine	Yes	Yes	*Yes*
	18. Did attrition from any group exceed 20% percent?	Cannot determine	Yes	Yes	No	*Cannot determine*
	19.Did attrition differ between groups by more than 20 percent?	Cannot determine	Yes	NA	NA	*NA*
Selection bias/confounding: - Analysis Comparability	20. Does the analysis control for baseline differences between groups?	Insufficient reporting to be able to determine	Insufficient reporting to be able to determine	NA	NA	*NA*
Information bias	21. Are confounding and/or effect modifying variables assessed using valid and reliable measures across all study participants?	Cannot determine or source of measurements not reported	Cannot determine or source of measurements not reported	Cannot determine or source of measurements not reported	Cannot determine or source of measurements not reported	*Cannot determine or source of measurements not reported*
Selection bias /confounding: -Analysis comparability	22. Were the important confounding and effect modifying variables considered in the design and/or analysis (e.g., through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment)?	No: not accounted for or not identified	Yes	No: not accounted for or not identified	No: not accounted for or not identified	*No: not accounted for or not identified*
Attrition bias: -Analysis outcome	23. In cases of high loss to follow-up (or differential loss to follow-up), is the impact assessed (e.g., through sensitivity analysis or other adjustment method)?	Cannot determine	No	No	No	*No*
Reporting bias: - Analysis outcome.	24. Are any important primary outcomes missing from the results?	No	No	NA	No	*No*

Precision: - Analysis outcome.	25. Are the statistical methods used to assess the primary benefit outcomes appropriate to the data?	Partially	Partially	NA	NA	*Partially*
Reporting bias: - Analysis outcome.	26. Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results?	Yes	Yes	Yes	Yes	*Yes*
Precision: - Analysis outcome.	27. Are the statistical methods used to assess the main harm or adverse event outcomes appropriate to the data?	Partially	Partially	NA	NA	*Partially*
Overall believability: Interpretation	28. Are results believable taking study limitations into consideration?	Partially	Partially	Partially	Partially	*Partially*
Reporting bias: - Presentation & reporting	29. Is the source of funding identified?	No	No	No	No	*No*
Number of items fulfilled/ total of items applicable		4/29	9/29	4/18	3/20	*5/22*
Scoring		0.14	0.31	0.22	0.15	*0.23*
Decision		*Poor quality /High risk of bias*	*Poor quality /High risk of bias*	*Poor quality /High risk of bias*	*Poor quality /High risk of bias*	*Poor quality /High risk of bias*

Table 9.3: OMERACT assessment of the clinical outcome measurements for reported data. [19]					
Outcome	**Urken et al 1990**[36]	**Christopoulos et al 1992**[20]	**Riddle et al 1997**[21]	**Bertrand et al 2000**[22]	**Gellrich et al 2002**[23]
TMJ/facial pain	--	Feasible	Feasible	Feasible	Feasible
TMJ motion	--	--	Feasible	Valid & Feasible	Feasible
Trismus	--	Feasible	Feasible	--	--
Interincisal opening	Valid, Reliable & Feasible	Valid, Reliable & Feasible	Valid, Reliable & Feasible	Valid, Reliable & Feasible	Feasible
Mouth deflection	--	Not clear	Feasible	--	--
Dental occlusion	--	Feasible	Feasible	Valid & Feasible	--
Prosthesis and dental rehabilitation	Feasible	Feasible	Feasible	--	--
Periodontal disease	--	--	--	Valid, Reliable & Feasible	--
Bite force	Valid, Reliable & Feasible	--	--	--	--
Speech	Valid, Reliable & Feasible	--	--	--	Feasible
Mastication, swallowing, deglutition	Feasible	Feasible	--	--	Feasible
Lip sensation	--	--	Valid, Reliable & Feasible	Valid, Reliable & Feasible	--
Cosmetic appearance, scar formation	Feasible	--	Valid & Feasible	Feasible	--
Overall well-being & length of hospitalization	Feasible	--	Feasible	--	--
Validity (Truth): "is the measure truthful, does it measure what it intends to measure? Is the result unbiased and relevant?"[19] Reliability (Discrimination): "does the measure discriminate between situations that are of interest?"[19] Feasibility: "Can the measure be applied easily, given constraints of time, money and interpretability?"[19]					

9.5 Discussion

Out of 271 papers that discussed the oral function and cosmetic outcome measures following the head and neck cancers, only five papers met the inclusion criteria and were included in this review.[20-23,26] The found papers were published between the years 1990 to 2002, and this finding highlights the relatively short interest in post-operative functional outcomes.

TMJ Pain and muscular tenderness

Clinicians and researchers should ensure they use a valid, reliable, and responsive pain measure to capture changes after an intervention. In addition, it should allow the clinician to discriminate a variety of pain conditions. Four out of the 5 included papers subjectively evaluated TMJ pain following surgical treatment in terms of questionnaires and on the basis of yes or no answers.[20-23] This approach is unable to discriminate pain severity or frequency. An increase of TMJ pain was noticed after mandibulectomy. This pain might be a result of large tissue resection or instability of the mandibular complex.[20] Oral and oropharyngeal cancer patients experience a different pain perspective than non-cancer patients. It has been suggested that patient's rating of pain was highest at the beginning of the cancerous disease.[23] The psychosocial aspect is considered a strong factor to control pain as well, especially when patients realize that they are likely cured.

TMJ motion, interincisal opening and jaw deflection

All papers included in this review evaluated mandibular movements and deflection during opening and closing following surgeries.[20-23,26] Evaluation of mandibular vertical and border movements by simply measuring interincisal, protrusion and lateral excursion distances in millimeters appears to be a valid, reliable and feasible method based on OMERACT quality assessment. Limitation in mandibular movement in both vertical opening and lateral movements following mandibulectomy was attributed to the scarring and prolonged muscle immobility. [26,27] Unlike mandibulectomy, mandibulotomy was found to have no influence on vertical or excursion movements especially with dentate patients.[20] Bertrand *et al* reported that patients that did not require radiotherapy did not have limited TMJ motion, suggesting that surgery itself was not the direct cause of restricted jaw movement.[22]

Concurrent resection of the tongue, palatal and pharyngeal soft tissues may interfere with the mandibular movements and/or TMJ stability. In spite of the successful microvascular reconstruction, the relative insensibility and weak nature of these tissues can still influence the normal TMJ function. Moreover, post-operative adjuvant therapy (chemo-radiotherapy) further complicates the situation.

It was clear from the included papers that limited jaw movements were detected after mandibulectomy surgery. The decrease of mouth opening and movement limitation was likely attributed to the simultaneous soft tissue resection such as pterygoid muscles, with attendant reconstruction and/or radiation therapy.

Dental occlusion and rehabilitation

Occlusion disturbance after mandibulotomy was attributed to the torque effect of the rigid plate resulting in a slight internal rotation of the mandible segments, which leads to premature contact of teeth.[22] The ability to restore the preoperative occlusion can be easily accomplished using the assistance of advanced visual modeling techniques.[31,32]

Dental implants and implant-borne dentures are common and stable post-operative prosthetic rehabilitation.[26] Post-operative dental rehabilitation may be necessary after changes involving extractions, pulp exposure and mandibular osteotomy. Dental prostheses were found to be stable and retentive based on the amount of oral tissue removed and the reconstruction. Less bone resection is associated with more retentive prostheses. Of the literature reviewed, other than merely descriptive data, there was no objective evaluation performed to evaluate the function of the postoperative prostheses. Therefore, data reported was weak and inconclusive.

Speech and swallowing

Tissue reconstruction after mandibulectomy interferes with patients' masticatory ability when compared to healthy subjects. Successful dental rehabilitation was extrapolated to be responsible for the high level of functional and patient compliance.[26] Changes in swallowing and speech, after mandibulectomy surgery, were not found to be significant in reconstructed as well as unreconstructed patients.[20] The fact that speech and swallowing were mainly determined by the involvement of oral cavity soft-tissues, especially the mobility of the remaining tongue, explained the weak influence of the reconstruction on these functions.[26] Reconstructing the gingival sulcus with skin grafts demonstrated better speech and swallowing functional results.[33]

According to the reviewed papers, post-operative dysfunction is more related to the amount of oral tissue resected in mandibulectomy patients. Reconstructed patients were found to chew and speak slightly better than unreconstructed patients. The more oral tissue that was removed, especially the tongue, the more impaired speech and swallowing functions were reported in the patients assessed.[23,26]

Lip sensation, scar formation and cosmetics

In the reviewed papers, the lip sensation and numbness was found to diminish over time after mandibulotomy surgery. Most of the patients were pleased with their final lip appearance, and reported significant improvement with the physical therapy exercise program after one year of the mandibulotomy surgery. The most accepted cosmetic appearance resulted from the mandibulotomy, however the post-operative decreased lip sensation is still a concern for some patients. Dziegielewski et al[13] examined the impact of the midline mandibulotomy surgery on the lower lip sensation and movements. The authors found that unlike the other incision shapes and sites, the straight midline incision spare the mental and marginal mandibular nerves from any direct damage.

After mandibulectomy, patients suffered from a lack of sensation in the denervated reconstructed areas of the oral cavity. These sensory deficits assist in multiple functional problems such as food trapping, reduced levels of mastication and oral incontinence. Kapur et al[34] evaluated the sensory feedback to muscles by selectively anesthetizing the oral cavity in dentulous subjects. The authors reported that altering sensation in the oral cavity negatively influenced the levels of mastication in the tested patients. Few authors suggested restoring the sensation to the lower lip through sensate cutaneous flaps. However, these proposed techniques were considered preliminary and required further analysis.[35,36] Facial scaring is known to influence patients' self-consciousness toward their appearance and this may consequently affect patients' quality of life. Cancer patients, though, seem to have less concern and anxiety on their appearance compared to cancer-control and post-operative functioning. [13]

Quality of the analyzed papers

The RTI item bank used to evaluate the quality/risk of bias of the analyzed papers was a more recently developed tool to be used for observational studies. Although the authors stated that this tool could be used for many different designs because of its flexibility,[15] many of the items from the item bank were not applicable. Future papers should test the applicability of this item bank in other similar systematic reviews to guide its use and improvement.

The risk of bias of the papers analyzed in this review was high. Lack of information regarding: histological diagnosis, tumor stage, exact location of the lesion surgical treatment applied, psychometric properties of the outcomes measures, control of confounding factors, blinding of outcome measures, rate of dropouts, subjects' comparability and isolation of the effect of the intervention on patients' outcomes are very important methodological factors that were missing in the selected papers. The abovementioned methodological flaws raised serious concern regarding the confidence of the reported outcomes in these papers. Therefore, based on a methodological standpoint, the drawbacks of the analyzed papers make the information inconclusive and limited. However, the reviewed papers opened areas for further research.[21,22,26]

OMERACT assessment and recommendations for future research:

The application of OMERACT principles is an area of work that needs to be seriously considered to establish appropriate clinical outcome measures for head and neck cancer care. OMERACT is the acronym that stands for International Initiative to Improve Outcome Measurement in Rheumatology. In the OMERACT process, an outcome measure is endorsed when it passes the OMERACT filter, which has three component criteria: truth, validity and feasibility. Each of these three criteria represents a question to be answered for the use of the measure in its intended setting on a yes or no basis. Clinical outcome measures approved by OMERACT are suggested for use in Cochrane Systematic Reviews.[19]

Based on the OMERACT assessment, major limitations were identified. Detected limitations and some suggestions for future research are as follows:

1. Ideally, a randomized controlled trial (RCT) would be the best approach since sample size is large enough to be clinically meaningful; individuals are randomly allocated to treatment and follow a standardized protocol. However, it is acknowledged that randomization in the area of surgical care of cancer is unethical.[11,37]
2. TMJ and facial pain were reported based on dichotomous *yes* or *no* answers, and sometimes compared to the pain before treatment. For valid and reliable pain measurement, a numerical scale such as the pain visual analogue scale (VAS) can be applied. An advantage of the pain VAS is its ease of scoring and strong validity and reliability across patient groups. [38,39]
3. Muscle soreness was also evaluated based on patients self-reporting. More objective, valid and reliable measurement of the muscle soreness can be conducted using algometry.[40,41]
4. TMJ lateral and protrusive movements can be simply measured in millimeters to achieve a valid and reliable evaluation. Limited mandibular movement subjective assessment is clearly biased.
5. Subjective evaluation alone for speech and swallowing is inadequate. Swallowing function assessment via modified barium swallows, diet history, weight, and the use of gastrostomy tube leads to the most valid and reliable outcome.[37] Speech intelligibility assessment does not provide a complete indication of the social impact of the reconstructive surgery. An interactional model that includes impact of speech perception should be considered.[42]

6. Subjective reporting of the cosmetic appearance and scar formation by the patients can be overstated or sometimes understated. A universal standardized assessment tool is necessary to avoid any bias and increase the outcome validity and reliability. Two validated objective scar assessment scales have been reported to be employed in observational studies;[37] 1) The Vancouver scar scale (VSS);[43] and 2) the patient and observer scar assessment scale (POSAS).[44]
7. Intra and/or inter-rater reliability of the examiners performing outcomes measures should always be reported in primary research to determine the accuracy of the results.
8. Using standard and valid functional assessment tools to measure the TMJ functional ability such as the RDC/TMD and Jaw Function Disability Scale (FDS) would lead to a better understanding of functional outcomes after head and neck cancer treatment.[45-47]

9.6 Conclusions

Based on the limited available evidence for this systematic review and a high risk of bias of the analyzed papers, no firm conclusions can be established regarding the effects of transmandibular surgery on morphological and functional changes of the TMJ and stomatognathic system. The results of this systematic review demonstrate the need for well-designed prospective research evaluating oral function associated with transmandibular surgery in cancer treatment.

There is a need to establish clinical outcomes measures that are valid, reliable and feasible. The application of the OMERACT principles to clinical outcomes measures in head and neck care was considered valuable for the future. Using MRI and/or CT scan in addition to clinically meaningful outcomes with recognized psychometric properties are suggested to objectively identify these changes after transmandibular surgery.

9.7 References

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Chapter 10: Three-Dimensional Assessment of Temporomandibular Joints Using MRI-CBCT Image Registration *

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Preface

This research project, which is a part of this thesis, is an original work and received research ethics approval from the University of Alberta Research Ethics Board Project #Pro00055827, May 5, 2015.

This project was a collaborative project between the department of Dentistry and the Faculty of Computer Sciences, University of Alberta. I conceived, prepared the study design, executed data acquisition, analysis, and interpretation, and finally drafted the manuscript Drs. Boulanger and Punithakumar (Computer sciences department) helped in the technical part represented in reconstructing the TMJ 3D models and measuring Dice Scores and Hausdorff distances. Drs. Lagravere, Jaremko and Major were involved in concept formation, manuscript drafting, critical revision of the intellectual content and final approval for manuscript submission.

10. Three-Dimensional Assessment of Temporomandibular Joints Using MRI-CBCT Image Registration

Abstract: Purpose: To introduce a new approach to reconstruct a 3D model of the TMJ using magnetic resonance imaging (MRI) and cone-beam computed tomography (CBCT) registered images, and to evaluate the intra-examiner reproducibility values of reconstructing the 3D models of the TMJ. **Methods:** MRI and CBCT images of five patients (10 TMJs) were obtained. Multiple MRIs and CBCT images were registered using a mutual information based algorithm (Mirada© XD software). The articular disc, condylar head and glenoid fossa were segmented at two different occasions, at least one-week apart, by one investigator, and 3D models were reconstructed. Differences between the segmentation at two occasions were automatically measured using the surface contours (*Average Perpendicular Distance*) and the volume overlap (*Dice Similarity Index)* of the 3D models. Descriptive analysis of the changes at 2 occasions, including means and standard deviation (SD) were reported to describe the intra-examiner reproducibility. **Results:** The automatic segmentation of the condyle revealed maximum distance change of 1.9±0.93mm, similarity index of 98% and root mean squared distance of 0.1±0.08mm, and the glenoid fossa revealed maximum distance change of 2±0.52mm, similarity index of 96% and root mean squared distance of 0.2±0.04mm. The manual segmentation of the articular disc revealed maximum distance change of 3.6±0.32mm, similarity index of 80% and root mean squared distance of 0.3±0.1mm. **Conclusion:** The MRI-CBCT registration provides a reliable tool to reconstruct 3D models of the TMJ's soft and hard tissues, allows quantification of the articular disc morphology and position changes with associated differences of the condylar head and glenoid fossa, and facilitates measuring tissue changes over time.

10.1 Introduction

TMJ internal derangement represents abnormal changes of the articular disc position in relation to the mandibular condyle and temporal bone glenoid fossa. The articular disc is a dense fibro-cartilaginous tissue that interposes between the articular surfaces of the TMJ. The articular disc allows smooth movement of the incongruent surfaces of the mandibular condyle, glenoid fossa, and articular eminence. Also, it dissipates the compression forces transmitted during the joint function. The changes in disc position alter the dynamic forces inside the joint, which stimulate an adaptive response that involves altered osseous contour. The association between TMJ internal derangement and changes in joint space and osseous contour has been established in the literature. [1-3]

Adequate diagnosis is essential for correct treatment. In addition to the observer's expertise, clear image information is a substantial factor that leads to correct diagnosis. Image processing has been very active in the past decade, and the recent advancements in 3D volume rendering of human anatomical tissues allowed better visualisation and assessment of the tissues morphology and dynamics. The TMJ articular disc derangement is a 3D problem that is commonly described and diagnosed from two-dimensional (2D) images. In addition, 3D models of the TMJ enable quantitative analysis of tissue changes in all directions. Multiple attempts have been conducted to visualise the TMJ articular disc and osseous structures in 3D using MRI.[4-13] However, differentiation of osseous contours from MRI is often insufficiently clear, especially in the TMJ region.[14]

The TMJ cartilaginous disc is best depicted on MRI and osseous surfaces are best seen in CT. The cone beam CT (CBCT) has a substantial lower radiation dose when compared to helical CT and has become the predominant CT approach in the fields of dentistry, maxillofacial orthognathic surgeries, and TMJ assessment. Fusing MRI and CBCT imaging have been recently introduced to assess TMJ pathology [15]. The MRI and CBCT images are registered in 3D coordinate system first before their final fusion. The fused images provide a desirable complementary image of the articular disc and osseous surfaces in one display image for optimum diagnosis. The registration process to generate MRI-CBCT images has been shown to be accurate and reliable in TMJ internal derangement assessment.[16,17]

In this study, we had two objectives: 1. to describe a new approach to construct a 3D model of the TMJ using MRI-CBCT registered images; and 2. to evaluate the intra-examiner reproducibility values of reconstructing the 3D models of the TMJ.

10.2 Materials and Methods:

Patients:

Five adult patients with no history of TMJ dysfunction, undergoing investigation for possible oral squamous cell carcinoma were recruited from the Division of Otolaryngology Head and Neck Department-University of Alberta. Patients had MRI and CBCT images for assessment of TMJ abnormality before going for surgery. The study was approved by the Human Research Ethics Board at the University of Alberta. Images were obtained at closed mouth with maximum inter-cuspation position using centric occlusion bite stent of polyvinylsiloxane material.

MRI acquisition:

The MR images were obtained in the supine position with a multi-channel 12-element head array coil in 1.5 Tesla scanner (Siemens Syngo MRB17, Erlangen, Germany), without sedation or intravenous contrast administration. Four MRI weighted sequences were obtained: Mouth-closed oblique sagittal Proton Density (PD)-weighted images with small FOV 13X13cm^2, slice thickness 3mm (14 slices per TMJ), inter-slice gap spacing 0.3mm, echo time 11msec and repetition time 1800 msec. Mouth-Closed oblique sagittal T2-weighted spoiled gradient echo 3D sequence was obtained with FOV 14x12cm^2, slice thickness 3mm, echo time 95msec and repetition time 36.3sec and 0.8x0.5x3mm^3 voxel size. Mouth-closed coronal sagittal PD-weighted images was obtained with small FOV 19x9.5 cm^2, slice thickness 2mm (16 slices per TMJ), inter-slice gap 2mm spacing, echo time 14msec and repetition time 1800msec. Mouth-open oblique sagittal PD-weighted images with FOV 12x12cm^2, 3mm slice thickness, 0.3mm inter-slice gap spacing, repetition time 1800msec and echo time 15msec and 0.6x0.5x3.0mm^3 voxel size.

CBCT image acquisition:

CBCT images were acquired for maxilla, mandible and both TMJ condyles. Scans were obtained in 360 degrees of rotation, using *Second Generation* i-CAT scanner (Imaging Sciences International, Hatfield, USA), with Frankfort plane parallel to the floor and proper subject upright positioning. Scan was obtained for medium FOV 16cm wide, 13cm height, voxel size was 0.25mm at 26 seconds' scan time (120KVp, 5mA).

Image-registration using mutual information:

Digital Imaging and Communication in Medicine (DICOM) files of all obtained images were transferred to Mirada® XD software (Mirada Medical, Oxford, UK) to perform multi-modality image registration for the multiple MRI sequences and CBCT data sets. All images were automatically registered to a common 3D Cartesian coordinate system (x, y, z) and fused into a common display (Figure 8.1). The multi-modality image registration process involves a combination of three processes; computation of similarity measure, optimization algorithm, and space transformation (Figure 8.2).

1. Similarity measure:

A rough initial 3D alignment of images is necessary, which can be done automatically by considering similarity of images. Among many similarity measure algorithms, normalized mutual information is considered the most common and reliable algorithm for multi-modal image registration.[18-21]

The grey-level intensity values from MRI and CBCT images do not linearly correspond. Therefore, a similarity measure function that utilize the statistical dependence of the voxels intensities' distribution was used, called "*normalized mutual information*". The normalization process starts with a joint entropy histogram to measure the similarity of intensities' distribution in both images, and the voxels' clusters of MRI and CBCT images are then matched accordingly. The joint histogram appears the sharpest when the two images are completely and perfectly aligned. In the case of images from different modalities, the images' intensities are entirely different, and finding a sharp joint histogram is not easily attainable. As seen in Figure 8.3, the highest attenuating or brightest points on CBCT scan (molar tooth enamel) correspond to a very low signal on MRI.

Mutual information is less subjective to the inherent noise of MRI and CBCT images compared to other common measures such as sum of squared differences. The mutual information based similarity measure is defined as:

$$MI\ (i,j) = \sum_{i=0}^{I_U} \sum_{j=0}^{I_V} p_{ij} \log \ \frac{p_{ij}}{p_i p_j}$$

Where p_{ij} is the joint probability that corresponding to voxels in CBCT (U) and transformed MRI volume (V) have intensities i and j, respectively; p_i is the probability of intensity i appearing in volume U; and p_j is the probability of intensity j appearing in transformed volume V. In other words, mutual information is the amount that the uncertainty in i is reduced when j is known.[18]

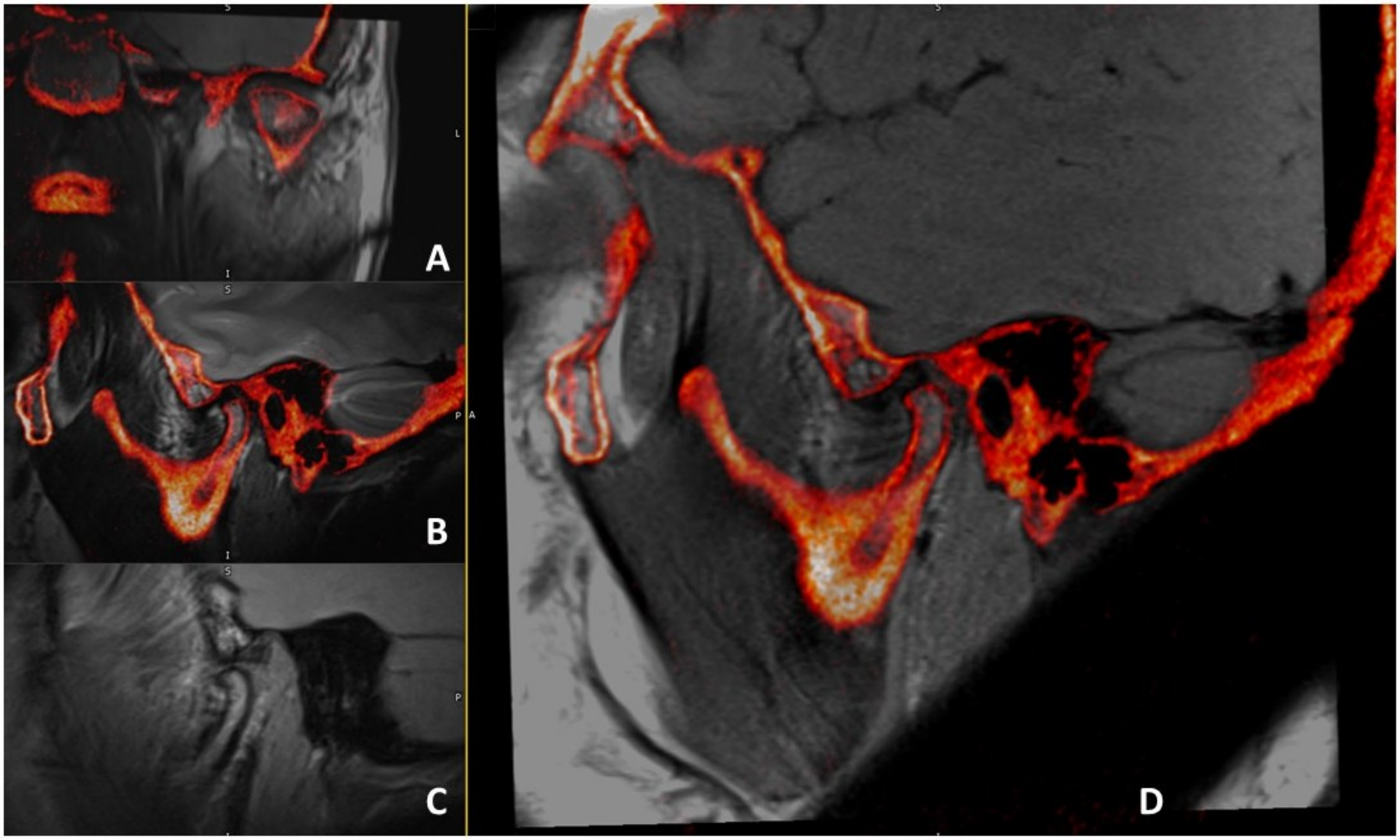

Figure 10.1: Multiple MRI sequences and CBCT images after registration. A: Oblique coronal PD-weighted MRI-CBCT registered image; B: Oblique sagittal T2-weighted MRI-CBCT registered image; C: Open mouth oblique sagittal PD-weighted MRI only. D: Oblique sagittal PD-weighted MRI-CBCT registered image.

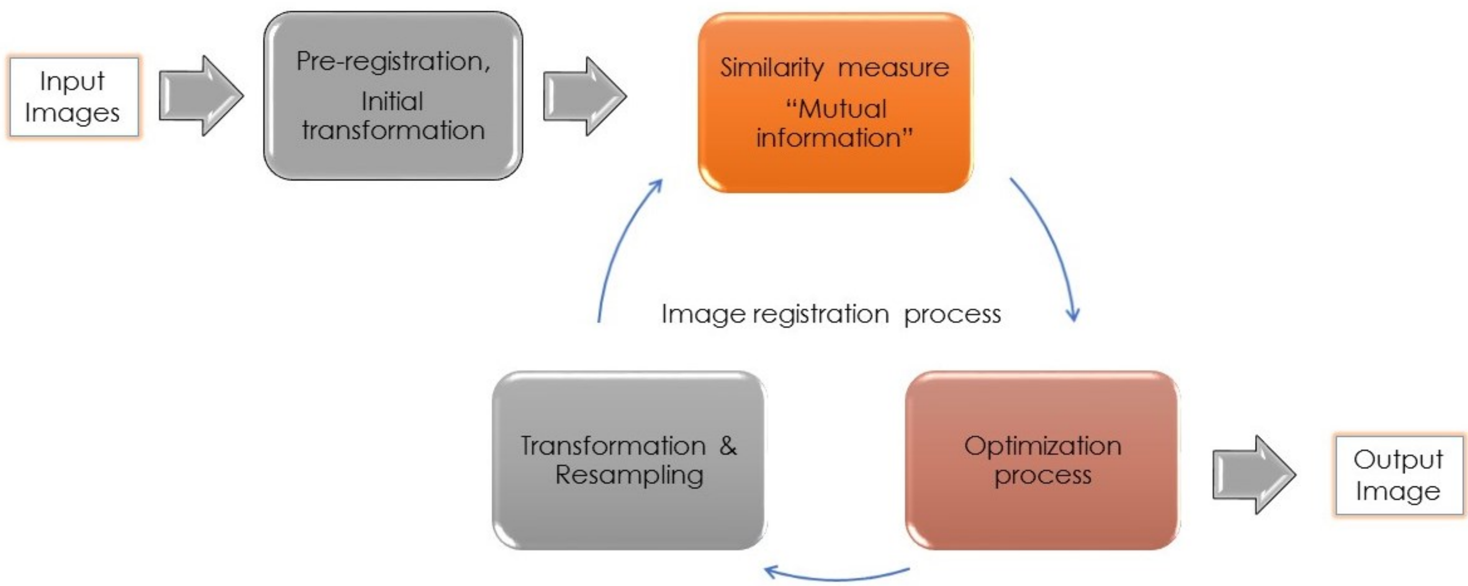

Figure 10.2: The sequence of different automated image processing steps from the set of two input images to the final fused output image.

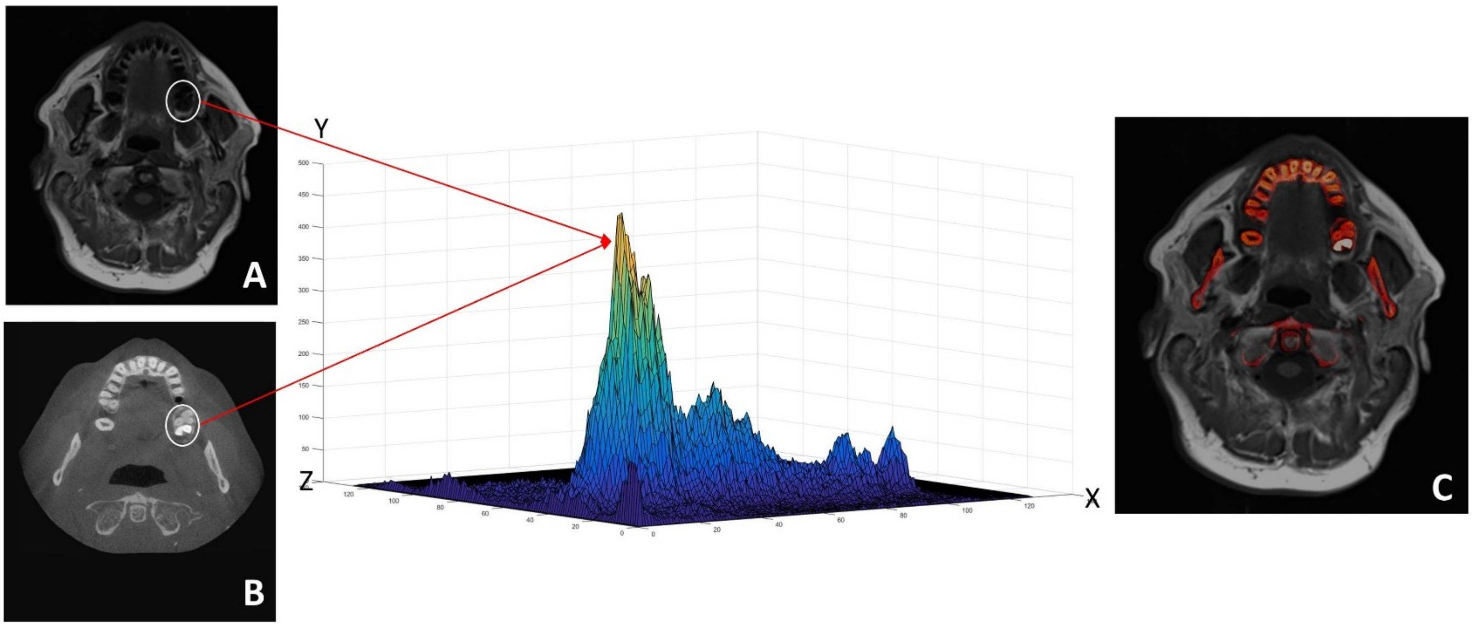

Figure 10.3: An illustration shows a joint histogram of 2 successfully registered multimodal images (A: MRI and B: CBCT) using normalized maximum mutual information approach. The Y-axis in the histogram represents the voxels intensities' distribution from MRI and CT, Z-axis represents the voxels' values of the MRI and X-axis represents the voxel's values of the CBCT image. The radio-opaque (bright) molar tooth in the CBCT has similar intensity distribution to the low intensity (dark) region in the MRI, therefore, voxels from both images were matched and correspond to each other in the histogram. The finally fused registered image using this technique is displayed in figure C.

2. Optimization algorithm.

The optimization process attempts to achieve the transformation that yields the highest similarity between the voxels clusters in the joint entropy histogram (Figure 8.2). This process is more complex in multimodal images since similarity is not easy to define This is an iterative process that optimizes the similarity measure of one criterion at a time, until no criterion or similarity measure is changing any longer. The above mutual information problem can be solved using Powell's conjugate direction method of optimization, which starts with fast rough optimization followed by an accurate slow one.[18,20]

3. Space transformation

Optimization progresses with subsequent image transformation and similarity measure to align two image volumes in a rigid/linear fashion (scale, translation and rotation only). The transformation matrix $\hat{T}$ is obtained using the registration algorithm to reconstruct the original image volumes. A resampling of one image (usually the image with lower spatial resolution to retain the image quality) is required to form the joint image histogram and compute similarity metric. An example of resampling an MRI and CBCT image set is illustrated in Figure 4. During the proposed registration process, the CBCT volume U is considered fixed and the MRI volume V is moving with transformation T. We state the problem of aligning image volumes as the optimization of a similarity measure based on mutual information:

$$\hat{T} = \arg\max_{T} \; MI\ (U, V, T)$$

Where *MI* is the mutual information between volumes U and V after transformation T.

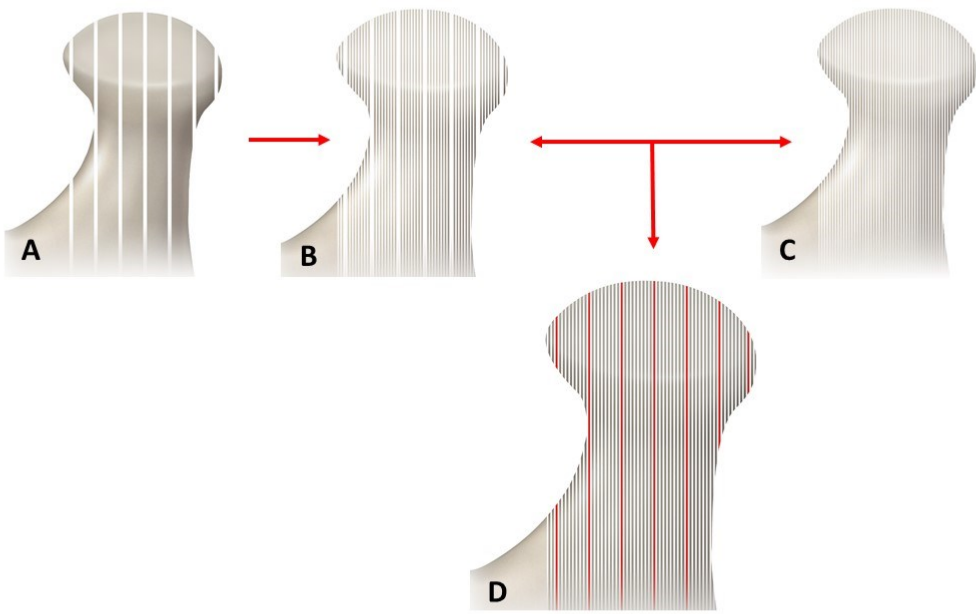

Figure 10.4: This illustration shows lateral (sagittal) view of the TMJ to explain the resampling process of 2 images of the TMJ. A: An MRI for the TMJ with 8 sagittal sections each with 3mm thickness and inter-section gap of 0.3mm. B: Resampled sagittal sections of the MRI to match section thickness of CBCT image. C: CBCT image with 0.3mm of section thickness. D: Merged MRI and CBCT images with similar section thickness. The red lines represent the intersection gap from the MRI that is filled with a repeated adjacent image section. The resampling process allows for the computation of mutual information for MRI and CBCT images with different resolutions.

Segmentation and 3D rendering of the disc, condyle and fossa

Using Mirada® XD software, the gray-value threshold of the condylar head and glenoid fossa on each sagittal section in the entire region of interest (~80 sections, of 0.25mm thickness) was automatically highlighted. The gray-value threshold represents pixel intensity of the osseous structures in the CBCT images from *Second Generation* i-CAT® machine exposure and measured by Mirada®, and roughly ranged between 300-1000 Hounsfield units based on the quality of the scan and the location of the section. By adding or erasing, the outlined structures were manually corrected by the first author to obtain accurate segmentation, and therefore, the process can be considered a semi-automatic segmentation (Figure 5). Once the condylar head and glenoid fossa were finally defined, a cropping box of about $2.5cm^3$ in dimensions was manually drawn to include the condylar head and glenoid fossa the posterior slope of the articular eminence (Figure 6). The pitch, roll and yaw values of the cropping box were saved and used again to crop the same tissues in the second time of segmentation. Finally, the delineated tissues were exported as 3D models in STereoLithography (STL) format using Scan IP software (Simpleware©, Exeter, UK).

The defined osseous structures of the TMJ outlined the joint space in the MRI-CBCT registered image. The first author, a TMJ disorders' specialist with 4 years' experience in TMJ MR diagnostic imaging, manually traced the voxels comprising the articular disc in all sections of the MRI. The manual segmentation took about 15-20 minutes for each disc. The articular disc is depicted by low signal intensity in all PD-weighted and T2-weighted images. The PD-weighted coronal sections were checked for further editing as well. Once the articular disc was finally defined, the 3D model was constructed and saved as STL format (Figure 7-A, B). To compute accurate values for the intra-observer variability, we abstained from applying any smoothing algorithms in generating the 3D segmented surfaces and retained the original user-defined manual contours.

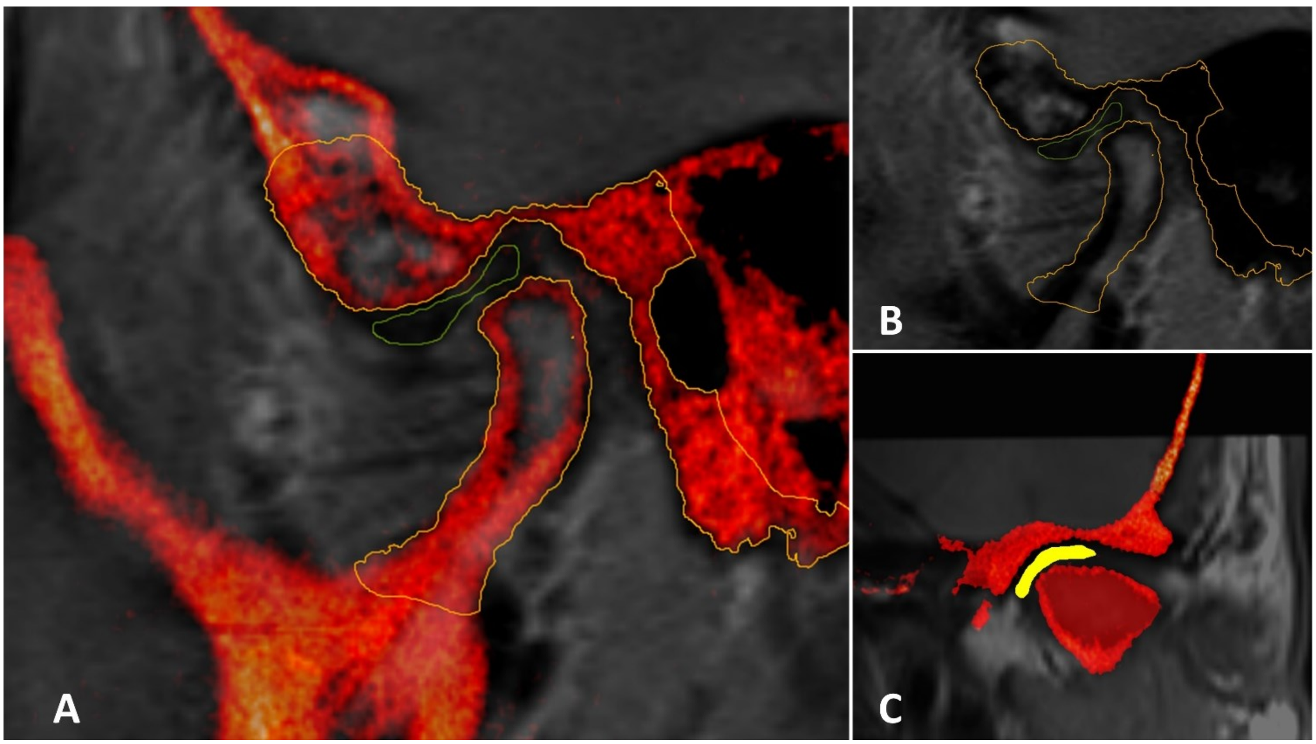

Figure 10.5: A: Oblique sagittal PD-weighted MRI(gray)-CBCT(red) registered image showing outlined/segmented articular disc and condylar head and TMJ structure of the temporal bone. B: Oblique sagittal PD-weighted MRI only showing the outlined/segmented osseous structures from the co-registered CBCT. C: Oblique coronal PD-weighted MRI-CBCT registered image showing the same outlined/segmented structures.

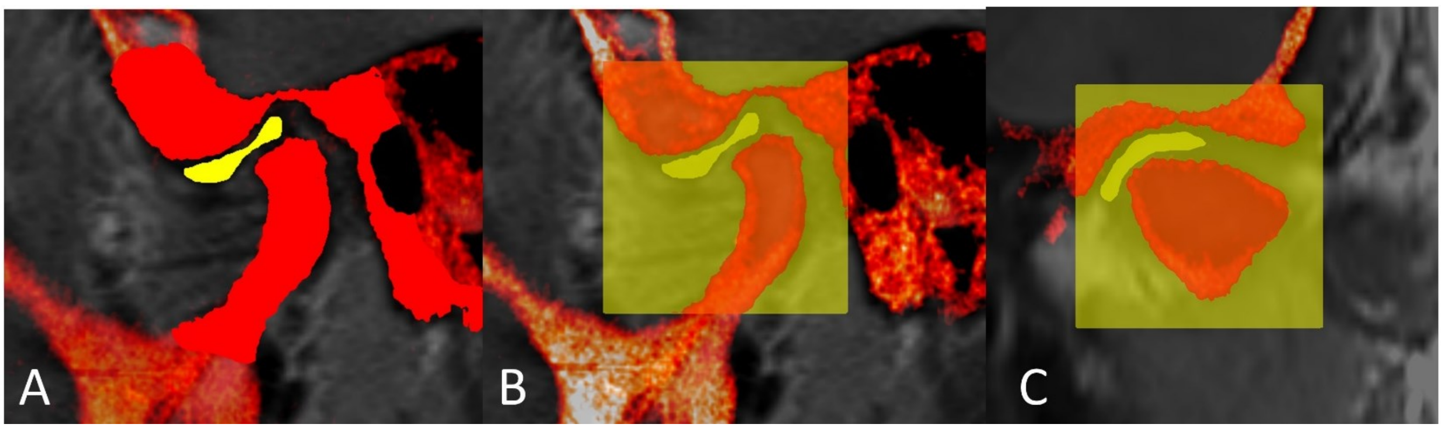

Figure 10.6: MRI(gray)-CBCT(red) registered images. A: Oblique sagittal PD-weighted MRI-CBCT registered image showing outlined/segmented articular disc (yellow) and condylar head and TMJ structure of the temporal bone (bright red). B: A yellow 3D cropping box of about 2.5cm^3 in dimensions was manually drawn to export the cropped TMJ structures only as STL files. C: Oblique coronal PD-weighted MRI-CBCT registered image showing the medio-lateral dimensions of the same cropping box highlighting the cropped TMJ structures.

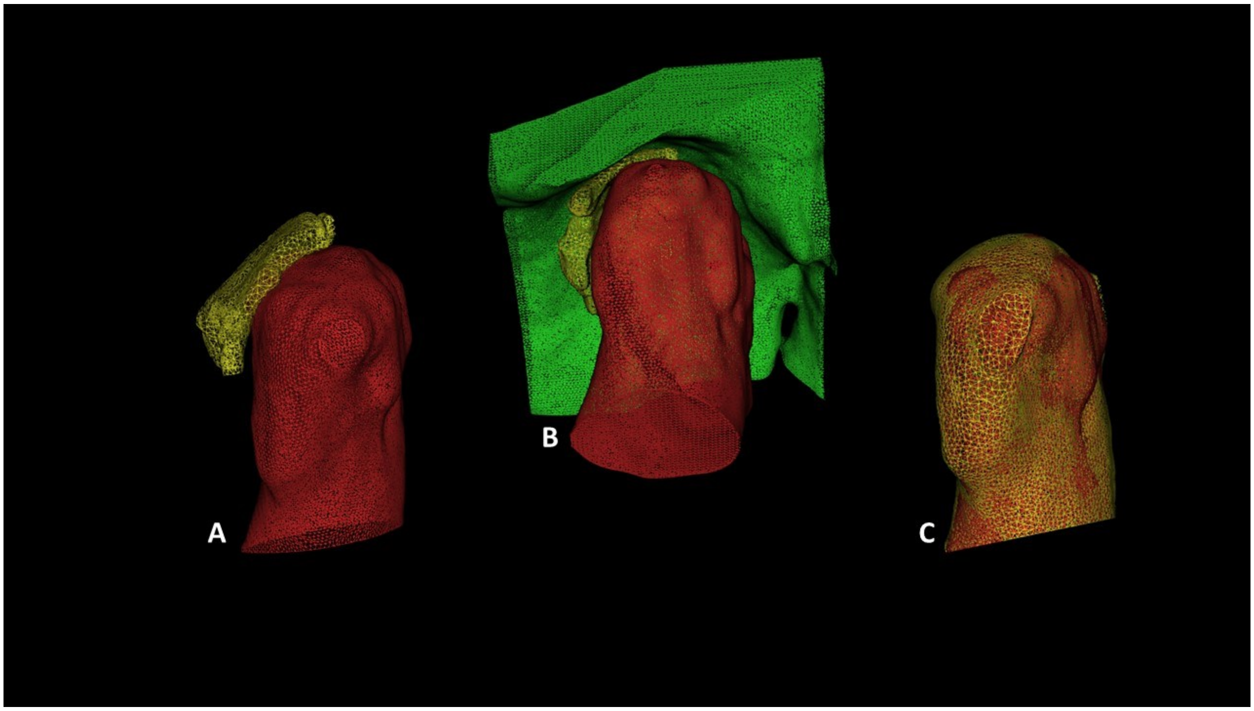

Figure 10.7: This illustration shows lateral (sagittal) view of the TMJ in 3D models rendered using STL files. A: shows the condylar head (red) and the articular disc (yellow). B: shows the condylar head (red); glenoid fossa (green) and articular disc in between the 2 structures (yellow); C: shows overlapped condyles from two trials of segmentation by the same reader.

Reproducibility assessment of tissue segmentation:

The 10 TMJs (articular disc, condyle and glenoid fossa) were segmented at two different occasions, with at least one-week apart, by the same reader to assess intra-examiner reproducibility (Figure 8.5- C). Differences were automatically measured using the *average perpendicular distance* of the models' surface contours and the *volume overlap* (*Dice Similarity Index*).

1. *Average Perpendicular Distance:*

The perpendicular distances between all corresponding surface contour points of the time 1 and time 2 models were measured and the *root mean squared distance (RMSD)* and *maximum distance (MD)* were detected. The higher the value of the *SMD and MD* the greater the mismatch between the 2 models.[22]

2. *Dice Similarity index (DSI):*

The volume overlap of the two models was measured using the DSI defined by:

$$DSI(M_1, M_2) = \frac{2M_1 \cap M_2}{(M_1 + M_2)}$$

Where M_1, M_2 *and* $M_1 \cap M_2$ are the volumes of the time 1 model, time 2 model and the intersection between them, respectively. The *DSI* value is between 0 – 1, where 1 means perfect match.[23]

Statistical analysis:

Descriptive analysis of the changes between the 3D models from 2 occasions, including means and standard deviation (SD) were reported to evaluate the intra-examiner reproducibility in reconstructing the TMJ 3D models.

10.3 Results:

Table 1 shows the descriptive analysis of the measured data. The condyle 3D models showed the lowest change between the 2 times of segmentations (*RMSD* =0.1±0.08; *MD* =1.9 ±0.93 & *DSI* =0.98 ±0.02), followed by the glenoid fossa 3D models (*RMSD* =0.22 ±0.04; *MD* =2 ±0.52 & *DSI* =0.96 ±0.03), then the articular disc (*RMSD* =0.3 ±0.1; *MD* =3.6 ±0.32 & *DSI* =0.80 ±0.1).

Table 10.1: Intra-observer variability in measurement of the surface contour changes and Dice Similarity Index for mandibular condyle, glenoid fossa and articular disc.

	Condyle			***Glenoid fossa***			***Articular disc***		
TMJ	*RMSD (mm)*	*MD (mm)*	*DSI*	*RMSD (mm)*	*MD (mm)*	*DSI*	*RMSD (mm)*	*MD (mm)*	*DSI*
1	0.18	2.92	0.97	0.24	1.42	0.97	0.26	3.92	0.88
2	0.28	0.87	0.94	0.28	1.86	0.93	0.27	2.97	0.89
3	0.1	2.60	0.99	0.19	2.1	0.99	0.36	3.95	0.78
4	0.08	2.36	0.99	0.17	1.9	0.96	0.33	3.84	0.75
5	0.05	1.45	1	0.20	1.81	0.99	0.41	3.81	0.86
6	0.09	2.79	1	0.21	2.27	0.99	0.29	3.5	0.76
7	0.05	1.45	0.93	0.20	1.81	0.97	0.41	3.81	0.80
8	0.09	2.79	1	0.20	2.27	0.99	0.29	3.5	0.73
9	0.09	2.02	0.98	0.28	1.43	0.90	0.23	3.2	0.71
10	0.02	0.15	1	0.27	3.26	0.99	0.29	3.7	0.90
Mean (SD)	0.1 (0.08)	1.9 (0.93)	0.98 (0.02)	0.22 (0.04)	2 (0.52)	0.96 (0.03)	0.3 (0.1)	3.6 (0.32)	0.80 (0.1)

RMSD: Root mean squared distance; MD: Maximum distance; DSI: Dice similarity index.

10.4 Discussion:

MRI has been considered as the standard, non-invasive, diagnostic imaging tool for patients with clinical symptoms of TMJ soft tissues pathology.[24-28] However, TMJ osseous structures are not well depicted in these routine MRI.[14] Since the articular disc position is evaluated according to its relationship with articular condyle and eminence,[24] poor contrast between the articular disc and outlining cortex of the condyle and posterior slope of the eminence make image interpretation a difficult task. Observer variation in detecting disc position in MRI has been cause of concern even among experienced radiologists.[24,29-32] Use of a MRI-CBCT registered image not only allows assessment of the articular disc shape and position, but also allows for analyzing the condyle shape and location. Fused MRI-CBCT image facilitates accurate 3D reconstruction of the articular disc, condylar head and articular eminence, and allows multi-dimensional quantification of the TMJ changes. Here, we explained and demonstrated the reliability of the process of image fusion and 3D reconstruction for TMJ.

Registration of Multiple MRIs:

During function, the normal articular disc interposes between the condylar head and articular eminence and moves antro-posteriorly. Internal disc derangement often includes medio-lateral and rotational displacements beside anterior displacement. The articular disc consists of dense fibrous collagenous connective tissue. It has low signal intensity and appears as void or dark biconcave structure in different MRI sequences. Muscle fibers in the lateral pterygoid muscle and the highly vascular retrodiscal tissues appear with higher signal intensity than the articular disc. Studies in the literature have used multiple MR protocols, include different acquisition planes, weighting sequences, repetition time, echo time and slice thicknesses, to image the TMJ.

The MRI PD-weighted image is considered the best sequence to visualize the TMJ anatomy.[4,5,10,33] Occasionally, the magic-angle phenomenon is encountered where the posterior band of the disc has high signal intensity and is confused with the highly vascularized retrodiscal tissues at the PD-weighted or T1-weighted sequences. Increasing the time of echo, as applied in T2-weighted sequence, exposes the magic angle phenomenon and prevents false-positive diagnosis of shortness in disc length or anterior disc displacement. Additionally, T2-weighted sequences add a clinical value in diagnosing inflammation in TMJ capsule, bone marrow edema and joint effusion around the articular disc.[33,34]

Reducing the slice thickness requires longer scanning time and increases the motion artifact chances. The inter-slice gaps are necessary to prevent the cross-talk artifact and poor signal to noise ratio, however, large gaps result in missing parts of the already small disc. To prevent interferences between MRI slices and reduce cross-talk artifact, inter-slice spacing is placed and to varies from 10-20% of the slice thickness in different imaging protocols. Imaging specifications suitable for routine clinical examination are challenging when used for articular disc 3D reconstruction. In our study, minimal inter-slice thickness was placed 0.3mm (10%) to reduce missing special anatomical information. Only minute deformities may be missed in these images. Registering multiple MRI sequences to CBCT image with unified x,y,z coordinates improves disc morphology visualization,[16] and potentially improves the disc segmentation accuracy and reduce the operator error.

Segmentation and 3D volume rendering of the articular disc:

MRI-CBCT registration as performed here uses routine imaging protocols widely performed in dentistry and TMD clinical practice. The overlapped CBCT image sharply outlined the condyle and articular eminence with clear strong contrast between osseous structure and articular disc in MRI. Attempts to depict the TMJ internal structures in 3D have been reported to better understand the cause and effect relationship between TMJ changes and dysfunction.[4,5,8-13] The 3D imaging quantifies the relationships and describes dynamics between the joint structures. 1992, Price *et al*, made the first attempt to build a TMJ 3D model by digitizing manually-traced sagittal and coronal MRI slices.[9] The tracings were imported as series of projections to form a 3D wireframe and the authors reported range of error between 0.5-3.2mm.[9] Digitizing the manually traced images adds an additional unquantifiable error to the segmentation process. Motoyoshi *et al*. reconstructed the TMJ model from 2D multi-slice T1-weighted MR images, using image processing software (Microsoft Visual Basic).[8] The darkest gray pixels where automatically selected to depict the articular disc. Although manual tracing of 2D slices was avoided in their study, the fully automatic detection of the articular disc in MRI using pixels' value was not clearly explained. Similarly, Smirg *et al*. assumed that the darkest voxels' clusters between the condyle and the glenoid fossa likely belonged to the articular disc, which was automatically segmented without separating the other surrounding tissues.[13] Chirani *et al.* reduced the slice thickness of the MRI to 2mm, which is below clinical standard (3mm), and applied image enhancement filter to minimize the residual noise due to narrow slice thickness.[10] Image enhancement added a potential error factor to the boundaries of the targeted object and may have led to underestimate or overestimate the boundaries of the low intensity articular disc. Hayakawa *et al.* [5] and Kober *et al.* [4] outlined the whole space between the condyle and the glenoid fossa/articular eminence, including the lateral pterygoid muscle from a PD-weighted sequence. The outlined area was processed in color scale to visualize the low intensity articular disc. Mikulka *et al.* introduced automatic technique to segment the articular disc based on edge analysis in addition to the statistical analysis of the region (active contouring).[11,12] The technique extracts the disc region between the condyle and the glenoid fossa, and subdivide it into sub-regions with different mean intensities. Median noise filtering was used, for images with low signal-to-noise ratio and poorly defined edges, to reduce noise without blurring the edges of the assumed disc region. These studies had two major limitations; First, the assumption that the articular disc lies always within the glenoid fossa; Second, dependency on the poorly outlined surrounding osseous structures that have low MRI signal intensity and may have been included in the segmentation process. It was not clear how was it possible for the authors to define the articular disc out of the other surrounding soft tissues, especially when the articular disc can be easily confused with the surrounded tissues such as the lateral pterygoid muscle tendon and the cortex layer of the condyle and articular eminence. The reported automatic techniques require high image quality with sharp resolution and contrast to clearly distinguish the articular disc from the surrounding soft and hard tissues.

The current studies in the literature mainly focus on segmenting the articular disc automatically within a reasonable period of time, and with the least possible level of operator interaction. Automatic segmentation is best applied when a clear difference in intensity between foreground region and background region is detected. In small tissues, such as articular disc that is represented by small number of voxels and lie within surrounding tissues with similar signal intensity at low signal-to-noise ratio MRI, manual or semi-automatic segmentation with experienced operator interaction is likely a more reliable technique to accurately detect the disc. We found manual segmentation was acceptable between attempts by the same operator, with maximum distance change in articular disc of 3.6±0.32mm, similarity index of 80% and root mean squared distance of 0.3±0.1mm. Unfortunately, there is no study in the literature reporting reproducibility or reliability of a manual disc segmentation to be compared with our findings.

Segmentation and 3D volume rendering of the TMJ osseous structures:

All studies in the literature that obtained MRI to visualize TMJ, have utilized less than optimal images to outline and segment osseous structures in 3D.[4,5,8-13] CT and CBCT remain the gold standard for osseous pathology diagnosis especially flattening, osteophyte and increased joint spaces of the TMJ. MRI cannot sufficiently differentiate osseous structures for 3D segmentation due to its inherent limitations (i.e. large slice thickness, inter-slice gaps, cross-talk artifact, and high signal-to-noise ratio). Hayakawa *et al.*[5] and Kober *et al*.[4] segmented the condyle semi-automatically from 3mm slice thickness with 20% inter-slice space, after filtering the condyle contour. The large gap between slices can result in deficient reconstruction of a 3D condyle. In addition, filtering was applied to reduce noise and reconstruction artifacts; however, the resulted blurred edges can lead to overestimated or larger region than the original structure. Smirg *et al.* used the marker-controlled watershed algorithm to outline the condyle, by separate areas with high signal intensity from the surrounding tissues.[13] The algorithm is very sensitive to signal-noise ratio, which renders it unsuitable for the routine TMJ MRI. Schilling *et al.* reported the reliability of superimposing two condylar heads' 3D models reconstructed from two TMJ CBCT images obtained at two occasions.[35] The images had 0.5mm voxels size and were co-registered using a best-match technique. Using semi-automatic segmentation, the authors reported interobserver mean difference ranged between 0.4-0.6mm with excellent reliability (Interclass coefficient >0.75). The reported values were similar to the values in this study (similarity index of 98% and root mean squared distance of 0.1±0.08mm).[35] The difference between the two studies may be attributed to the difference in voxels' size and registration technique. Bone segmentation reliability is more dependent on the intensity threshold that varies by different machines and software, and less dependent on the operator experience and/or judgement.

10.5 Limitations and future recommendations:

1. Patient motion during imaging remains an inherent error source. Patients should be asked to remain immobile during scanning, and heads can be stabilized by being fastened into a special head holder. Occlusal splints in the maximum inter-cuspation position are necessary to guarantee the condylar position in both MRI and CBCT images. Other MRI inherent artifacts such as metallic susceptibility (dental work, vascular clips), chemical shift, aliasing, truncation and pounce point artifact should be considered as well.

2. Although, the MRI-CBCT image registration in open mouth is technically possible, additional open-mouth CBCT images may not be necessary since they don't provide additional diagnostic information. Images were taken in close-mouth position to standardize the measurements of the disc changes.

3. The manual segmentation of the disc by an experienced operator seems to be the most reliable approach, however, it's a tedious process and highly operator dependent. Operator fatigue, low experience and repeatability are all potential error sources.

4. The measured differences in the structures' segmentation were subject to an inevitable software quantization and the choice of points (the software truncates the numerical contour location values to the nearest pixel location) potential errors.

Although the proposed method is, somewhat, time consuming and requires operator interaction, it's the first method that incorporates TMJ structure from two imaging sources. Also it allowed outlining the articular disc from multiple overlapped MRI sequences. The mutual information multimodal image co-registration has substantial potential for further exploration in this field. Further research shall be continued to improve the time factor and the operator dependency.

10.6 Conclusion:

This study presented a new approach to simultaneously visualize the TMJ osseous and soft tissue structures in 3D, from a multiple MRI sequence images that were spatially registered with CBCT image. The MRI-CBCT registration provides a reliable tool to reconstruct 3D models of the TMJ's soft and hard tissues and allows quantification of the articular disc morphology and position changes with associated differences of the condylar head and glenoid fossa. The reconstructed 3D models are quantifiable in terms of volume and x-y-z linear measurements, which facilitate measuring tissue changes over time. The MRI-CBCT image registration has a potential to be used in other research and clinical applications.

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Chapter 11: Three-dimensional Morphological Changes of the Temporomandibular Joint and Functional Effects After Mandibulotomy *

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Preface

This research project, which is a part of this thesis, is an original work and received research ethics approval from the University of Alberta Research Ethics Board Project #Pro00055827, May 5, 2015.

This project was a collaborative project between the department of Dentistry, Department of Otolaryngology Head-Neck Surgery and the Faculty of Computer Sciences, University of Alberta. I conceived, prepared the study design, executed data acquisition, analysis, and interpretation, and finally drafted the manuscript. Drs. Boulanger and Punithakumar (Computer sciences department) helped in the technical part represented in reconstructing the TMJ 3D models and measuring Dice Scores and Hausdorff distances. Drs. Wolffardt and Seikaly helped in conceptualizing the study, patient recruitment and manuscript drafting. Drs. Lagravere, Jaremko and Major were involved in concept formation, manuscript drafting, critical revision of the intellectual content and final approval for manuscript submission.

11. Three-dimensional Morphological Changes of the Temporomandibular Joint and Functional Effects After Mandibulotomy.

Abstract:

Purpose: To prospectively evaluate the temporomandibular joint (TMJ) functional and morphological changes after mandibulotomy using a reconstructed 3D models of the TMJ.

Methods: Sixteen adult patients diagnosed with oral and oropharyngeal tumors with planned surgical mandibulotomy (test group, 9 patients) or transoral (control group, 7 patients) treatments were included in the study. MRI and CBCT images were obtained immediately preceeding surgery and 6-8 weeks after surgery. Using the MRI-CBCT registered images, TMJ tissues were segmented at the two occasions by the same operator and 3D models were reconstructed for morphological assessment. Changes across time were measured using the volume overlap and Hausdorff distance of the disc and condyle 3D models. Disc-condyle relationship was measured using point-based and color map analysis. To assess the early functional changes, the Jaw function limitation scale (*JFLS*) and the maximum mouth opening were measured. Two-sample Hotelling T^2 *t*-test was performed to determine the significance of the morphological and clinical outcomes' differences between the two groups.

Results: The two-sample Hotelling T^2 *t*-test showed significant differences (T^2 (df1,df2)= 0.97 (5,26), $p<0.01$) between the mean values of all outcomes among the 2 groups. The change in disc displacement was significantly different between the two groups ($p<0.05$). However, the condylar displacement was not significantly different between the two groups ($p=0.3$). The average of the *JFLS* score was 5 times larger after mandibulotomy, and was 2 times larger after transoral surgery ($p<0.01$). Patients showed decrease in the average of the maximum interincisal mouth opening by 11mm after mandibulotomy, and by 5.4mm after transoral surgery.

Conclusion: The quantitative assessment of the TMJ showed minimal changes of the condylar position and variable degrees of articular disc displacement associated with the paramedian split mandibulotomy. As well, limited jaw functions and vertical mouth opening were noticed more in the mandibultomy group compared to the transoral group in 6- weeks after surgery.

11.1 Introduction:

The mandible plays an important role supporting the muscles of mastication in executing the stomatognathic functions, involving speech, chewing and swallowing, and in the cosmetic appearance of the lower third of the face.[1] The midline and paramedian mandibulotomy are surgical procedures that divide the mandibular bone into two halves and disconnects the condylar heads of the TMJ from each other. Midline and paramedian mandibulotomy were first introduced in the eighteenth century to gain access to parapharyngeal tumors and the surgical oncologic value of mandibulotomy has been well established in the literature.[2] The same procedure was introduced to manage chronic TMJ dislocation by rotating the condyles separately in an outward direction.[3] Because of the ability to separately rotate the condyle in the glenoid fossa of the temporal bone with midline split mandibulotomy, it was suggested to improve the TMJ stability and transverse discrepancy in orthognathic mandibular advancement surgeries.[4-6]

Squamous cell carcinoma (SCC) of the oropharynx and oral cavity represent approximately 50% of the SCC of the head and neck, which today is the 6th most common malignancy.[7,8] Mandibulotomy remains a common procedure in the management of SCC of the oropharynx and the oral cavity. Midline and paramedian split mandibulotomy provides the widest and most comfortable access to most regions of the aerodigestive tract.

The reported complications of the mandibulotomy include exposure of metal fixation plate, mal-union or non-union defects, oro-cutaneous fistula, malocclusion, tooth loss or mucogingival tissue loss, and lower lip splitting.[9-12] Also, disturbances of the oral functions can result from the interruption of the mandibular continuity and the inevitable associated condylar head dislocation.[13,14] Various modifications have been suggested to avoid or reduce the mandibulotomy's associated post-surgical functional and esthetic morbidities.[14,15] [9-12] The surgical complications versus the procedure's benefits have been debated in the literature.[9-12] In contrast to the thoroughly studied esthetic and tissue healing consequences of mandibulotomy, the post-surgical functional and morphological changes of the TMJ have been poorly investigated and reported in the literature.[14] Forces applied to the TMJ during mandibulotomy may injure the TMJ capsule and/or disc. Internal disc derangement alters force dynamics, which stimulate maladaptive responses, potentially resulting in altered osseous contours and jaw dysfunction.[16,17]

The purpose of this study was to prospectively evaluate the morphological and functional changes of the TMJ after midline split mandibulotomy compared to a minimally invasive transoral surgery, using 3D models of the TMJ reconstructed from fused MR-CBCT images, Jaw Function Limitation Scale (JFLS), and maximum mouth opening.

11.2 Materials and Methods:

Subject recruitment:

All adult patients diagnosed with oral and oropharyngeal malignant tumors with planned surgical mandibulotomy or transoral treatments, at the Division of Otolaryngology Head and Neck Surgery, University of Alberta Hospital, were approached to participate in the study. Exclusion criteria were: history of TMJ trauma, mandibular fracture, jaw pain, TMJ noises, TMJ surgery or chemo-radiotherapy; full dentures, severe systemic co-morbid conditions. Thirty-two subjects met the inclusion criteria and agreed to participate in the study. Patients were divided into 2 groups (n = 16) based on the surgery type: 1. *Mandibulotomy surgery* (test-group); 2. *Transoral surgery* (control-group). The patients who agreed to participate in the study were provided with an informed consent clarifying the nature and purpose of the study following the Human Research Ethics Board at the University of Alberta's policies on research using human subjects (Pro00055827). The TMJ assessment was performed in two forms, *imaging assessment* and *clinical assessment* at 2 occasions, 1-2 weeks before surgery (Time 1) and 6-8 weeks after surgery and just before starting any planned adjuvant chemo-radiotherapy (Time 2).

Imaging protocol:

Patients underwent Magnetic Resonance Imaging (MRI) and Cone Beam Computed Tomography (CBCT) for the TMJ with mouth closed and teeth in maximum intercuspation using occlusal bite stents made of polyvinylsiloxane.[18]

The CBCT scan was acquired with patient in an upright position and Frankfort plane parallel to the floor. Radiation was collimated to avoid the sensitive structures (thyroid and orbits). Scans were performed using the *Second Generation i*-CAT scanner (Imaging Sciences International, Hatfield, USA) at a medium field of view (FOV) setting, 16 cm x 13cm, scan time of 26 seconds, voxel size of 0.25 mm, 120 Kvp and 5 mA. The scan included maxilla, mandible and TMJ condyles.

The MRI scan was performed in a supine position without sedation or intravenous contrast agent administration, using a 1.5 Tesla scanner (Siemens, Munich, Germany) with a multi-channel head array coil. Three MRI sequences were obtained: Mouth-closed oblique sagittal Proton Density-weighted (PD) with a small FOV of 13cm x 13cm, a slice thickness of 3 mm (14 slices per TMJ), an inter-slice gap of 0.3 mm, an TE 11 msec and a TR of 1800 msec. Mouth-closed mouth oblique sagittal T2 spoiled gradient echo 3D sequence was obtained with a FOV of 14 cm x 12 cm, a slice thickness of 3 mm, an TE of 95 msec, a TR of 36.3 sec and a voxel size of 0.8 x 0.5 x 3 mm^3. Mouth-open oblique sagittal PD was also obtained, with a small FOV 12 cm x 12 cm, a slice thickness of 3 mm (14 slices per TMJ), an inter-slice gap of 0.3 mm spacing, an TE of 15 msec, a TR of 1800 msec and a voxel size of 0.6 x 0.5 x 3.0 mm^3.

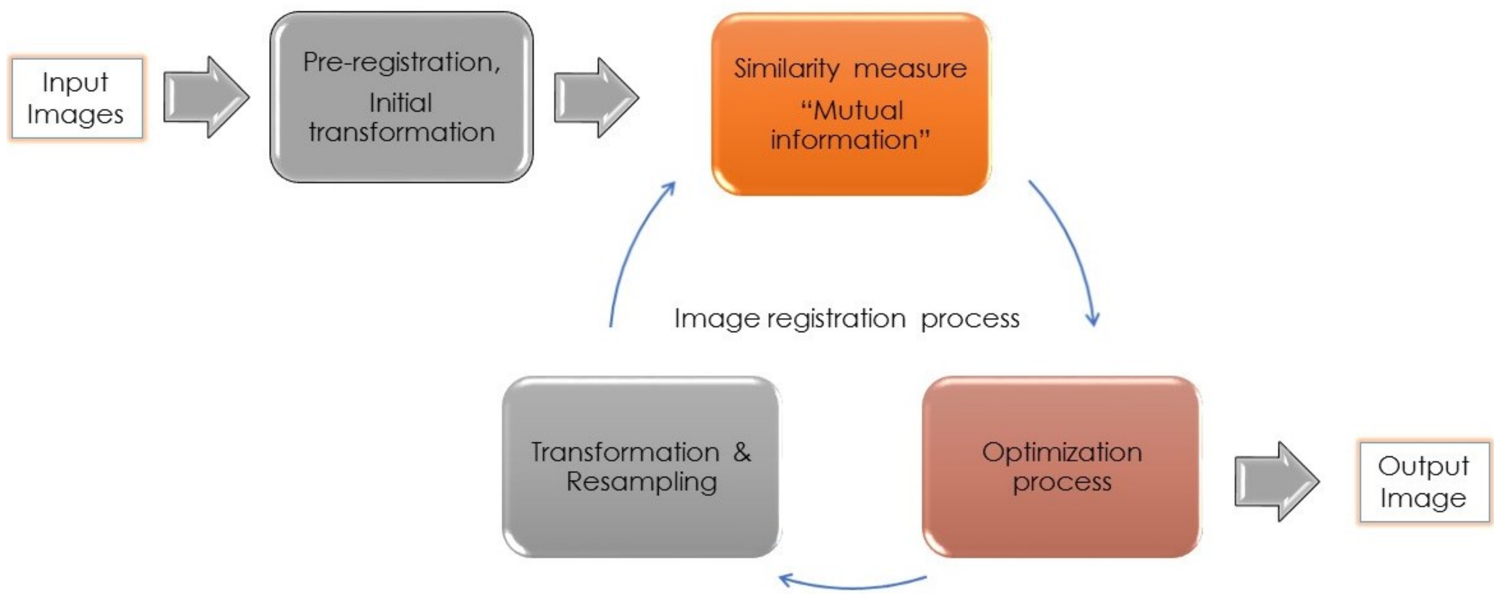

Figure 11.1: The sequence of different automated image processing steps from the set of two input images to the final fused output image. (*Reproduced from Al-Saleh et. al.*[51*] *Three-Dimensional Assessment of Temporomandibular Joint in Using MRI-CBCT Image Registration. 2016-Submitted*).

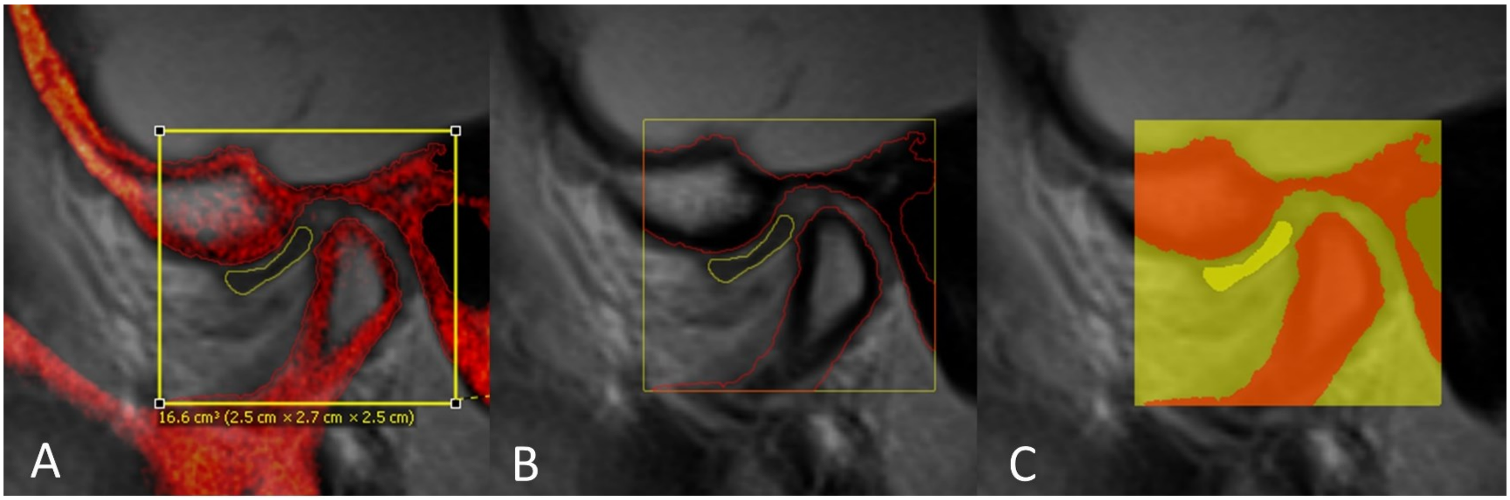

Figure 11.2: Process of segmentation. A: Oblique sagittal PD-weighted MRI(gray)-CBCT(red) registered image showing 3D cropping box (2.5 x 2.7 x 2.5cm^3) that was manually drawn to include TMJ articular disc, condylar head, and temporal components. B: Oblique sagittal PD-weighted MRI only showing the outlined osseous structures (red) and articular disc (yellow) from the co-registered CBCT image. C: Same image as B. with highlighted cropped structures to be exported as STL files.

Imaging assessment of the morphological changes:

The MRI and CBCT images of the TMJs were transferred in the form of Digital Imaging and Communication in Medicine (DICOM) files to Mirada® XD software (Mirada Medical, Oxford, UK) for multi-modality image registration. The multiple MRI sequences of each patient were automatically co-registered with the CBCT image of the same patient. Mutual information rigid image registration algorithm was applied to create common 3D Cartesian coordinate system (x, y, z), for all registered images, which were finally fused into a common display for assessment (Figure 1). Using the fused image, the gray-value threshold representing the pixel intensity of the condylar head and the glenoid fossa in the CBCT image on each sagittal section was automatically highlighted by Mirada® software. The first author, with post-graduate training in TMD/Orofacial Pain and 5 years dedicated experience working with TMJ MRI and CBCT diagnostic imaging, corrected the outlined structures by adding and erasing as necessary to obtain accurate segmentation of the structures. In the MRI part of the fused image, the articular disc is depicted by low signal intensity in the PD-w and T2-w images. The voxels comprising the articular disc were manually segmented by the first author (Figure 2). Finally, the segmented tissues were exported in STereoLithography (STL) format and utilized to reconstruct 3D models of the segmented structures using Scan IP software (Simpleware, Exeter, United Kingdom). The segmentation and 3D models reconstruction have been described previously.[51*]

Changes in condyle, disc, and their relationship, of all joints, from the two occasions were measured and quantified using the 3D model analysis:

1. Changes in the disc from T1 to T2:

Disc changes were measured using two parameters:

A. Dice Similarity Index (DSI):[19] It measures the degree of overlap between 2 bodies or volumes.

$$DSI\ (M_1, M_2) = 2\ M_{1,2} / M_1 + M_2$$

Where M_1, M_2 *and* $M_{1,2}$ are the volumes of Time 1 and Time 2 models and the intersection between them respectively (Figure 3). The *DSI* value is between 0 – 1, where 0 means no overlap between M_1 and M_2 (full disc displacement) and 1 means perfect overlap (no disc displacement).

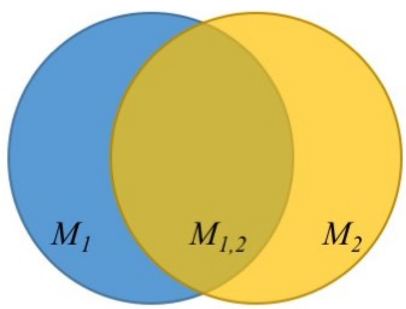

Figure 11.3: *DSI* measures the overlap between M_1 and M_2 contours. *DSI* value of 1 indicates full overlap between M_1 and M_2, DSI value of 0 indicates no overlap between M_1 and M_2.

B. The Hausdorff distance:[20] To quantify the amount of the displacement by measuring the distance between all corresponding surface contour points, in millimeters, at Time 1 and Time 2 (see Figure 4). The *average perpendicular distance or root mean square distance (RMSD)* was reported as a quantification measure of the *Hausdorff distance*. The relationship between the *DSI* and *RMSD* is not always a linear relationship. Small *RMSD* value does not necessarily indicate excellent overlap (low *DSI*) between two bodies or volumes, but can highlight difference in shape.

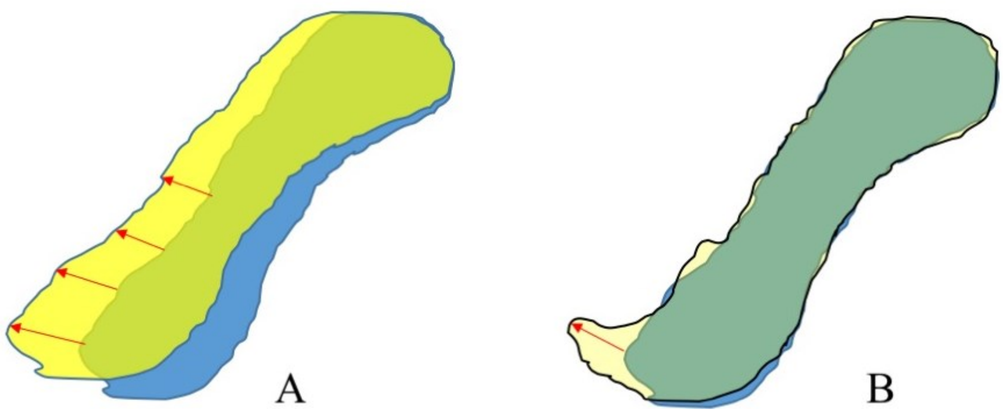

Figure 11.4: Red arrows represents Hausdorff distance. A: Illustrates two overlapped discs with linear relationship between the *DSI* and the *RMSD* (*i.e.* low *DSI* value due to displaced disc and high *RMSD*). B: Illustrates two perfectly overlapped discs with non-linear relationship between the *DSI* and the *RMSD* (*i.e.* high *DSI* value due to excellent disc overlap, but high *RMSD* value).

2. Changes in the condyle from T1 to T2:

Condylar changes were measured using the same two parameters used in measuring the changes in the dis (i.e. *DSI* and *Hausdorff RMSD*).

3. Changes in the disc-condyle relationship from T1 to T2:

To assess changes in *disc-condyle relationship*, point-based analysis was used to produce a color map that quantifies the maximum distance (*MxD*) between the disc and condyle at Time 1 and Time 2. Figures 5-8 illustrated the point-based analysis *MxD* in a color mapping scale.

As well, two radiologists with expertise in TMJ imaging subjectively evaluated the disc position and the osseous condition of the subjects' TMJ before and after surgery. The disc anterior displacement was classified as normal, mild, moderate and severe based on disc position relative to the articulating bony surfaces.[18,21] The osseous condition of the condyle, articular eminence and glenoid fossa were classified as normal, remodeling (surface flattening and subchondral sclerosis) and DJD (surface erosions, subchondral cyst, osteophyte and joint foreign bodies).

Clinical assessment of the functional changes:

The principal investigator clinically examined all patients at Time 1 and Time 2 and measured the maximum interincisal mouth opening using a millimeter-calibrated Boley gauge. Also, patients were asked to answer 10 questions of the Jaw Function Limitation Scale (*JFLS)* to qualitatively evaluate the mandibular movements' limitation on their oral activities.[22] The *JFLS* is a numeric scale from 0= no limitation to 5= extreme limitation. Patients were asked: 'How much does your present jaw problem prevent or limit your daily functions?' Low scores indicated minimum jaw function limitation (Table 1).

Table 11.1: Jaw Function Limitation Scale.[22]
Score from 0= No limitation to 5= Extreme limitation.
How much does your present jaw problem prevent or limit you from….

1	Talking for a long period of time including telephone conversations.
2	Grinding thin foods.
3	Prolonged chewing during meals.
4	Activity at home, school, and/or work.
5	Clenching teeth when participating in sports (contact teeth together during sports).
6	Opening your mouth widely.
7	Yawning.
8	Brushing your back teeth.
9	Falling asleep.
10	Sleeping through the night.

Power, Sample size and Statistical analysis

The sample size and power were calculated based on published outcomes of the *JFLS*, which was used by Olivo et al.[23] to compare TMJ functions between healthy and TMJ dysfunction group.

When f = Sample mean/SD; Sample mean = √(mean – grand mean/ number of groups).

According to Portney and Watkins tables, using α of 0.05 and a power of 0.8, a total minimal number of participants that is required to show a difference between the groups, with an effect size of 0.8 and minimum clinically important difference of 5.4 points (~10%), would be 7 patients in each arm.[23] Gellrich *et al* reported a high dropout rate (50%) in a similar patient group. Therefore, 16 patients were recruited, in each arm, to count for 50% dropout rate.[24]

Statistical analysis:

Two-sample Hotelling T^2 *t*-tests were performed to determine the significance of the morphological and clinical outcomes' differences between the two surgery types.

The correlation between the imaging and clinical outcomes (*RMSD, DSI*, difference in disc *MxD*, difference in *JFLS* and difference in mouth opening) was investigated. Spearman's correlation test ($-1 \geq r \geq 1$) was performed to compare data that are not normally distributed. The correlation strength was described using the following guide: (0-0.3= negligible; 0.31-0.5= low; 0.51-0.7= moderate; 0.7-0.9= high; 0.9-1= very high).[25]

11.3 Results:

Out of 32 patients, only 16 patients (9 patients from mandibulotomy; 7 patients from transoral) were involved in Time 2 assessments and completed the study. The dropout rate was 43% in mandibulotomy group and 56% in transoral group. Details of the patients' demographics, tumor type and stage, and treatment type were summarized in Table 2. The changes in disc and condyle as measured by *DSI* and *RMSD* were reported in Tables 3, 4 and charts 1 and 2. As well, the *disc-condyle* relationship, mouth opening and *JFLS* values at Time 1 and Time 2 were reported in Tables 3 and 4. Figures 5-8 showed 3D models of 4 representative TMJs from the 2 groups illustrating the *condyle-disc relationship* in color mapping scales.

The two-sample Hotelling T^2 *t*-test showed significant differences (T^2 (df1,df2)= 0.97 (5,26), $p < 0.01$) between the mean values of all outcomes among the 2 groups. Pairwise comparisons tests showed significant differences among all outcomes ($p<0.01$) except for 2 outcomes, the condyle's *RMSD* and *DSI*. Mean difference and confidence interval of all outcomes were reported in Table 5.

The average of the maximum mouth opening in the mandibulotomy group before surgery was 51.7 mm and after surgery was 40 mm. For the transoral group, the average of the maximum mouth opening before surgery was 54.5 mm, and after surgery was 49.1 mm. The average of the *JFLS* score in the mandibulotomy group before surgery was 3.3 and after surgery was 16.4. For the transoral group, the average of the *JFLS* score before surgery was 2.1, and after surgery was 4.7.

Spearman's correlation showed significant and high correlations when:

- The condyle's *DSI* decreased, the *RMSD* increased ($r = -0.77$, $p < 0.05$).
- The disc *DSI* decreased, the *MxD* increased ($r = -0.88$, $p < 0.05$), and *JFLS* increased ($r = 0.76$, $p < 0.05$).
- The *JFLS* increased, the mouth opening limitation increased ($r = 0.74$, $p < 0.05$).

Spearman's correlation showed significant and moderate correlations when:

- The disc *RMSD* increased, the *MxD* increased ($r = 0.61$, $p < 0.05$).
- The disc *DSI* decreased, the mouth opening limitation increased ($r = 0.57$, $p < 0.05$).

Table 6 illustrates the pairwise correlations between all outcomes.

In the subjective evaluation of the disc and the osseous structures for the 2 groups the findings were as follows:

- *Before mandibulotomy*: Normal disc= 4 joints; Mild disc displacement= 4 joints; Moderate disc displacement= 4 joints; Severe disc displacement= 6 joints; Normal osseous condition= 3 joints; Osseous surface remodeling= 6 joints; DJD= 9 joints.
- *After mandibulotomy*: 2 joints progressed from mild & moderate to severe disc position, and no changed in the osseous condition was noticed.
- *Before transoral*: Normal disc= 5 joints; Mild disc displacement= 5 joints; Moderate disc displacement= 3 joints; Severe disc displacement= 1 joints; Normal osseous condition= 2 joints; Osseous surface remodeling= 7 joints; DJD= 5 joints.
- *After transoral*: neither disc position nor osseous conditions changed after transoral surgery.

Table 11.2: Details of the patients' demographics, tumor type and stage and treatment type.		
Age & gender	*Tumor type, location (Stage)*	*Tumor resection surgery*
50 years Female	SCC, left tongue and tonsils (T4N2M0)	Mandibulotomy
62 years Male	SCC, base of tongue (T3N2M0)	
67 years Male	SCC, base of tongue and right tonsils (T3N2M0)	
60 years Male	SCC, base of Tongue + right tonsils (T3N1M0)	
67 years Male	SCC, left tonsils (T4N2M0)	
64 years Male	SCC, base of tongue (T3N3M0)	
27 years Female	SCC, left lateral tongue (T3N0M0)	
34 years Female	SCC, left tongue (T3N2M0)	
57 years Male	SCC, left tonsil & left tongue (T3N2M0)	
35 years Female	Adenoid cystic carcinoma, palate and U Lip.	Transoral
33 years Male	Adeno carcinoma, left cheek.	
63 years Male	SCC, right lateral tongue, (T4N0M0)	
55 years Female	Papillomatous lesion in the left tonsils.	
54 years Male	SCC, base of tongue and tonsils. (T3N2M0)	
53 years Male	SCC, left tonsil (T1N2M0)	
61 years Male	SCC, right base of tongue (T2N2M0)	

SCC: Squamous cell carcinoma. The TNM Staging System is based on the extent/size of the tumor (T), the extent of spread to the lymph nodes (N), and the presence of metastasis (M).[26]

<table>
<tr><th colspan="11">Table 11.3: The morphological and functional findings of the mandibulotomy group.</th></tr>
<tr><th rowspan="2">Joint #</th><th colspan="2">Condyle</th><th colspan="2">Disc</th><th colspan="2">Disc-condyle relationship (MxD mm)</th><th colspan="2">Mouth opening (mm)</th><th colspan="2">JFLS</th></tr>
<tr><th>DSI</th><th>RMSD</th><th>DSI</th><th>RMSD</th><th>T1</th><th>T2</th><th>T1</th><th>T2</th><th>T1</th><th>T2</th></tr>
<tr><td>1</td><td>0.82</td><td>0.46</td><td>0.31</td><td>0.91</td><td>3.46</td><td>5.77</td><td rowspan="2">37</td><td rowspan="2">29</td><td rowspan="2">5</td><td rowspan="2">18</td></tr>
<tr><td>2</td><td>0.93</td><td>0.25</td><td>0.39</td><td>0.8</td><td>2.1</td><td>4.2</td></tr>
<tr><td>3</td><td>0.89</td><td>0.8</td><td>0.45</td><td>0.75</td><td>4.9</td><td>7.1</td><td rowspan="2">52</td><td rowspan="2">40</td><td rowspan="2">8</td><td rowspan="2">22</td></tr>
<tr><td>4</td><td>0.59</td><td>1.46</td><td>0.33</td><td>3.65</td><td>2.43</td><td>5.85</td></tr>
<tr><td>5</td><td>0.87</td><td>0.9</td><td>0.27</td><td>1.4</td><td>2.96</td><td>6.5</td><td rowspan="2">55</td><td rowspan="2">42</td><td rowspan="2">0</td><td rowspan="2">26</td></tr>
<tr><td>6</td><td>0.93</td><td>0.43</td><td>0.2</td><td>0.97</td><td>2.3</td><td>5.1</td></tr>
<tr><td>7</td><td>0.62</td><td>1.3</td><td>0.31</td><td>0.95</td><td>5.11</td><td>7.8</td><td rowspan="2">59</td><td rowspan="2">43</td><td rowspan="2">3</td><td rowspan="2">18</td></tr>
<tr><td>8</td><td>0.91</td><td>0.79</td><td>0.1</td><td>4.3</td><td>5.1</td><td>1.2</td></tr>
<tr><td>9</td><td>0.96</td><td>0.32</td><td>0.6</td><td>1.62</td><td>3.1</td><td>4.5</td><td rowspan="2">54</td><td rowspan="2">45</td><td rowspan="2">7</td><td rowspan="2">19</td></tr>
<tr><td>10</td><td>0.94</td><td>0.28</td><td>0.39</td><td>1.16</td><td>2.46</td><td>5.2</td></tr>
<tr><td>11</td><td>0.96</td><td>0.19</td><td>0.33</td><td>1.08</td><td>1.9</td><td>4.3</td><td rowspan="2">56</td><td rowspan="2">44</td><td rowspan="2">2</td><td rowspan="2">9</td></tr>
<tr><td>12</td><td>0.97</td><td>0.15</td><td>0.48</td><td>1.13</td><td>2.2</td><td>4.1</td></tr>
<tr><td>13</td><td>0.96</td><td>0.18</td><td>0.4</td><td>0.92</td><td>3.97</td><td>5.1</td><td rowspan="2">47</td><td rowspan="2">36</td><td rowspan="2">3</td><td rowspan="2">13</td></tr>
<tr><td>14</td><td>0.95</td><td>0.22</td><td>0.23</td><td>1.8</td><td>5.2</td><td>2.1</td></tr>
<tr><td>15</td><td>0.97</td><td>0.41</td><td>0.61</td><td>0.39</td><td>2.31</td><td>3.7</td><td rowspan="2">49</td><td rowspan="2">42</td><td rowspan="2">2</td><td rowspan="2">10</td></tr>
<tr><td>16</td><td>0.9</td><td>0.81</td><td>0.65</td><td>0.43</td><td>2.1</td><td>3.3</td></tr>
<tr><td>17</td><td>0.96</td><td>0.3</td><td>0.31</td><td>0.88</td><td>4.9</td><td>2.2</td><td rowspan="2">57</td><td rowspan="2">47</td><td rowspan="2">0</td><td rowspan="2">13</td></tr>
<tr><td>18</td><td>0.94</td><td>0.43</td><td>0.68</td><td>1.32</td><td>4.69</td><td>5.7</td></tr>
<tr><td>Average</td><td>0.9</td><td>0.5mm</td><td>0.4</td><td>1.4mm</td><td>3.4mm</td><td>4.7mm</td><td>51.7mm</td><td>40.8mm</td><td>3.3</td><td>16.4</td></tr>
<tr><td colspan="5">Average of difference between T1& T2</td><td colspan="2">1.3mm</td><td colspan="2">10.9</td><td colspan="2">13.1</td></tr>
<tr><td colspan="11">DSI= Dice score index; RMSD= Root mean squared distance; JFLS= Jaw function limitation scale.</td></tr>
</table>

Table 11.4: The morphological and functional findings of the transoral group.

Joint #	*Condyle*		*Disc*		*Disc-condyle relationship (MxD mm)*		*Mouth opening*		*JFLS*	
	DSI	*RMSD*	*DSI*	*RMSD*	*T1*	*T2*	*T1*	*T2*	*T1*	*T2*
1	0.91	0.3	0.62	0.36	2.5	3.6	53	48	0	2
2	0.95	0.28	0.58	0.49	2.5	1.5				
3	0.89	0.59	0.75	1.7	2.9	3.8	59	53	4	3
4	0.91	0.37	0.63	1.1	4	5.3				
5	0.96	0.28	0.76	0.42	5.1	6.05	56	49	5	7
6	0.86	0.62	0.57	0.81	3.3	4.3				
7	0.95	0.23	0.92	0.55	1.59	2.01	49	48	4	8
8	0.91	0.25	0.33	0.79	2.11	3.8				
9	0.97	0.21	0.86	0.27	1.88	2.5	53	49	0	4
10	0.83	0.37	0.49	0.57	1.47	3				
11	0.97	0.19	0.88	0.22	2.71	3.5	57	48	0	3
12	0.89	0.29	0.78	0.32	2.52	3				
13	0.87	0.51	0.52	0.83	3.04	3.8	55	49	2	6
14	0.98	0.22	0.67	0.38	2.16	0.3				
Average	*0.9*	*0.3mm*	*0.7*	*0.6mm*	*2.7mm*	*3.3mm*	*54.5mm*	*49.1mm*	*2.1*	*4.7*
***Average** of difference between T1& T2*					*0.6mm*		*5.4mm*		*2.6*	

DSI= Dice score index; RMSD= Root mean squared distance; JFLS= Jaw function limitation scale.

Table 11.5: The effect of the surgery type on the imaging and the clinical outcomes. Mean differences were of the outcomes were evaluated a two-sample Hotelling T^2 *t*-test. Pairwise comparisons between the outcomes were as follows: *Significance = p < 0.05.*

Outcomes		Mean difference	Std. Error	Significance	95% Confidence interval for difference	
					Lower bound	Upper bound
Condyle	*DSI*	0.03	0.03	0.25	-0.10*	0.02
	RMSD (mm)	0.21	0.10	0.05	0.00	0.43
Disc	*DSI*	- 0.26	0.05	<0.01	-0.38*	-0.14*
	RMSD (mm)	0.70	0.28	0.02	0.11	1.29
Disc-condyle relationship (MxD mm)		1.25	0.25	<0.01	0.73	1.78
Mouth opening (mm)		5.00	0.98	<0.01	2.99	7.00
JFLS		9.00	1.69	<0.01	5.54	12.45

** = Transoral surgery values were larger than the mandibulotomy surgery values, hence the negative sign.*

Table 11.6: Spearman's (r) correlation between the different outcomes of both groups.							
		Condyle		*Disc*		*Disc-condyle relationship (MxD)*	*Mouth opening*
		DSI	*RMSD*	*DSI*	*RMSD*		
Condyle	*DSI*						
	RMSD	-0.77*					
Disc	*DSI*	0.31	-0.26				
	RMSD	-0.26	0.31	-0.59*			
Disc-condyle relationship (MxD)		-0.18	0.26	-0.88*	0.61*		
Mouth opening		-0.09	0.25	-0.61*	0.57*	0.67*	
JFLS		-0.18	0.37*	-0.70*	0.49*	0.76*	0.74*
(=p <0.05). 0-0.3=negligible; 0.31-0.5= low; 0.51-0.7=moderate; 0.7-0.9= high; 0.9-1=very high. P.S. negative value indicates negative correlation.*							

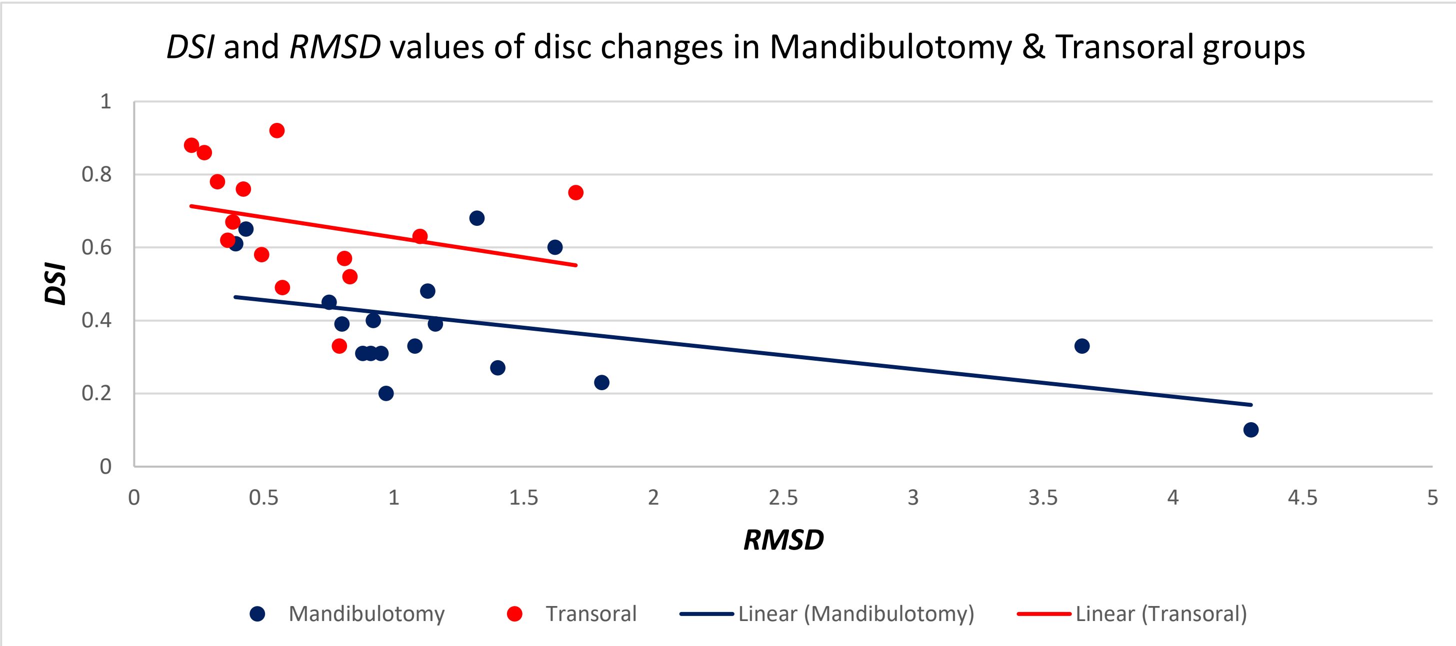

Chart 1: A chart illustrates the values of the *DSI* (Y-axis) and the *RMSD* (X-axis) for disc in mandibulotomy and transoral groups.

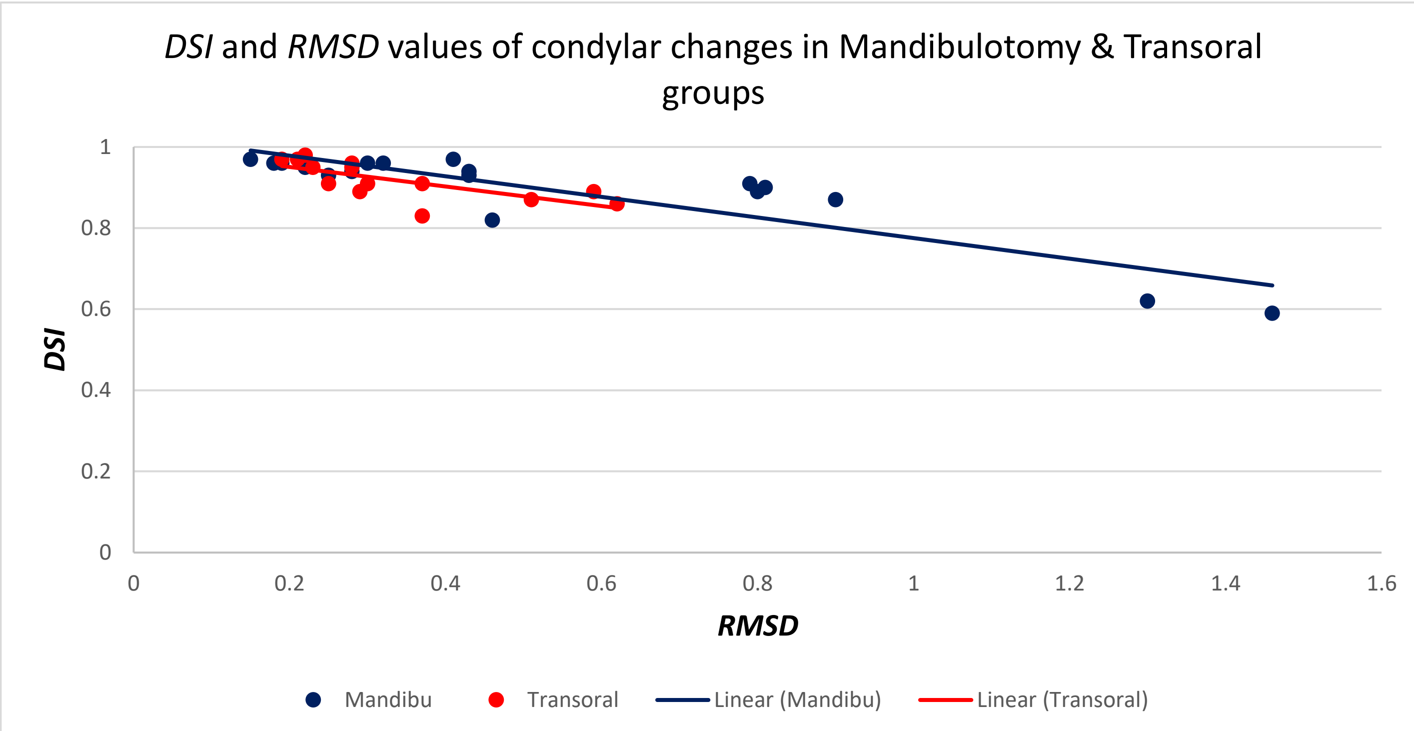

Chart 2: A chart illustrates the values of the *DSI* (Y-axis) and the *RMSD* (X-axis) for condyle in mandibulotomy and transoral groups.

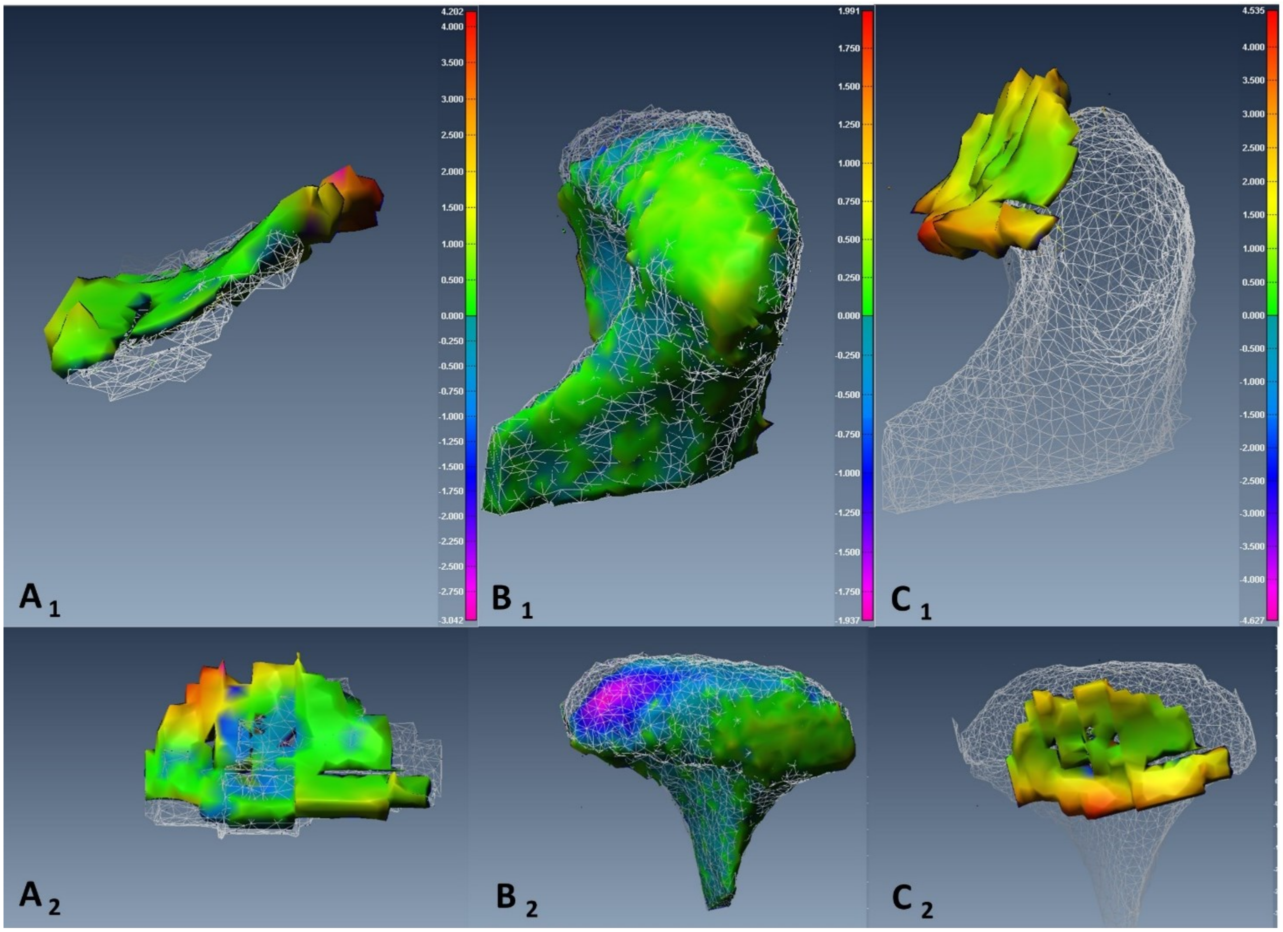

Figure 5: TMJ 3D reconstructed models representative of TMJ from an MRI-CBCT co-registered image of subject number 5 pre- and post-mandibulotomy surgery. The TMJ showed small displacement of the disc and condyle post-surgery compared to pre-surgery. *A* $_{1,\ 2}$: Sagittal and axial views of the same disc illustrate the point-based between pre-operative (white mesh) and post-operative (smooth body) of the disc (*Color code ranges from 4.0 to -3.0mm*). *B* $_{1,\ 2}$: Sagittal and axial views of the same condyle illustrate the point-based analysis between pre-operative (white mesh) and post-operative (smooth body) of the condyle (*Color code ranges from 1.9 to -1.9mm*). *C* $_{1,\ 2}$: Sagittal and axial views illustrate the point-based analysis of the disc-condyle relationship pre-operatively (*Color map ranged from 4.5 to -4.6mm*).

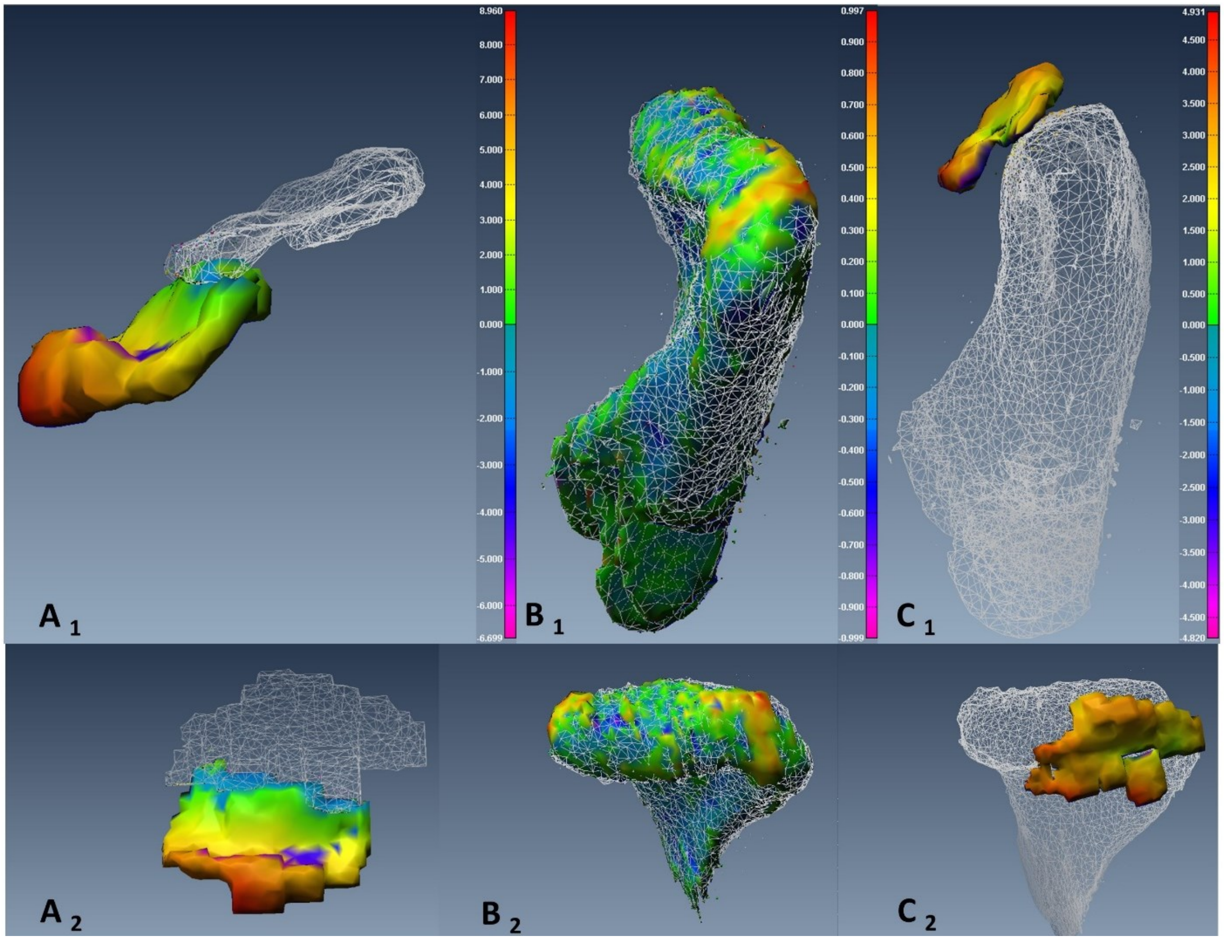

Figure 6: TMJ 3D reconstructed models representative of TMJ from an MRI-CBCT co-registered image of subject number 4 pre- and post-mandibulotomy surgery. The TMJ showed small condylar change and large disc anterior displacement post-surgery compared to pre-surgery. *A* $_{1,\ 2}$: Sagittal and axial views of the same disc illustrate point-based analysis between pre-operative (white mesh) and post-operative (smooth body) of the disc surfaces (*Color code ranges from 9.0 to -6.7mm*). *B* $_{1,\ 2}$: Sagittal and axial views of the same condyle illustrate point-based analysis between pre-operative (white mesh) and post-operative (smooth body) of the condyle surfaces (*Color code ranges from 1 to -1mm*). *C* $_{1,\ 2}$: Sagittal and axial views illustrate point-based analysis of the disc-condyle relationship pre-operatively (*Color code ranges from 4.9 to -4.8mm*).

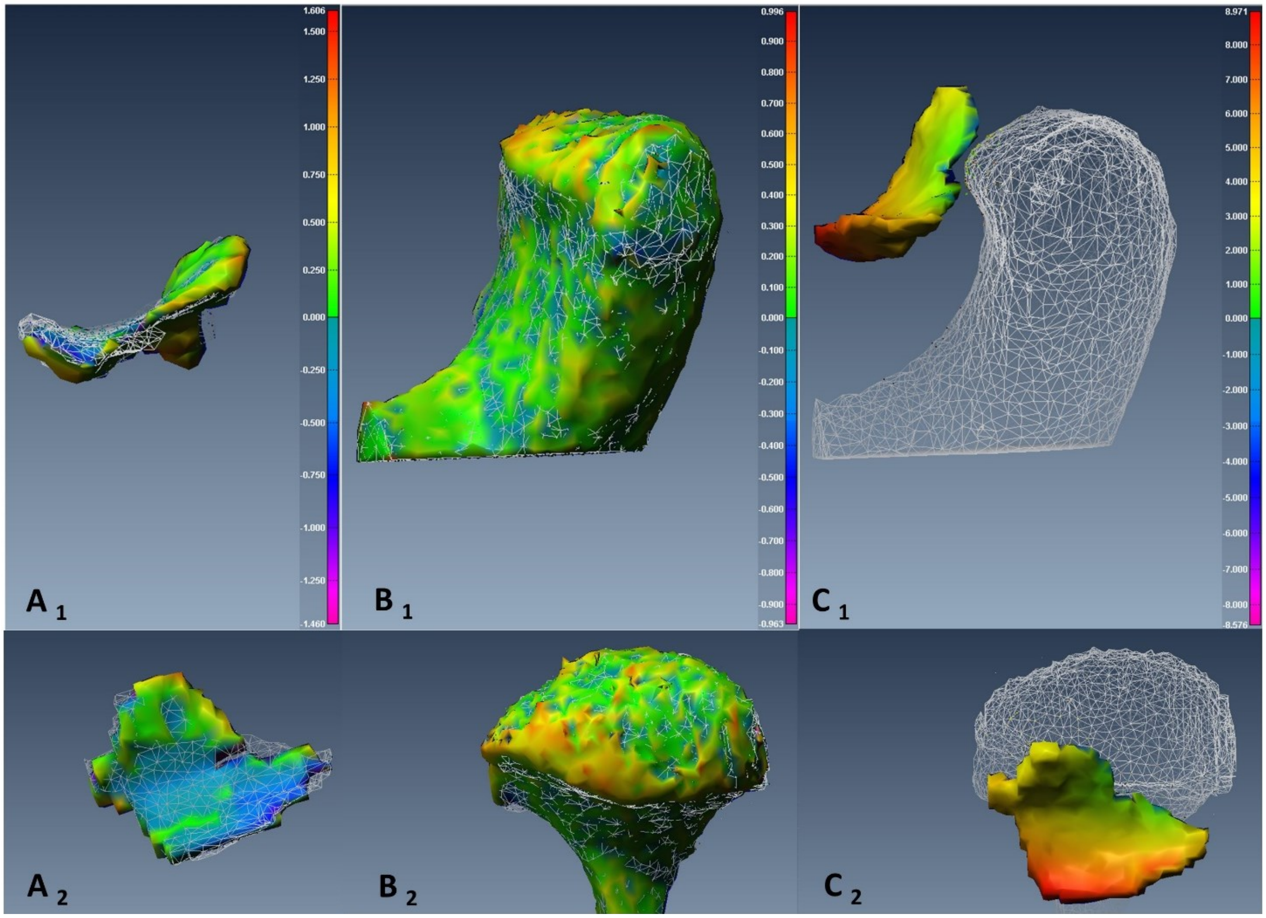

Figure 7: TMJ 3D reconstructed models representative of TMJ from an MRI-CBCT co-registered image of subject number 3 pre- and post-transoral surgery. The TMJ showed small change in disc and condyle positions between pre- and post-surgery. *A* $_{1,\ 2}$: Sagittal and axial views of the same disc illustrate point-based analysis between pre-operative (white mesh) and post-operative (smooth body) of the disc surfaces (*Color code ranges from 1.6 to -1.5mm*). *B* $_{1,\ 2}$: Sagittal and axial views of the same condyle illustrate point-based analysis between pre-operative (white mesh) and post-operative (smooth body) of the condyle surfaces (*Color code ranges from 1 to -1mm*). *C* $_{1,\ 2}$: Sagittal and axial views illustrate point-based analysis of the disc-condyle relationship pre-operatively (*Color code ranges from 8.9 to -8.5mm*).

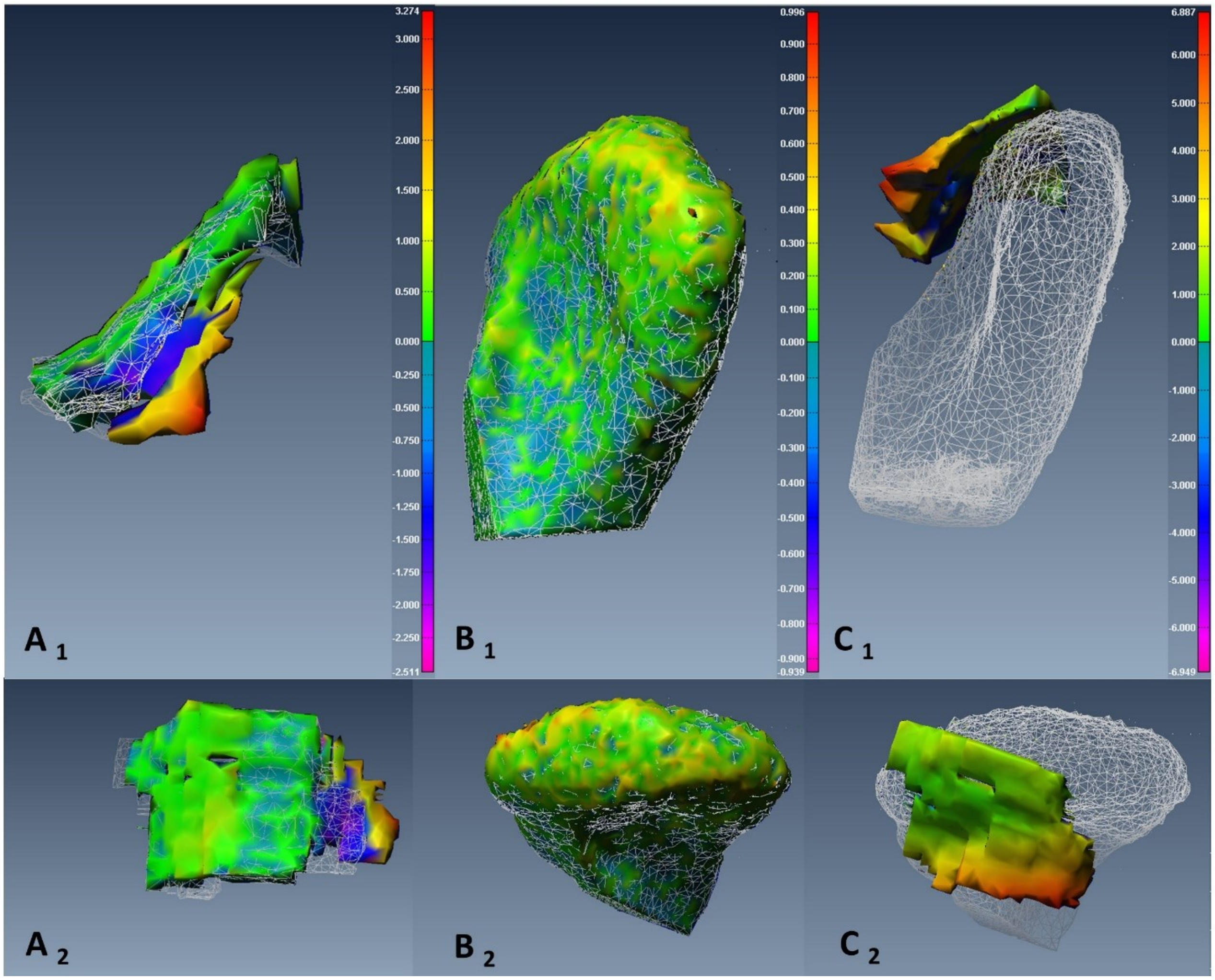

Figure 8: TMJ 3D reconstructed models representative of TMJ from an MRI-CBCT co-registered image of subject number 7 pre- and post-transoral surgery. The TMJ showed small change in disc and condyle positions between pre- and post-surgery. *A* $_{1,\,2}$: Sagittal and axial views of the same disc illustrate point-based analysis between pre-operative (white mesh) and post-operative (smooth body) of the disc surfaces (*Color code ranges from 3.2 to -3.5mm*). *B* $_{1,\,2}$: Sagittal and axial views of the same condyle illustrate point-based analysis between pre-operative (white mesh) and post-operative (smooth body) of the condyle surfaces (*Color code ranges from 1 to -1mm*). *C* $_{1,\,2}$: Sagittal and axial views illustrate point-based analysis of the disc-condyle relationship pre-operatively (*Color code ranges from 6.9 to -6.9mm*).

11.4 Discussion:

The matter of whether the midline or paramedian mandibulotomy negatively impacts the oral functions has been a cause of controversy in the literature.[9-12,14] In the last decade, several surgical techniques and options have been introduced in the area of head and neck and craniofacial surgery to avoid the potential TMJ trismus or functional limitation. However, morphological and clinical changes of the TMJ due to mandibulotomy have not been adequately investigated in the literature.[14] A well-designed experimental study, using valid assessment tools and cohort subjects, was recommended to determine the effect of the mandibulotomy on the TMJ and lead to better understanding of the resultant changes.[14]

Adjuvant chemo-radiotherapy was reported to delay healing capacity and restrict the mouth movement.[14,27-31] In present study, 6-8 weeks follow up appointment just before starting the chemo-radiotherapy was selected to avoid the radiation effect on the TMJ tissues and functions. The follow up period may have not been long-enough for patients to completely heal after surgery, however, the long-term evaluation was outside the purpose of the present study.

The high dropout rate (43% and 56%) in the present study was similar to another study in the literature.[24] Sixteen patients from both groups were not involved in the follow-up appointment for different reasons: (1 died after surgery, 2 had mandibulectomy surgery instead of mandibulotomy, 1 became edentulous and 12 withdrew from the study due to inconveniency). It’s our belief that the intervention-independent reasoning and the almost similar dropout rates in both groups had minimized the resultant bias on the study’s findings. Despite the high dropout rate, the sample size was still at the required level in the transoral group (*n*= 7 patient/group) or slightly higher in the mandibulotomy group (*n*= 9 patient/group).

Morphological changes:

Despite multiple studies in the literature discussing complications and functional outcomes after mandibulotomy and transoral surgeries, none has deeply investigated the morphology changes of the TMJ.[24,32-36] In the present study, the condylar head and articular disc changes, and their relationship were quantitatively evaluated using reconstructed 3D models representative of TMJ from MRI-CBCT registered images. The MRI-CBT registration process used was recognized as an accurate technique,[37] and was reliable when evaluating the TMJ internal disc derangement.[18]

The changes of the articular disc and condylar head in 3D space relative to the pre-surgical position were measured independently using 2 different, yet complementary, parameters. The *DSI* reflected the disturbance of the overall body displacement in a Likert-type scale (score from 0 to 1). However, the amount of the displacement at any direction was measured using the *RMSD*. The articular disc *DSI* and *RMSD* values were more variable than the condyle values and their relationship were not absolutely linear in both groups (chart 1) and with only moderate correlation (r = -0.59). Chart 1 illustrated a higher range of the disc displacement in the mandibulotomy group compared to the transoral group. The change in disc displacement was significantly different between the two groups, with mean *DSI* difference of 0.25±0.5 (p <0.01, *CI* = [-0.38 – -0.14]), and mean *RMSD* difference of 0.7±0.28 mm (p =0.02, *CI* = [0.1 – 1.2]). Two discs (joints no. 4 and 8) in the mandibulotomy group showed maximum displacement with low *DSI* values (Joint no. 4 *DSI* =0.33; *RMSD*=3.6mm), (Joint no. 8 *DSI* =0.1; *RMSD*=4.3mm). The disc changes between the two groups remained significantly different even when joints no. 4

and 8 were removed and data were re-analyzed (mean *DSI* difference of 0.23±0.4 (p <0.01, *CI* = [-0.38 – -0.10]), and mean *RMSD* difference of 0.51±0.18 mm (p =0.01, *CI* = [0.1 – 1.01]). The fact that these two joints were severely anteriorly displaced disc before surgery could have substantially influenced the surgical effect on them after surgery (Figure 6 illustrated the change in joint no. 4 in 3D model). The condylar head changes showed linear relationship between the *DSI* and *RMSD* values in both groups (chart 2), and showed very high correlation (r = -0.77). Chart 2 illustrated a higher range of *RMSD* but a small range of the *DSI* indicating limited displacement in of condyle in both groups. The change in condylar displacement was not significantly different between the two groups, with mean *DSI* difference of 0.03±0.03 mm (p =0.3, *CI* = [-0.1 - 0.02]), and mean *RMSD* difference of 0.21±0.1 mm (p=0.05, *CI* = [0 - 0.43]). Two condyles (joints no. 4 and 7) in the mandibulotomy group showed maximum displacement values with moderate *DSI* values (Joint no. 4 *DSI* =0.62; *RMSD*=1.3mm), (Joint no. 7 *DSI* =0.59; *RMSD*=1.4mm). On another note, the point-based analysis of the *disc-condyle relationship* is an accumulative result of the displacement amount of the disc and condyle. The mean difference of the maximum distance (*MxD*) that measured the *disc-condyle relationship* was found to be significantly different between the two groups (*MxD*= 1.25±0.25mm, p <0.01, *CI* = [0.73 – 1.78]).

The observed larger change in articular disc compared to the condyle can be attributed to many factors related to the nature of the articular disc anatomy, surgical procedures and the 3D segmentation errors. The articular disc ligaments are not elastic and upon stretching they irreversibly elongate. Even routine dental procedure or mild trauma can, sometimes, cause an internal disc derangement, which alters force dynamics and potentially result in long-term consequences. The severe stretching action of the mandible halves for long hours during mandibulotomy surgery likely resulted in more accentuated disc displacement compared to the transoral surgery group. Moreover, the manual 3D segmentation of the articular disc was found to have a higher marginal error (0.3±0.1 mm) than the semi-automatic condylar 3D segmentation (0.1±0.1 mm).[51*] The successful reunion of the two halves of the mandible using a reliable surgical template and internal rigid fixation could be another factor of the minimal change of the condylar head. The clinical significance of the condylar position is controversial in the current literature.[39] The condylar position was quite variable in the mandibulotomy group, however, the long-term consequences of the change in condylar position remains unknown. As well, the relatively short follow-up period would likely be insufficient to see change in bone morphology due to osseous degeneration. Harris and Heaney reported that a decrease of 30% – 50% of the skeletal mass is required in order to detect erosive lesions in the radiograph.[38] The gradual demineralization of the bone matrix, however, is a slow process that takes many weeks in humans depends on many factors including age, trauma, dysfunctions and hormonal disturbance.[38]

Clinical changes:

The main goal of any cancer surgery is complete excision of the lesion with a clear margin, however, maintaining oral functions to the best possible degree is another important goal. One of the major shortcomings in the published oral and oropharyngeal cancer studies is insufficient description of the clinical examination methods and criteria. Mandibulotomy was suggested to play a causative role in reducing vertical mouth opening and jaw dysfunction.[14,15] The majority of the literature evaluated oral and oropharyngeal cancer treatment impact on quality of life

(QoL), which is a common generic head and neck QoL measure that is not sensitive to oral functions impairment.[40,41]

The *JFLS* is a valid and reliable organ–specific scale that measures the oral and TMJ dysfunctions and the patients' perception of the social impact on their well-being.[22,42,43] In the present study, the average of the *JFLS* score in the mandibulotomy group was 16.4 (almost 5 times larger after surgery), whereas, the average of the *JFLS* score in the transoral group was 4.7 (2 times larger after surgery). The *JFLS's* mean difference between the two surgery groups was 9±1.69mm (p <0.01, CI = [5.5 - 12.4]). The severity of the TMJ dysfunction in a typical TMD patient was reported to range between 21 to 28 points of the *JFLS* scoring system, and the difference between the healthy group and TMD patients was reported to be 11 points.[22,44] The highest impairment scores after mandibulotomy were mainly given to three questions: 1. "*Talking for long period of time*"; 2. "*Prolonged chewing*"; and 3. "*Activity at home/work*". It is possible that with more healing time, these functional limitations may resolve. However, this does not negate the substantial effect of the post-operative tissue injuries on the high *JFLS* scores, which was highly correlated to the differences in the disc *DSI* value (r = -0.70), *disc-condyle relationship* (r =0.76), and maximum mouth opening (r =0.74). The findings of the present study regarding functional changes were in line with the studies in the literature. Christopoulos *et al* reported long-term (1-10 years) functional performance, and compared mandibulotomy patients versus mandibulectomy patients.[35] Ninety-seven percent of the mandibulectomy patients reported more dysphagia and having soft diets versus 43% of mandibulotomy patients. Riddle *et al* reported 1 year post-operative symptoms of local pain and discomfort in mandibulotomy patients using yes or no answers.[33] Six percent reported remaining pain at the midline split site, 32% reported TMJ pain with chewing or speaking, 41% had tenderness or discomfort at the temporalis or masseter muscles associated with TMJ movements. Lee *et al* used self-reporting questionnaire to asses swallowing dysfunction in 1 year after transoral-robotic versus transoral/transmandibular surgeries.[36] There was a significant difference in the recovery of full swallowing ability in the three groups of patients who underwent transoral-robotic, transoral and mandibulotomy on average of 6.5±4 days, 7±8 days and 16.7±5 days respectively. Gellrich *et al* surveyed 1650 patients who underwent different types of surgical and chemo-radiotherapy treatments for oral SCC tumors.[24] The authors found that the highest impairment reported was in chewing, swallowing and tongue mobility 6 months after surgery in all patients. Likely, the post-operative dysfunction is more related to the amount of the resected oral tissues. [24,45]

Tenderness provoked by TMJ movement correlates to jaw dysfunction,[46,47] Measuring jaw movement capacity in millimeters, especially the vertical movement, is sensitive to over time change and has excellent reliability to determine the severity of limitation of jaw movement.[48,49] The mandibulotomy group patients showed decreased in the average of the maximum interincisal mouth opening after surgery of about 11 mm. However, 16 out of 18 patients in mandibulotomy group were able to open more than 40 mm, which is considered an acceptable vertical range of movement after a relatively short period of surgical recovery.[50] The transoral group patients showed a slight decrease in the average of the maximum interincisal mouth opening after surgery (~5.4 mm) and all of them were able to open about 50 mm. The mouth opening mean difference between the two groups was 5±0.9 mm (p <0.01, CI = [2.9 – 7.0]). Although no direct influence of the joints with severe disc displacement (joints no. 4 and 8) on vertical mouth opening was noticed, the mean difference of the maximum mouth opening was moderately correlated to the change in disc displacement (*RMSD*, $r = 0.57$), morphology (*DSI*, $r = -0.61$) and *disc-condyle* relationship ($r = 0.67$). Christopoulos *et al* found no significant difference in mouth opening between mandibulotomy patients (~50 mm) and mandibulectomy patients (~40 mm).[35] Riddle *et al* found that 30% of 93 mandibulotomy patients reported reductions in vertical mouth opening with post-operative average of 41mm.[33] Bertrand *et al* found that 73% had severe mouth opening limitation (< 25mm) after 6 months of their mandibulotomy due to postoperative radiotherapy.[34] Overall, limitation in mandibular movement in both vertical mouth opening and lateral movements after mandibulectomy seemed to be attributed to the scarring and prolonged muscle immobility.[15,45] In some cases, the decrease in mouth opening and movement limitation is likely attributed to the simultaneous soft tissue resection such as pterygoid muscles, adjuvant chemo-radiotherapy and/or attendant reconstruction.

The findings of the present study confirmed the higher TMJ related morbidity of the mandibulotomy when compared to transoral surgery. The associated morphological changes emphasized the minimal condylar changes in both groups, but higher disc displacement in mandibulotomy group compared to transoral group. These changes may be partially responsible for the functional limitation after mandibulotomy and a potential source of future TMJ internal derangement and TMJ dysfunction. The slow recovery in the mandibulotomy group could, also, be attributed to the injury of the floor of mouth muscles, constrictor muscle, and pharyngeal nerve plexus, which were minimally injured with the transoral surgery.[36] The 3D reconstructed models from the MRI-CBCT registered images reflected a clear picture of the morphological changes of the TMJ after mandibulotomy and transoral surgeries. To the authors best knowledge, no study has investigated the morphological changes of the TMJ tissues in a similar surgical intervention or patient population. The lack of similar studies made it difficult to compare the present study findings with other studies in the literature. The reported morphological changes provided an important source of information in the field of oral and oropharyngeal surgical management field.

This study had several limitations. The follow-up period was short and another study can be attempted to evaluate the long-term effects on the same cohort. Although the patients of both groups were matched in age and gender, the tumor type, size and extension were not completely matched, which may have been a source of bias when the outcomes of the both groups were compared. Also, exploring the morphological changes of the TMJ after the chemo-radiotherapy can be useful in understanding the associated morphological changes to the resulted functional limitations of the TMJ.

11.5 Conclusions:

The quantitative assessment of the TMJ using the 3D reconstructed models of MRI-CBCT registered images, showed minimal changes of the condylar position and variable degrees of articular disc displacement associated with the paramedian mandibulotomy. As well, limited jaw functions and vertical mouth opening were noticed more in the mandibultomy group compared to the transoral group in 6- weeks after surgery. A future study with long-term evaluation is advised to detect potential long-term morphological and functional changes of the TMJ.

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***51.** Al-Saleh M.A.Q., Punithakumar K., Lagravere M., Boulanger P., Jaremko J., Major P. *Three-dimensional Assessment of Temporomandibular Joints Using MRI-CBCT Image Registration.* (Submitted to the DMFR Journal).

Chapter 12: Thesis conclusions

12.1 General Discussion

12.1.1 Multimodal image co-registration (Technique):

The co-registration of two or more comparative images from different imaging sources such as MRI, CT, CBCT, PET-scan and Ultrasound is referred to as "multimodal" image co-registration. The co-registration of two or more comparative images from a single imaging source is referred to as "monomodal" image co-registration. The primary goal of merging two images from different imaging modalities is to utilize the complementary nature of the displayed information. The process of image registration is composed of two main steps: 1. the spatial alignment of the target images, which is commonly defined as "registration", and 2. the fused display of the target images, which is described as "fusion". The registration process is classified into two models:[1,2] 1. the intrinsic model that depends on anatomical landmarks, segmented bodies or voxel values; and 2. the extrinsic model that depends on fiducial markers (surface-attached or screw-mounted). Anatomical landmarks in the intrinsic registration models are often conspicuous and easy to locate in the human head, however; registration of large tissues in complex regions requires detection of a significant number of anatomical landmarks.[3] Identifying matched anatomical landmarks when co-registering the MRI, and CT or CBCT is a challenging task. On the contrary, monomodal image registration is a much easier process compared to the multimodal registration due to the high degree of similarity between the images of the same modality. Another common intrinsic approach is to use the voxel values (gray values) of the involved images to spatially align the orientation of the two images and their center of gravity. A method is known as "maximization of mutual information" distributes the full image content of gray values in a relative entropy histogram to detect the similarities between the connected voxels. This method employs the mathematical concept of the mutual information theory; which is conceptually appealing technique due to its flexibility, easy implementation, automatic and fast use in multimodal image registration.[4] Proper co-registration of the MRI and CT/CBCT is crucial especially when used for clinical applications. However, sophisticated computational requirements/costs and accuracy concerns have delayed the clinical application of this registration technique.

For TMJ pathology, MRI or CBCT are the choices of diagnostic imaging depending on availability and the therapeutic indication. Despite advancement in MR imaging quality, it has not entirely overcome the limitations of the low-quality presentation of the complex osseous structure of the TMJ.[5,6] CBCT is superior at identifying cortical bone contouring, remodeling, developmental abnormality and pathological changes.[6] Both imaging techniques have their limitations and remain complementary to each other in the TMJ diagnostic field. Lin *et al* [7] and Dai *et al* [8] highlighted the importance of merging the MRI and CT images to visualize TMJ tissues. However, several challenges in multimodality image registration starting with, but not limited to, the different receivers, FOV, voxel size, voxel value, image-acquired orientation, slice thickness, image resolution, field inhomogeneity and image artifacts, should be overcome before it can be considered for clinical or diagnostic use. The mutual-information-based technique represents a robust multi-modality image co-registration model that has been used extensively in the medical imaging field.[9-12] Although MRI and CT/CBCT co-registration has multiple clinical applications in the medical practice, a very limited effort has been done to explore the benefits of such useful tool in the clinical practice of dentistry. For example, Tai *et al* [13] introduced full FOV fused MRI-CBCT images to visualize face profile as a tool for orthodontic and orthognathic treatments evaluation. Gaudino *et al* [14] displayed the lamina dura and periodontal ligament in

MRI-CBCT images. However, the mutual-information-based multimodality image co-registration has not been adequately explored to visualize and assess the TMJ tissues until this Ph.D. project was initiated. Chapter 2 presented a systematic review that discussed the importance, clinical applicability and practicality of the MRI-CBCT image co-registration for TMJ assessment.

<u>12.1.2 Technique optimization:</u>

Considering the challenges of the MRI and CBCT image co-registration, the two most common types (intrinsic and extrinsic) of the multi-modality image co-registration were performed and compared to the final image alignment and quality of fusion display. The intrinsic registration was completely automatic, did not require operator's interaction, and hence eliminated the operator bias by using an algorithm to maximize the image match (mutual information).[11,15] The technical details of the mutual-information-based co-registration method were explained in Chapter 11. On the contrary, the extrinsic registration relied on five skin-surface-attached fiducial markers and required an operator to manually locate the homologous markers in both MRI and CBCT images for final registration. Once the images of 20 TMJs were registered, the quality of image alignment was assessed using a voxel-by-voxel overlap of one image overlaid the other, by three radiologists at two occasions. Adding fiducial markers, in the extrinsic registration, to the region of interest with a uniformed appearance in the MRI and CBCT images was expected to reduce the potential error of the final registration. However, the fiducial markers deformation due to motion artifact or due to change in patient's position (supine during MRI versus upright during CBCT) imposed certain image alignment errors (Figure 3.3 and 3.4). As well, the operator's interaction was required to identify the markers, which potentially have implicated an operator-bias. This markers mismatch between the images resulted in considerable variation in the tissue contours and low quality of the final registration reported by the examiners.

The extrinsic accuracy is reportedly much higher in neurosurgical studies,[16] likely because markers in those studies are attached directly to bone such as the calvarium by screws, preventing the movements inevitable in the use of markers taped to the skin as we did in the study presented in Chapter 2. The high signal intensity and complex and unique shapes of the bony structures in the head area provided a reliable foundation for well-defined intrinsic MRI-CBCT image co-registration (Figure 3.2). As a result, the superior quality of the intrinsic registered MRI-CBCT images over the extrinsic images rendered the latter inadequate for the TMJ assessment. The intrinsic, mutual-information-based, co-registration was found to result in high-quality images by all radiologists with high intra- and inter-examiner agreement. Therefore, intrinsically registered images were chosen for further analysis and TMJ soft and hard tissue assessment in Chapters 3, 5,8 and 11.

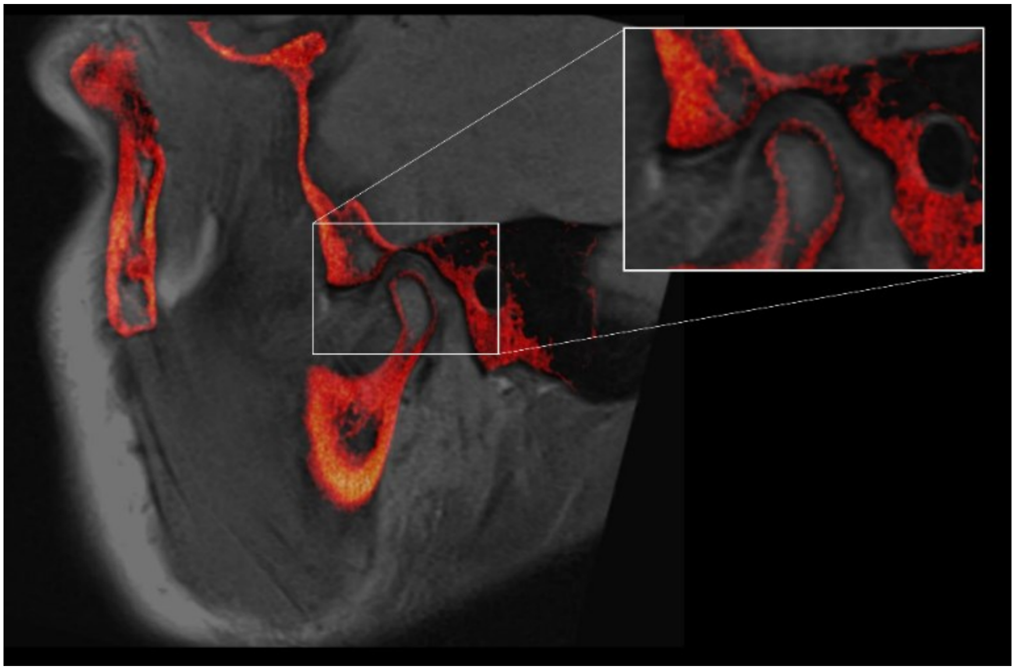

Figure 3.2: Sagittal view of registered MRI (gray color) and CBCT image (Red color) using maximum mutual information algorithm (intrinsically based registration). The image shows excellent superimposition of the anatomical tissues of the TMJ, despite the different receivers, FOV size, voxel size, voxel value, image-acquired orientation, slice thickness, image resolution, and field inhomogeneity.

12.1.3 Technique accuracy:

Registration technique accuracy is a substantial issue when it comes to multimodality image co-registration. Previous accuracy studies of the *in-vivo* brain,[17] or skull base/nasopharynx,[18,19] MRI with medical CT image co-registration revealed an accurate intrinsic mutual-information-based co-registration process with linear errors ranging from 0.41-1.6 mm. Two other *in-vitro* studies fused and used screw-mounted fiducial markers to assess the accuracy and measure co-registration linear error of 3D full-head MRI and C-arm CBCT images.[13,20] Both studies reported accurate mutual-information-based image co-registration.[13,20] The co-registration technique used by these researchers was cumbersome and somewhat impractical for clinical use. Inaccuracy and complicated registration procedure can be challenging in multimodality image registration especially with routine TMJ/MRI protocol that includes small FOV and limited sectional images. In Chapter 4, the accuracy of the usual TMJ (small FOV) MRI and regular CBCT images were measured.[21] Screw-mounted fiducial markers were used as gold standard markers to measure the linear measurement/target errors of the intrinsic mutual-information-based MRI-CBCT co-registration. The fiducial markers were mounted into five cadaver swine heads and the distances between markers were measured using a laser scanner. The findings demonstrated a small linear target error (0.2±1.2mm) of MRI-CBCT co-registration when compared to the gold standard (laser scanned fiducial markers).[21] The operator's reproducibility error was low (maximum error of 0.1mm) indicating high reproducibility- reliability.[21]

The findings, of the study in Chapter 4,[21] were similar to the previously reported values in the *in-vivo* and *in-vitro* studies.[13,17-19,22] The mutual-information-based image co-registration provided an easy, fast, and automatic steps without the burden for extra steps by the clinicians, which rendered it practical for clinical or research use. The findings in Chapter 4 revealed that despite the differences in the imaging sensors and voxel sizes between MRI and CBCT, the applied multi-modality image registration was robust and yielded numerically accurate and visually satisfying overlap. However, the accuracy of the MRI-CBCT image co-registration extends beyond the satisfactory visualization of the TMJ to many clinically significant applications such as diagnostic and treatment outcome evaluations.

12.1.4 Technique validation of the TMJ subjective assessment:

MRI has been considered as the prime imaging modality to analyze the soft tissue changes in the TMJ. However, the accuracy of determining disc morphology and position relative to the osseous joint components is challenging and has been the subject of numerous studies.[23-27] Proper classification of the disc position improves the diagnostic interpretation of the imaging modality and allows the clinical application in treatment planning and outcome assessment.

The CBCT has been reported to have excellent ability to evaluate osseous pathology of the TMJ.[28-31] CBCT showed high reliability to detect cortical erosions of the TMJ articular surfaces with 95% accuracy.[29] Alkhader *et al* reported MRI low sensitivity 30-82% in detecting osseous pathology of 106 TMJs, and poor inter-examiner agreement (k <0.4) for detecting bone sclerosis.[5] Different studies reported fluctuating MRI sensitivity (50-87%) and specificity (71-100%) values to identify the osseous pathology of the TMJ.[5,18,32]

Examiners' consistency/agreement in detecting the articular disc displacement using MRI has been well-reported in the literature.[26,27,34-38] Some studies reported fair to moderate inter-examiners agreement with *k* values ranged from 0.4 to 0.6.[27,34,35] when examiners were calibrated and guided how to classify the disc position. Ahmad *et al.* reported strong inter-examiner agreement (*k*= 0.8) when the four examiners underwent an extensive 2-day calibration program.[38] Although the calibration sessions seemed to result in encouraging agreement levels among examiners, they do not seem to be clinically practical when professionals from different specialties interpret the TMJ MRIs individually and independently. Widmalm *et al.* and Butzke *et al.* reported poor inter-examiner agreement (*k*= 0.1-0.2) when no calibration sessions were offered to examiners.[36,37] Their findings confirmed that highly experienced radiologists (oral & maxillofacial or medical) were subject to the poor agreement when diagnosing disc displacement without calibration sessions. Widmald *et al.* suggest that the most reliable MRI interpretation requires a group of observers who are calibrated, experienced, and jointly discuss these images before confirming a diagnosis.[36] Nebbe *et al*[27] reported moderate to substantial agreement (*k*=0.49-0.61) when standardized criteria for categorization were used in image analysis. It thus appears that regardless of the superiority of MR imaging as a modality for identification of soft tissue structures of the jaw joint, the above-noted limitations hamper ideal interpretation of joint anatomy, and provides an opportunity for improvement in joint imaging interpretation. It has been suggested that examiners' reliability in MRI interpretation improved when using the functional position of the intermediate zone of the articular disc and well-defined criteria for classification of disc-condyle relation are employed.[23,25-27,39,40]

In this Ph.D. project, MRI-CBCT co-registered images were used to evaluate the TMJ soft and hard tissues changes, standardize the disc position classification and to improve the reliability of the examiners in disc evaluation.[27] In a pilot study of 20 TMJs (Chapter 3), the MRI-CBCT co-registered images were found appropriate to detect changes in osseous morphology; however, CBCT alone exceeded the fused MRI-CBCT in detecting minor abnormalities such as erosion (Table 3.5). The findings were attributable to the overlying MR images masking small osseous changes in the MRI-CBCT fused images.[33] The pilot study highlighted the importance of viewing well-defined osseous contours and articular disc tissue in one image.[33] As well, it revealed that the MRI-CBCT co-registered images can improve the inter-examiners' reliability in reporting disc derangement (MRI alone, ICC=0.5 at T1 and 0.56 at T2; MRI-CBCT registered images, ICC=0.80 at T1 and 0.84 at T2).[33]

Examiners' consistency in classifying disc position was found to improve when the new assessment method using MRI-CBCT image registration to visualize TMJ was recently introduced.[33] The study in Chapter 5 was conducted to confirm the positive influence of the MRI-CBCT image registration on the examiners' reliability. The study confirmed that using MRI alone, experienced radiologists with clearly defined criteria of disc position classification (Chapter 3, Figure 3.2), was almost perfectly consistent across time (ICC 0.85-0.91), but moderately consistent when compared to each other (ICC 0.52-0.71). With MRI-CBCT images, the findings demonstrated improvement in reliability over time and between the two radiologists (intra-examiner: ICC 0.95-0.97; k= 0.91-0.92; inter-examiner: ICC 0.97-0.98; k= 0.96). The MRI-CBCT fused images reduced the disagreement gap within and between each examiner(s) such that the subjectivity of diagnosis was reduced, and more standardized diagnosis/classification was reached.

The image registration itself provides no additional information on disc morphology and displacement, does not change the composite image properties, and preserves image signal intensity, resolution, contrast, and quality. However, by improving the identification and definition of the surrounding osseous structures (such as condylar outline, condylar head inclination, depth of glenoid fossa and articular eminence slope) the diagnostic value of the disc displacement was enhanced and the decision-making errors were reduced.[33] The PD, T1, and T2 MRI sequences are commonly used for the TMJ diagnostic imaging. The TMJ articular disc has low signal intensity similar to that of the cortical bone of the condylar head, glenoid fossa, and articular eminence in PD, T1, and T2 MRI sequences. In some cases, where the joint space is reduced, the articular disc is in a very close position to the cortical boundaries of the condylar head or posterior slope of the articular eminence (Figure 5.2). These tissues present with similar low signal and may easily be confused, resulting in error or inconsistency in the diagnoses of internal derangement. Moreover, in severe cases of TMJ degeneration, the size, shape of the articular disc may be altered, and increased bone marrow signal may impact the ability to identify the structures of the joint (Figures 5.3 and 5.4). MRI-CBCT image co-registration offered the opportunity to reduce these common sources of diagnostic errors in TMJ-MRI interpretation. Although the MRI-CBCT image registration in the open-mouth position is technically possible, additional CBCT imaging for open mouth position does not appear feasible since it does not provide additional osseous information while exposing subjects to additional radiation exposure.

Teaching medical and dental imaging for novice clinicians is challenging. In oral radiology, some educators suggest that learners follow analytical-reasoning strategy (shape, size, location, borders and interaction with surrounding structures) to reach an accurate diagnosis.[41-43] Others suggest that novice clinicians should start with "backward-reasoning" where they can compare a radiographic image to another that was seen previously.[44,45] Both approaches, however, are limited by the variations in the radiographic appearance of an abnormality, in addition to the limited experience of the clinician.[41] The success of expert interpretation is due to the ability to picture-match to previously known pathologies, ability to understand what a 2D image of a 3D structure represents, and understanding of physiology and pathophysiology.[42,43,46,47] Ambiguity of the radiographic image to the novice may interfere with the complicated process of image interpretation, especially when they struggle with recognizing the anatomy or detecting pathological features.[48] Two errors can be identified; recognition error (failed to see the abnormality) and decision error (wrong analysis of the abnormality).[42,49,50] Both errors can result from challenging visual images, radiographic characteristics and location of abnormality, and lack of training and experience.[48] Typically, novices or even radiologists expert in different imaging domains find an accurate and consistent diagnosis of TMJ disc position challenging. Even radiologists with TMJ interpretation experience demonstrate low reliability when diagnosing TMJ disc derangement on MRI.[36]

When diagnosing the TMJ internal disc derangement from MRI, the position of the low-intensity bow-tie shaped articular disc (interposing between the head of the condyle and the articular eminence), is the diagnostic key. The articular disc can be variably displaced from this functionally appropriate position representing internal derangement. The degree of disc displacement is evaluated based on its location related to the head of the condyle. Since osseous structures are not clearly visualized in MRI, overlapping MRI on CBCT image provides a precise bone definition, which improves the diagnostic ability to visualize disc position relative to the condyle.[33] The study in Chapter 6 investigated the effect of the MRI-CBCT co-registered images on diagnosing TMJ internal disc derangement by novice examiners. Twenty novice examiners (graduate and undergraduate dental students) revealed poor reliability in detecting the disc position with the MRI only when individually compared to the experts' readings (k mean=0.07±0.12). However, their reliability improved in MRI-CBCT images (k mean=0.55±0.25). The improvement was also identified in the students' inter-examiner reliability (α = 0.40 and α = 0.84 for MRI only and MRI-CBCT images respectively). The poor reliability in determining disc position from MRI alone was probably influenced by the lack of the examiners' experience in anatomy and therefore lack of decision. Adding the colored outline of the condyle and articular eminence from CBCT improved the visualization of the space where the articular disc is positioned and appeared to aid in the identification of the disc, and reinforce their understanding of internal derangement. The findings clearly illustrate the usefulness of the CBCT osseous outlines in the MR image on the students' diagnostic decision-making.

Internal disc derangement disturbs the congruity between the functional components of the TMJ, which may potentially have an effect on the normal condylar development in the adolescents. Altered condylar morphology can lead to altered craniofacial morphology in actively growing patients.[51-53] However, the association between internal disc derangement and degenerative changes of the condyle has been a source of controversy in the literature.[54,55] Chapter 7 represented a systematic review that discussed the effect of different mandibular repositioning appliances on TMJ of adolescents orthodontic patients.[56] The review revealed that the level of evidence regarding the change in disc position and disc morphology with mandibular anterior positioning appliances was low, and a validated tool to objectively evaluate the disc position was necessary.[56] The MRI-CBCT co-registered images seemed to reduce variations in the examiners' subjectivity and introduced standardized diagnosis/classification of the disc position.[33] The pilot study in Chapter 9 employed the MRI-CBCT co-registered images, as a validated tool, to evaluate the examiners' reliability in diagnosing the TMJ disc positions in 10 adolescent patients. The examiners' reliability values with the MRI alone, (intra-examiner: ICC 0.74-0.88; inter-examiner: ICC 0.75-0.88), were similar with the reliability values reported in the study in Chapter 5 (intra-examiner: ICC 0.85-0.91; inter-examiner: ICC 0.52-0.71). However, the reliability values with the MRI-CBCT images, (intra-examiner: ICC 0.43-0.71; inter-examiner: ICC 0.48-0.75), were less than the values reported in the study in Chapter 5 (intra-examiner: ICC 0.95-0.97; k= 0.91-0.92; inter-examiner: ICC 0.97-0.98; k= 0.96). The unimproved examiners' reliability, with the MRI-CBCT co-registered images, was attributed to the low signal-to-noise ratio, and occasionally the poor identification of anatomical structures displayed by the overlapped MRI and CBCT co-registered images (Figure 8.1). In this case, the fused images did not help to reduce the inconsistency gap between and within each examiner(s).

The used CBCT protocol in the studies from Chapters 3-6 was designed for adult patients with high resolution setting (5 mA, 120 Kvp, and 0.25 mm voxel size) and longer radiation exposure time (7 seconds) compared to the lower resolution images (4 seconds with 5 mA, 120 Kvp, and 0.3 mm voxel size) obtained for the adolescent patients in Chapter 8.[21,33] The longer exposure time allowed higher resolution of the CBCT images with a high signal-to-noise ratio; and therefore, allowed better alpha-blending intensity between the MRI and CBCT in the finally displayed image (Figure 8.2). Studies in the literature suggested that low-quality images can be diagnostically unacceptable in the case of subtle degenerative changes of the TMJ osseous surface, especially in children.[57-60] It was suggested that specific exposure parameters should be customized according to specific machines' models, investigated tissues, diagnostic questions, clinical factors and patients' age and size.[61,62] The pilot study in Chapter 8 revealed that the CBCT acquisition protocol might be sufficient for orthodontic assessment purposes, but insufficient to result in high-quality MRI-CBCT co-registered images or to accurately diagnose the TMJ small osseous degenerative changes.

12.1.5 Technique validation of the TMJ three-dimensional assessment:

Iatrogenic over-extension of the mandible during intubation in general anesthesia, extended dental procedure orthognathic surgeries, oropharyngeal cancer transmandibular surgeries are potential initiating and predisposing factors for structural damage to the TMJ. The above procedures may apply excessive forces that may cause TMJ capsular injury, ligaments elongation, disc displacement leading to symptoms the TMJ dysfunction.[63-66] Patients at the University of Alberta, Otolaryngology-Head and Neck Surgery Department are known to suffer from impaired oral functions after having oral and oropharyngeal cancer transmandibular surgeries. Chapter 9 represented a systematic review that critically analyzed the literature discussing complications and functional outcomes after mandibulotomy and transoral surgeries. The matter of whether the midline mandibulotomy negatively impacts the oral functions has been a cause of controversy in the literature.[67-71] The review revealed no study has properly investigated the morphology changes of the TMJ after mandibulotomy.[72-77] A well-designed experimental study, using valid assessment tools and cohort subjects, was recommended to determine the effect of the mandibulotomy on the TMJ and lead to better understanding of the resultant changes.[67]

Three-dimensional imaging of the TMJ articular disc helps to understand the cause and effect relationship between disc changes and dysfunction.[78-85] Previously published studies in the literature mainly focused on segmenting the articular disc automatically within a reasonable period, and with the least possible level of operator interaction.[78-85] However, automatic segmentation is best applied when a clear difference in intensity between foreground region and the background region is detected. In small tissues, such as an articular disc that are represented by a limited number of voxels and lie within surrounding tissues with similar signal intensity at low signal-to-noise ratio MRI, manual or semi-automatic segmentation with experienced operator interaction is likely a more reliable technique to detect the disc accurately. Also, all studies in the literature utilized MRI alone to outline and segment the TMJ condyle and glenoid fossa.[78-85] CT and CBCT remain the gold standard for osseous pathology diagnosis especially flattening, osteophyte and increased joint spaces of the TMJ. MRI cannot sufficiently differentiate osseous structures for 3D segmentation due to its inherent limitations (i.e. large slice thickness, inter-slice gaps, cross-talk artifact, and high signal-to-noise ratio). Fused MRI-CBCT images potentially facilitate accurate three-dimensional reconstruction of the articular disc, condylar head, and articular eminence, and allow multi-dimensional quantification of the TMJ changes.

Chapter 10 demonstrated the ability to evaluate in 3D TMJ disc position and shape with from MRI-CBCT co-registered images. MRI specifications suitable for routine clinical examination are challenging when used for TMJ disc three-dimensional reconstruction. The minimal inter-slice thickness was placed at 0.3mm (10%) to reduce missing unique anatomical information, and only insignificant information is missing at this thickness. Fusing multiple MRI sequences (PD, T1, and T2) to the CBCT image improved the visualization of the articular disc morphology,[33] and potentially improved the disc segmentation accuracy and reduced the operator error. The articular disc manual segmentation revealed acceptable reproducibility between attempts by the same operator, with maximum distance change in the articular disc of 3.6±0.32mm, Dice similarity index (*DSI: overall displacement*) of 80% and root mean squared distance (*RMSD: amount of displacement*) of 0.3±0.1mm. Unfortunately, there is no study in the literature reporting reproducibility or reliability of a manual disc segmentation to be compared with our findings. For the semi-automatic segmentation of the TMJ condyle and glenoid fossa, our study revealed excellent reproducibility between attempts by the same operator, with *DSI* of 98% and *RMSD* of 0.1±0.08mm. The findings were almost similar to another study by Schilling et al.[86] who reported inter-observer mean difference ranged between 0.4-0.6mm with excellent reliability (Interclass coefficient >0.75).[86] The different values may be attributed to the difference in voxels' size and registration technique between the two studies. Bone segmentation reliability is more dependent on the intensity threshold that varies by different machines and software, and less reliant on the operator experience and judgment.

Chapter 11 quantified the three-dimensional changes of the TMJ disc and condylar head pre- and post- mandibulotomy (test group, n=8) and transoral (control group, n=7) surgeries.-The articular disc *DSI* and *RMSD* values revealed a higher range of the disc displacement in the mandibulotomy group compared to the transoral group with mean *DSI* difference of 0.25±0.5 (*p*

<0.01) and mean *RMSD* difference of 0.7±0.28 mm (*p* =0.02). The change in condylar displacement was not significantly different between the two groups, with mean *DSI* difference of 0.03±0.03 mm (*p* =0.3), and mean *RMSD* difference of 0.21±0.1 mm (*p*=0.05). On another note, the point-based analysis of the *disc-condyle relationship* is an accumulative result of the displacement amount of the disc and condyle. The mean difference of the maximum distance (*MxD*) that measured the *disc-condyle relationship* was found to be significantly different between the two groups (*MxD*=1.25±0.25mm, *p* <0.01). The observed larger change in articular disc compared to the condyle may be attributed to many factors related to the irreversibly elongated ligaments, surgical procedures, and the higher manual disc segmentation errors (0.3±0.1 mm) compared to the semi-automatic condylar segmentation error (0.1±0.1 mm). Also, the smooth fixation of the two halves of the mandible and the relatively short follow-up period would likely be insufficient to see a change in bone morphology due to osseous degeneration, could be the reasons for the minimal change of the condylar head.

The jaw function limitation scale and the vertical mouth opening records confirmed the higher, TMJ-related, morbidity of the mandibulotomy compared to transoral surgery. The associated morphological changes emphasized the minimal condylar variations in both groups, but greater disc displacement in mandibulotomy group compared to the transoral group. These changes may be partially responsible for the functional limitation after mandibulotomy and a potential source of future TMJ internal derangement and TMJ dysfunction. The slow recovery in the mandibulotomy group could, also, be attributed to the injury of the floor of mouth muscles, constrictor muscle, and pharyngeal nerve plexus, which were minimally injured with the transoral surgery.[76] The reconstructed three-dimensional models from the MRI-CBCT registered images reflected a clear picture of the morphological changes of the TMJ after mandibulotomy and transoral surgeries.

To date, no study in the available literature has investigated the morphological changes of the TMJ tissues in a similar surgical intervention or patient population. The reported morphological changes provided an important source of information in the field of oral and oropharyngeal surgical management field.

12.2 Limitations and future recommendations

- Cadaver pig heads were used to mimic human head tissues during MRI and CBCT scanning and measuring the MRI-CBCT co-registration process accuracy (Chapter 4). The movement factor during image scanning was absent in this study, which may have overestimated the measured accuracy. The fiducial markers were used to measure the accuracy of the intrinsic co-registration (mutual-information-based) process. However, the presence of markers in the images was inevitable and may have positively influenced the co-registration algorithm when the mutual information between CBCT and MR images was computed. Also, the study measured the accuracy in image co-registration between MRI (PD) and CBCT. Other MRI weighted sequences such as (TI & T2) may have different results and can be evaluated in the future.
- The small number of examiners (2 radiologists), in the study in Chapter 5, was a chief limitation. Given that the MRI-CBCT tool is likely of the most value in aiding novice users; further evaluation in a broad spectrum of examiners of different level of expertise is needed for further validation. Images of various groups of patients with different TMJ conditions should be used to explore the advantages of MRI-CBCT registered images over MRI alone in TMJ diagnostic imaging.
- Similarly, the study in Chapter 6, included a small number of images and single spectrum of novice examiners with the same level of experience (Graduate and undergraduate dental students), which were limitations that may have affected the power of the study's conclusions. A web-based evaluation tool can be used in the future to facilitate evaluation of a larger number of images by a wider spectrum of novice examiners with different

levels of experience, such as medical students, diagnostic radiology residents and TMJ disorders specialists.

- The low signal-to-noise ratio of the obtained CBCT images for adolescents, in Chapter 8, compromised the MRI-CBCT co-registration quality and negated the value of the fused imaging tool in improving examiners' reliability to diagnose disc positions. Conceptually, images of higher exposure parameters should be considered when TMJ osseous changes are to be diagnosed and evaluated over time. Small FOV high-resolution CBCT images of the TMJ should be obtained for adolescents, and the co-registration of the small FOV CBCT with MRI should be attempted and optimized in the future. Although this was a pilot study, the limited number of the obtained images and the participating examiners reduced the strength of the present study conclusions.
- During MRI and CBCT scanning, inherent artifacts such as (motion artifact, metallic susceptibility (dental work, vascular clips), may potentially affect the quality of the MRI and CBCT image co-registration process and should be avoided. Patients should be asked to remain immobile during scanning, and heads can be stabilized by being fastened to a particular head holder. Occlusal splints in the maximum intercuspation position are necessary to guarantee the condylar position in both MRI and CBCT images.
- Although the MRI-CBCT image registration in the open mouth is technically possible, additional open-mouth CBCT images may not be necessary since they don't provide additional diagnostic information. Throughout the studies of this Ph.D. project, images were taken in a close-mouth position to standardize the measurements of the disc changes.

- The manual segmentation of the TMJ disc by an experienced operator (Chapter 11) seems to be the most reliable approach. However, it's a tedious process and highly operator dependent. Operator fatigue, little experience, and repeatability are all potential error sources.
- The measured differences in the structures' segmentation using Dice Similarity Index and Mean Root Squared Distance (Chapter 11) were subject to an inevitable software quantization, and the choice of points (the software truncates the numerical contour location values to the nearest pixel location) were potential errors.
- Although the three-dimensional segmentation of the TMJ (Chapter 11, 12) was, somewhat, time-consuming and requires operator interaction. Further research should be continued to improve the time factor and the operator dependency of the disc manual segmentation.
- Measuring the TMJ morphological changes in a short period following the surgical treatments for oral/oropharyngeal cancer (Chapter 12) may not have allowed complete healing of the tissues and may have influenced the findings of the study. Another study can be conducted to evaluate the long-term healing effects and the chemo-radiotherapy effects on the same cohort to help to understand the association between the morphological and functional changes of the TMJ. Although the patients of both groups, in Chapter 12, were matched by age and gender, the tumor type, size, and extension were not completely matched, which may have been a source of bias when the outcomes of the both groups were compared.

12.3 General Conclusions

Within the limitations of this research, the following can be concluded:

1. The intrinsic co-registration (mutual-information-based) of the MRI-CBCT images was proved to produce superior image quality compared to extrinsic co-registration. The intrinsic (mutual-information-based) iterative algorithm provided an accurate and reliable tool to co-register MRI and CBCT images of the head.

2. The MRI-CBCT registered images significantly improved the intra- and inter-examiner reliability among experienced readers to evaluate the TMJ disc position in relation to the condyle compared to MRI alone in adults. However, the diagnostic value of the MRI-CBCT co-registered images to detect osseous pathology was comparable to CBCT alone except for small osseous changes such as surface erosions. The low signal-to-noise ratio of the CBCT images obtained for the adolescents affected the quality of the resultant MRI-CBCT co-registered images, and did not improve the intra- and inter-examiners' reliability to evaluate the TMJ disc position compared to MRI alone.

3. The MRI-CBCT registered images significantly improved the reliability and accuracy of the TMJ disc position assessment by novice examiners compared to MRI alone, and therefore was considered useful for TMJ educational diagnostic purposes.

4. The MRI-CBCT co-registered images provided a reliable tool to reconstruct three-dimensional models of the TMJ soft and hard tissues. The reconstructed TMJ models allowed quantification of the morphological and position changes regarding x-y-z-linear measurements, which facilitate measuring changes over time and after interventions. The quantitative assessment using the three-dimensional models of the TMJ from MRI-CBCT co-registered images, showed minimal changes of the condylar position and variable degrees of articular disc displacement associated with mandibulotomy surgical intervention.

The MRI-CBCT image co-registration combines the optimum imaging modalities to visualize both soft tissues and hard tissues in one display without affecting the quality or the nature of the original MRI or CBCT images. The present Ph.D. project focused on improvement of diagnosis accuracy and reliability of disc position by clearly outlining the surrounding osseous structures (such as condylar outline, condylar head inclination, depth of glenoid fossa and articular eminence slope), using MRI-CBCT image co-registration. The above conclusions highlighted the potential use of MRI-CBCT co-registered images as a clinical and an educational tool, for medical/dental students who might find the MRI of the hard to understand. Also, the MRI-CBCT image co-registration provided a three-dimensional representation of TMJ tissues that allowed quantification of changes in TMJ soft and hard tissues and helped understanding remodeling changes and treatment outcomes in the field of dentistry.

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List of abbreviation

2D: Two-dimensional.

3D: Three-dimensional.

AE: Articular eminence.

ANOVA: Analysis of variance.

CBCT: Cone-beam computed tomography.

DICOM: Digital imaging and communication in medicine.

DJD: Degenerative Joint Disease.

DSI: Dice similarity index.

FDS: Function Disability Scale.

FOV: Field of view.

ICC: Intra-class Correlation Coefficients

ID: Interincisal distance.

ID: Internal derangement.

JFLS: Jaw Function Limitation Scale.

JIA: Juvenile idiopathic arthritis.

Kv: kilovoltage.

mA: milliAmber.

MD: Maximum distance.

MI: Mutual information.

MRI: Magnetic resonance imaging.

MxD: Maximum distance.

PD: Proton density.

PET: Positron emission tomography.

POSAS: Patient and observer scar assessment scale.

RCT: Randomized controlled trial.

RDC/TMD: Research Diagnostic Criteria for TMD.

RMSD: Root mean squared distance.

SCC: Squamous cell carcinoma.

SD: Standard deviation.

STIR: Short tau inversion recovery

STL: STereoLithography.

TE: Time to echo.

TMD: TMJ disorder.

TMJ: Temporomandibular Joint.

TR: Time to repetition.

VAS: Visual analogue scale.

VSS: Vancouver scar scale.

VTK: Visualization toolkit.

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Appendix A: Search Strategy

Database	Keywords	Results After abstract	Selected	
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>	1 exp Magnetic Resonance Imaging/ or MRI.mp. (396001) 2 exp Tomography, X-Ray Computed/ or CT.mp. (439315) 3 exp Cone-Beam Computed Tomography/ or CBCT.mp. (5907) 4 cone beam CT.mp. (2084) 5 1 or 2 or 3 or 4 (753812) 6 TMJ.mp. or exp Temporomandibular Joint/ (14080) 7 exp Temporomandibular Joint Disorders/ or TMD.mp. or exp Temporomandibular Joint Dysfunction Syndrome/ (16654) 8 Craniomandibular disorder.mp. or exp Craniomandibular Disorders/ (15165) 9 internal derangement.mp. (1088) 10 Temporomandibular Joint Disc.mp. or exp Temporomandibular Joint Disc/ (1638) 11 temporomandibular Joint Disk.mp. (110) 12 6 or 7 or 8 or 9 or 10 or 11 (24634) 13 exp Image Processing, Computer-Assisted/ or registration.mp. (237947) 14 Integration.mp. (124984) 15 merging.mp. (5001) 16 fusion.mp. (239841) 17 matching.mp. (54912) 18 superimposition.mp. (2655) 19 13 or 14 or 15 or 16 or 17 or 18 (649700) 20 5 and 12 and 19 (464)	11	4	
Embase <1974 to 2016 January 18>	1 exp Magnetic Resonance Imaging/ or MRI.mp. (648560) 2 exp Tomography, X-Ray Computed/ or CT.mp. (811160) 3 exp Cone-Beam Computed Tomography/ or CBCT.mp. (8822) 4 cone beam CT.mp. (3525) 5 1 or 2 or 3 or 4 (1274044) 6 TMJ.mp. or exp Temporomandibular Joint/ (15601) 7 exp Temporomandibular Joint Disorders/ or TMD.mp. or exp Temporomandibular Joint Dysfunction Syndrome/ (13781) 8 Craniomandibular disorder.mp. or exp Craniomandibular Disorders/ (11521) 9 internal derangement.mp. (1212)	4	1	

	10 Temporomandibular Joint Disc.mp. or exp Temporomandibular Joint Disc/ (12017) 11 temporomandibular Joint Disk.mp. (107) 12 6 or 7 or 8 or 9 or 10 or 11 (24743) 13 exp Image Processing, Computer-Assisted/ or registration.mp. (123359) 14 merging.mp. (5516) 15 fusion.mp. (197471) 16 matching.mp. (73230) 17 superimposition.mp. (3017) 18 Integration.mp. (140940) 19 13 or 14 or 15 or 16 or 17 or 18 (532017) 20 5 and 12 and 19 (214)			
EBM Reviews - Cochrane Database of Systematic Reviews <2005 to January 13, 2016>, EBM Reviews - ACP Journal Club <1991 to December 2015>, EBM Reviews - Database of Abstracts of Reviews of Effects <2nd Quarter 2015>, EBM Reviews - Cochrane Central Register of Controlled Trials <December 2015>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <4th Quarter 2015>, EBM Reviews - NHS Economic Evaluation Database <2nd Quarter 2015>	1 (Magnetic Resonance Imaging or MRI).mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] (11865) 2 (CT or computed tomography).mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] (61531) 3 (CBCT or Cone Beam Computed Tomography).mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] (165) 4 (TMJ or Temporomandibular Joint).mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] (861) 5 (Temporomandibular Joint Disorder or TMD).mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] (342) 6 Temporomandibular Joint Disc.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] (72) 7 Temporomandibular Joint Disk.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] (12) 8 Craniomandibular disorder.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] (10) 9 Image processing.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] (1751) 10 Registration.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] (14090) 11 Integration.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] (2271) 12 Merging.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] (92) 13 Fusion.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] (3891) 14 Matching.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] (5429) 15 Superimposition.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] (53) 16 1 or 2 or 3 (71109) 17 4 or 5 or 6 or 7 or 8 (982) 18 9 or 10 or 11 or 12 or 13 or 14 or 15 (26994) 19 16 and 17 and 18 (4)	0	0	

Scopus 2016January 18	1. History Search TermsTITLE-ABS-KEY ("Cone beam CT" OR cbct) 6,364 document results 2. History Search Terms(TITLE-ABS-KEY ("Magnetic Resonance Imaging" OR mri)) OR (TITLE-ABS-KEY ("Computed Tomography" OR ct)) OR (TITLE-ABS-KEY ("Cone beam CT" OR cbct)) 998,049 document results 3. History Search TermsTITLE-ABS-KEY ("Temporomandibular Joint" OR tmj OR "Temporomandibular Joint Disorder" OR tmd OR "Craniomandibular Disorder" OR "Temporomandibular Joint Disc" OR "Temporomandibular Joint Disk") 30,918 document results 4. History Search TermsTITLE-ABS-KEY (registration OR "image processing" OR superimposition OR fusion OR matching OR integration OR merging) 1,704,426 document results 5. History Search Terms((TITLE-ABS-KEY ("Magnetic Resonance Imaging" OR mri)) OR (TITLE-ABS-KEY ("Computed Tomography" OR ct)) OR (TITLE-ABS-KEY ("Cone beam CT" OR cbct))) AND (TITLE-ABS-KEY ("Temporomandibular Joint" OR tmj OR "Temporomandibular Joint Disorder" OR tmd OR "Craniomandibular Disorder" OR "Temporomandibular Joint Disc" OR "Temporomandibular Joint Disk")) AND (TITLE-ABS-KEY (registration OR "image processing" OR superimposition OR fusion OR matching OR integration OR merging)) **298** document results.	1	1	
Subtotal			6	
Repeated			3	
Total to be analyze for inclusion		16	3	
Manual search to be analyze for inclusion		00	00	
Total			3	

Appendix B: Search Strategy

Database	Keywords	Results after abstract screening	Included after full article review
MEDLINE <1946 to 2015 May 5>	1 exp orthodontic appliances/ or orthodontic appliances, functional/ or activator appliances/ (19000) 2 Functional appliance*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (581) 3 (Crossbow or Forsus or Jasper Jumper or Herbst or MARA or Functional Mandibular advancer).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1292) 4 1 or 2 or 3 (20057) 5 temporomandibular joint/ or temporomandibular joint disc/ (10100) 6 (temporomandibular joint or TMJ or craniomandibular joint or jaw joint or mandibular joint).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (22650) 7 5 or 6 (22650) 8 (comment or editorial or historical article or letter or newspaper article or published erratum).pt. (1630279) 9 (4 and 7) not 8 (1305) 10 tomography, x-ray computed/ or tomography, spiral computed/ (289586) 11 cone-beam computed tomography/ or spiral cone-beam computed tomography/ (3276) 12 (CT or CBCT).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (213691) 13 Magnetic Resonance Imaging/ (278522) 14 MRI.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (140831) 15 10 or 11 or 12 or 13 or 14 (646289) 16 9 and 15 (140)	17	10
EMBASE <1974 to 2015 Week 19>	1 exp orthodontic device/ (16877) 2 orthodontic appliance*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1749) 3 Functional appliance*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (579) 4 (Crossbow or Forsus or Jasper Jumper or Herbst or MARA or Functional Mandibular advancer).mp. (1482) 5 1 or 2 or 3 or 4 (18614) 6 exp temporomandibular joint/ (11184) 7 (temporomandibular joint or TMJ or craniomandibular joint or jaw joint or mandibular joint).mp. (22887) 8 6 or 7 (22887) 9 5 and 8 (659)	8	2

	10 cone beam computed tomography/ or computer assisted tomography/ (498124) 11 (computed tomography or CT or cone-beam tomography or CBCT).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (418656) 12 nuclear magnetic resonance imaging/ (452414) 13 (Magnetic resonance imaging or MRI).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (532666) 14 10 or 11 or 12 or 13 (1058379) 15 9 and 14 (65)		
EBM Reviews - Cochrane Database of Systematic Reviews <2005 to March 2015>, EBM Reviews - ACP Journal Club <1991 to April 2015>, EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2015>, EBM Reviews - Cochrane Central Register of Controlled Trials <April 2015>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2014>, EBM Reviews - Health Technology Assessment <1st Quarter 2015>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2015>	1 orthodontic appliance*.mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw] (937) 2 Functional appliance*.mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw] (90) 3 (Crossbow or Forsus or Jasper Jumper or Herbst or MARA or Functional Mandibular advancer).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw] (86) 4 1 or 2 or 3 (1001) 5 (temporomandibular joint or TMJ or craniomandibular joint or jaw joint or mandibular joint).mp. (808) 6 4 and 5 (50) 7 (computed tomography or CT or cone-beam tomography or CBCT).mp. (32869) 8 (Magnetic resonance imaging or MRI).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw] (9085) 9 7 or 8 (40291) 10 6 and 9 (9)	4	-
Scopus 1965 to May 4, 2015	TITLE-ABS-KEY("orthodontic appliances" OR "functional appliance") (15,013) TITLE-ABS-KEY(crossbow OR forsus OR "Jasper Jumper" OR herbst OR mara OR "Functional Mandibular advancer") (4,132) ((TITLE-ABS-KEY("orthodontic appliances" OR "functional appliance")) OR (TITLE-ABS-KEY(crossbow OR forsus OR "Jasper Jumper" OR herbst OR mara OR "Functional Mandibular advancer"))) (18,823) TITLE-ABS-KEY("temporomandibular joint" OR tmj OR "craniomandibular joint" OR "jaw joint" OR "mandibular joint") (26,255) TITLE-ABS-KEY("computed tomography" OR ct OR "cone-beam tomography" OR cbct OR "Magnetic resonance imaging" OR mri) (886,237) ((((TITLE-ABS-KEY("orthodontic appliances" OR "functional appliance")) OR (TITLE-ABS-KEY(crossbow OR forsus OR "Jasper Jumper" OR herbst OR mara OR "Functional Mandibular advancer")))) AND (TITLE-ABS-KEY("temporomandibular joint" OR tmj OR "craniomandibular joint" OR "jaw joint" OR "mandibular joint"))) AND (TITLE-ABS-KEY("computed tomography" OR ct OR "cone-beam tomography" OR cbct OR "Magnetic resonance imaging" OR mri)) (55)	1	-

Total to be analyze for inclusion			-
Manual search to be analyze for inclusion		2	2
Total		32	14

Appendix C: Ethics approvals

Approval Form

Date:	October 25, 2012	
Principal Investigator:	Paul Major	
Study ID:	Pro00032935	
Study Title:	**Temporomandibular Joint, Masticatory Muscles and Jaw Functions Changes Associated with Transmandibular Surgery in Oral and Oropharyngeal Cancer Management.**	
Approval Expiry Date:	October 24, 2013	
Date of Informed Consent:	Approval Date 10/25/2012	Approved Document Consent form.doc
Funding/Sponsor:	PFFM Autism Center - Saudi	

Thank you for submitting the above study to the Health Research Ethics Board - Biomedical Panel. All issues arising from the review of your application have been addressed. There are no outstanding issues and your study has been approved.

The Health Research Ethics Board assessed all matters required by section 50(1)(a) of the Health Information Act. Appropriate processes have been put in place related to the disclosure and use of identifiable health information for the research described in the ethics application. Consent for the disclosure of identifiable health information will be obtained by an appropriate Custodian. In order to comply with the Health Information Act, a copy of the approval form is being sent to the Office of the Information and Privacy Commissioner.

A renewal report must be submitted next year prior to the expiry of this approval if your study still requires ethics approval. If you do not renew on or before the renewal expiry date (October 24, 2013), you will have to re-submit an ethics application.

The membership of the Health Research Ethics Board - Biomedical Panel complies with the membership requirements for research ethics boards as defined in Division 5 of the Food and Drug Regulations and the Tri-Council Policy Statement. The HREB - Biomedical Panel carries out its functions in a manner consistent with Good Clinical Practices.

Approval by the Health Research Ethics Board does not encompass authorization to access the patients, staff or resources of Alberta Health Services or Covenant Health for the purposes of the research. Enquiries regarding Alberta Health administrative approval, and operational approval for areas impacted by the research, should be directed to the Alberta Health Services Research Administration office, #1800 College Plaza, phone (780) 407-6041. Covenant Health approvals can be obtained by contacting 780-735-2274.

Sincerely,

S. K.M. Kimber, MD, FRCPC
Chair, HREB Biomedical

Note: This correspondence includes an electronic signature (validation and approval via an online system).

Alberta Health Services

AHS ADMINISTRATIVE APPROVAL FOR RESEARCH

NACTRC
The Northern Alberta Clinical Trials and Research Centre

Northern Alberta Clinical Trials and Research Centre
Research Administration
1800 College Plaza
8215 - 112 Street NW
Edmonton, AB T6G 2C8
www.nactrc.ca

Protocol Acronym: ________ **Protocol #:** ________ **REB #:** Pro00032935 **Ethics Approved:** Oct 25, 2012

Protocol Title:
Temporomandibular Joint, Masticatory Muscles and jaw Functions Changes Associated with Transmandibular Surgery in Oral and Oroharyngeal Cancer Management

Principal Investigator:	Dr. Paul Major	**Funding Agency:**	PFFM Autism Centre
Faculty:	Medicine & Dentistry	**Funding Type:**	Investigator-Initiated/Grant
		Overhead Rate:	0%

AHS Operational Approvals:

15631: University of Alberta Hospital - Otolaryngology Clinic (Surgery)

Comments:

AHS Admin File #:	31663
Approved:	Dec 13, 2012
Approved By:	Carlos Miranda NACTRC Research Administration On Behalf of Alberta Health Services

TMJ

Human Ethics Research Online (HERO)
Office of the Vice-President (Research), University of Alberta

Gail Schaffler | My Home | Logoff

HERO Home

REB Studies > Temporomandibular Joint, Masticatory Muscles and Jaw Functions Changes Associated with Transmandibular Surgery in Cancer Management.

1 / 4 Next >

Activity Details (Ancillary Committee Approval Issued)

Used by an ancillary committees to approve the study.

Author:	Gail Schaffler (MH Radiology/Diagnostic Imag)
Logged For (HERO Study):	Temporomandibular Joint, Masticatory Muscles and Jaw Functions Changes Associated with Transmandibular Surgery in Cancer Management.
Activity Date:	10/1/2012 2:33 PM MDT

Activity Form | Property Changes | Documents / Tasks / Notifications

The following is the list of Ancillary Committee(s) required to approve this application:
Radiation Safety

The following Ancillary Committees that have already submitted their approval:
There are no items to display

* **Select the Ancillary Committee your are providing approval on behalf of:**
- [x] **Radiation Safety**

Additional Review Comments:
Approval is granted on behalf of the AHS Regional Radiation Safety Committee.

Exit

APPLICATION FOR OPERATIONAL APPROVAL
to Conduct Research at Alberta Health Services

CROSS CANCER INSTITUTE
RADIATION ONCOLOGY

RESEARCH TITLE:

Temporomandibular Joint, Masticatory Muscles and Jaw Functions Changes Associated with Transmandibular Surgery in Oral and Oropharyngeal Cancer Management.

Expected Start Date:	2013-01-01
Expected End Date:	2014-01-30
Expected Number of Research Subjects:	50
Research Category:	Observational
Research Type:	Outcomes Research
REB / REB #:	HREB (EDM) / Pro00032935

PI INFORMATION:

Name:	Paul Major
Zone:	Edmonton
Faculty:	Medicine and Dentistry
Department:	Dentistry and Dental Hygiene
Phone:	780-492-3312
Email:	major@ualberta.ca

PRIMARY CONTACT:

AREA IMPACT:

1) Will AHS staff from this area be expected to participate and/or carry out any duties related to this study?

No

2) Will AHS staff from this area require any training or education?

No

3) Are you expecting this AHS area to provide you with supplies and/or equipment?

No

4) Funding Type: Investigator-Initiated / Internal and/or Contingency Funding

NOTE: If the area being impacted determines that there are costs associated with your research, they will contact you prior to issuing Operational Approval.

QUESTIONS SPECIFIC TO THE AREA:

1) Indicate all requirements for scanning or contouring that would not be considered departmental standard of practise.

Subjects will not have any special procedures out of the department standard of practise.
In this study, subjects will undergo dental exam, MRI and CT imaging for the tumour area and quality of life questionnaire, which are considered routine procedures for this group of patients.

2) Indicate all requirements for adherence to specific timelines for planning and start of treatment that is directly related to the research.

Assessments will take placed before treatment (surgery or radiotherapy) and 9 months after treatment to allow tissue healing and rehabilitation.
No specific timeline will be determined as assessments will be performed at the routine oncology appointments to reduce drop out rates.

3) Does the research involve a fractionation scheme or specific technical requirements that would not be considered departmental standard?

Alberta Health Services

APPLICATION FOR OPERATIONAL APPROVAL to Conduct Research at Alberta Health Services

NACTRC The Northern Alberta Clinical Trials and Research Centre

CROSS CANCER INSTITUTE RADIATION ONCOLOGY

RESEARCH TITLE:

Temporomandibular Joint, Masticatory Muscles and Jaw Functions Changes Associated with Transmandibular Surgery in Oral and Oropharyngeal Cancer Management.

Expected Start Date:	2013-01-01
Expected End Date:	2014-01-30
Expected Number of Research Subjects:	50
Research Category:	Observational
Research Type:	Outcomes Research
REB / REB #:	HREB (EDM) / Pro00032935

PI INFORMATION:

Name:	Paul Major
Zone:	Edmonton
Faculty:	Medicine and Dentistry
Department:	Dentistry and Dental Hygiene
Phone:	780-492-3312
Email:	major@ualberta.ca

PRIMARY CONTACT:

AREA IMPACT:

1) Will AHS staff from this area be expected to participate and/or carry out any duties related to this study?

No

2) Will AHS staff from this area require any training or education?

No

3) Are you expecting this AHS area to provide you with supplies and/or equipment?

No

4) Funding Type: Investigator-Initiated / Internal and/or Contingency Funding

NOTE: If the area being impacted determines that there are costs associated with your research, they will contact you prior to issuing Operational Approval.

QUESTIONS SPECIFIC TO THE AREA:

1) Indicate all requirements for scanning or contouring that would not be considered departmental standard of practise.

Subjects will not have any special procedures out of the department standard of practise.
In this study, subjects will undergo dental exam, MRI and CT imaging for the tumour area and quality of life questionnaire, which are considered routine procedures for this group of patients.

2) Indicate all requirements for adherence to specific timelines for planning and start of treatment that is directly related to the research.

Assessments will take placed before treatment (surgery or radiotherapy) and 9 months after treatment to allow tissue healing and rehabilitation.
No specific timeline will be determined as assessments will be performed at the routine oncology appointments to reduce drop out rates.

3) Does the research involve a fractionation scheme or specific technical requirements that would not be considered departmental standard?

Approval Form

Date:	March 2, 2015
Principal Investigator:	Paul Major
Study ID:	Pro00053614
Study Title:	Assessment of Temporomandibular Joint Internal Derangement using MRI-CBCT Image Registration
Approval Expiry Date:	February 29, 2016

Date of Informed Consent:	Approval Date 3/2/2015	Approved Document Final information sheet

Funding/Sponsor: Fund for Dentistry

Thank you for submitting the above study to the Health Research Ethics Board - Biomedical Panel. Your application has been given a delegated review and has been approved on behalf of the committee.

The Health Research Ethics Board assessed all matters required by section 50(1)(a) of the Health Information Act. Subject consent for access to identifiable health information is required for the research described in the ethics application, and appropriate procedures for such consent have been approved by the HREB - Biomedical Panel. In order to comply with the Health Information Act, a copy of the approval form is being sent to the Office of the Information and Privacy Commissioner.

A renewal report must be submitted next year prior to the expiry of this approval if your study still requires ethics approval. If you do not renew on or before the renewal expiry date (February 29, 2016), you will have to re-submit an ethics application.

The membership of the Health Research Ethics Board - Biomedical Panel complies with the membership requirements for research ethics boards as defined in Division 5 of the Food and Drug Regulations and the Tri-Council Policy Statement. The HREB - Biomedical Panel carries out its functions in a manner consistent with Good Clinical Practices and the Canadian General Standads Board (CAN/CGSB-101.1-2013).

Approval by the Health Research Ethics Board does not encompass authorization to access the patients, staff or resources of Alberta Health Services or other local health care institutions for the purposes of the research. Enquiries regarding Alberta Health administrative approval, and operational approval for areas impacted by the research, should be directed to the Alberta Health Services Research Administration office, #1800 College Plaza, phone (780) 407-6041.

Re-Approval Form

Date:	March 11, 2015
Principal Investigator:	Paul Major
Study ID:	Pro00045191
Study Title:	Skeletal, Functional and Dental Changes During Treatment of Mild to Moderate Class II Malocclusions With Fixed Class II Correctors: A Randomized Clinical Trial.
Approval Expiry Date:	March 23, 2016
Sponsor/Funding Agency:	Fund for Dentistry

The Health Research Ethics Board - Biomedical Panel has reviewed the renewal request and file for this project and found it to be acceptable within the limitations of human experimentation.

The re-approval for the study as presented is valid for another year. It may be extended following completion of the annual renewal request. Beginning 45 days prior to expiration, you will receive notices that the study is about to expire. Once the study has expired you will have to resubmit. Any proposed changes to the study must be submitted to the HREB for approval prior to implementation.

All study-related documents should be retained so as to be available to the HREB on request. They should be kept for the duration of the project and for at least five years following study completion. In the case of clinical trials approved under Division 5 of the Food and Drug regulations of Health Canada, study records must be retained for 25 years.

The membership of the Health Research Ethics Board - Biomedical Panel complies with the membership requirements for research ethics boards as defined in Division 5 of the Food and Drug Regulations and the Tri Council Policy Statement. The HREB - Biomedical Panel carries out its functions in a manner consistent with Good Clinical Practices and the Canadian General Standards Board (CAN/CGSB-101.1-2013).

Sincerely,

J. Stephen Bamforth, MD
Associate Chair, HREB Biomedical

Note: This correspondence includes an electronic signature (validation and approval via an online system).

Approval Form

Date:	May 8, 2015
Principal Investigator:	Paul Major
Study ID:	Pro00055827
Study Title:	Temporomandibular Joint, Masticatory Muscles and Jaw Functions Changes Associated with Transmandibular Surgery in Oral and Oropharyngeal Cancer Management.
Approval Expiry Date:	May 07, 2016

Date of Informed Consent:	Approval Date	Approved Document
	5/8/2015	Consent form-12APR15-Clean copy

Funding/Sponsor: PFFM Autism Center - Saudi

Thank you for submitting the above study to the Health Research Ethics Board - Biomedical Panel. Your application and the attached documentation has been reviewed and approved on behalf of the committee.

The Health Research Ethics Board assessed all matters required by section 50(1)(a) of the Health Information Act. Subject consent for access to identifiable health information is required for the research described in the ethics application, and appropriate procedures for such consent have been approved by the HREB - Biomedical Panel. In order to comply with the Health Information Act, a copy of the approval form is being sent to the Office of the Information and Privacy Commissioner.

A renewal report must be submitted next year prior to the expiry of this approval if your study still requires ethics approval. If you do not renew on or before the renewal expiry date (May 07, 2016), you will have to re-submit an ethics application.

The membership of the Health Research Ethics Board - Biomedical Panel complies with the membership requirements for research ethics boards as defined in Division 5 of the Food and Drug Regulations and the Tri-Council Policy Statement. The HREB - Biomedical Panel carries out its functions in a manner consistent with Good Clinical Practices and the Canadian General Standads Board (CAN/CGSB-101.1-2013).

Approval by the Health Research Ethics Board does not encompass authorization to access the patients, staff or resources of Alberta Health Services or other local health care institutions for the purposes of the research. Enquiries regarding Alberta Health administrative approval, and operational approval for areas impacted by the research, should be directed to the Alberta Health Services Research Administration office, #1800 College Plaza, phone (780) 407-6041.

Activity Details (Ancillary Committee Approval Issued)

Used by an ancillary committees to approve the study.

Author:	Gail Schaffler (MH Radiology/Diagnostic Imag)
Logged For (HERO Study):	Skeletal, Functional and Dental Changes During Treatment of Mild to Moderate Class II Malocclusions With Fixed Class II Correctors: A Randomized Clinical Trial
Activity Date:	3/5/2014 10:26 AM

Activity Form | Property Changes | Documents | Notifications

Property	Old Value	New Value
name		Ancillary Committee Approval Issued
Ancillary Approvals		Added elements: • HERO Radiation Safety
Set of Person		Added elements: • Paul Major

APPLICATION FOR OPERATIONAL APPROVAL
to Conduct Research at Alberta Health Services

UNIVERSITY OF ALBERTA HOSPITAL
ENT CLINIC SURGERY

RESEARCH TITLE:

Temporomandibular Joint, Masticatory Muscles and Jaw Functions Changes Associated with Transmandibular Surgery in Oral and Oropharyngeal Cancer Management.

Expected Start Date:	2015-07-01
Expected End Date:	2017-06-30
Expected Number of Research Subjects:	20
Research Category:	Observational
Research Type:	Technology Assessment
REB / REB #:	HREB / Pro00055827

PI INFORMATION:

Name:	Paul Major
Zone:	Edmonton
Faculty:	Medicine and Dentistry
Department:	Dentistry and Dental Hygiene
Phone:	780-492-3312
Email:	major@ualberta.ca

STUDY COORDINATOR:

AREA IMPACT:

1) Will AHS staff from this area be expected to participate and/or carry out any duties related to this study??

NO

2) Will AHS staff from this area require any training or education??

NO

3) Are you expecting this AHS area to provide you with supplies and/or equipment? ?

NO

4) Funding Type: Investigator-Initiated / Internal and/or Contingency Funding

NOTE: If the area being impacted determines that there are costs associated with your research, they will contact you prior to issuing Operational Approval.

QUESTIONS SPECIFIC TO THE AREA:

PROTOCOL SYNOPSIS:

APPLICATION FOR
OPERATIONAL APPROVAL
to Conduct Research at Alberta Health Services

UNIVERSITY OF ALBERTA HOSPITAL
ENT CLINIC SURGERY

Jaw movements are made possible by the contraction of the chewing muscles and articulation of the jaw joints (TMJ). Mandibulotomy is the surgical splitting of the jaw bone to provide access to tumors located in the upper throat region for surgical removal. This procedure is controversial as several studies have found that, during post-surgical follow-ups, the function of the jaw and related muscles can be impaired. The primary purpose of this study is to assess the impact of mandibulotomy and associated radiotherapy on jaw movements with specific interest on the bone and cartilage disc components of the jaw joint and chewing muscles. The study will utilize data from multiple sources including; quality of life questionnaires, clinical jaw movement measurements, masticatory muscles tenderness, magnetic resonance imaging (MRI), computed tomography (CT) and cone-beam computerized tomography (CBCT) images to determine and compare the structure and function of the tissues before and after cancer management. Study patients will be adults from the Edmonton region with a confirmed diagnosis of either oral or oropharyngeal cancer undergoing routine treatment at the Department of Head and Neck Surgery at the University of Alberta Hospital. Patients will undergo imaging immediately prior to treatment and again 9 months after treatment to allow sufficient time for healing and rehabilitation. Findings from this study will provide high quality evidence that will describe the long-term effect of mandibulotomy on jaw function and structure. Using this evidence, routine treatment practices can be amended as needed, and rehabilitation programs can be implemented to best preserve the oral function for this patient population.

SUBMITTED BY / ASSESSORS / APPROVERS:

Requested By: Mohammed Al-Saleh — Date Requested: 2015-06-20

Assessed By: Shelly Scheideman — Date Assessed: 2015-06-24

There is no operational impact resulting from this study in ENT

Assessed By: Elizabeth Seib — Date Assessed: 2015-07-02