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Review Article

Radiation-Induced Changes in the Temporomandibular Joint and Synovial Fluid Leading to Radiation-Induced Trismus

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Abstract

Radiation therapy (RT) is an integral and indispensable treatment modality for most head and neck cancers (HNCs). Ionizing RT's impact on the temporomandibular joint (TMJ) and the synovial fluid is pivotal yet often overlooked. Although radiation therapy successfully combats cancer, it may also cause complex changes in the surrounding tissues, such as the TMJ and synovial fluid, which can lead to serious radiation-induced damage in these tissues. It is crucial to gain a comprehensive understanding of these changes to maximize the quality of patient care and achieve positive outcomes. Radiation-induced inflammation and fibrosis in the soft tissues can lead to stiffness, limited mobility, and persistent pain around the TMJ. Additionally, changes in the movement and flow of synovial fluid, including decreased production and damage to the synovial membrane, can accelerate the deterioration and development of osteoarthritic changes within the joint. The impact of ionizing radiation on the TMJ carries significant clinical implications, resulting in diminished oral functions, osteoradionecrosis, and degenerative TMJ disorders. Effective collaboration between related disciplines and proactive management strategies is vital for mitigating adverse repercussions and optimizing patient outcomes. By elucidating these consequences, healthcare professionals can customize treatment modalities, advance patient care, and ultimately enhance results for individuals undergoing RT for HNCs. Accordingly, this review has been meticulously prepared to amalgamate current knowledge about the multifaceted effects of RT on the TMJ and its associated synovial fluid.

Keywords: Radiotherapy; Head and Neck Cancer; Temporomandibular Joint; Synovial Fluid

Abbreviations

TMJ: Temporomandibular Joint; ORN: Osteoradionecrosis; TNF: Tumor Necrosis Factor; IL: Interleukin

Introduction

Radiation therapy (RT) plays an essential role in the treatment protocols for head and neck cancer (HNC) patients, offering distinct advantages in terms of locoregional control rates and overall survival outcomes. RT may be utilized as a standalone treatment modality or in conjunction with chemotherapy, surgical intervention, targeted therapies, and immunotherapy [1]. Unfortunately, despite notable advancements in RT methodologies, such as intensity-modulated RT (IMRT), the temporomandibular joint (TMJ) is frequently subjected to substantial radiation doses due to its proximity to the primary target volumes in individuals with HNCs [2]. A prevalent long-term complication of RT in HNC patients is TMJ impairment, specifically radiation-induced trismus (RIT), which impacts around 35-45% of patients [3-5], with a reported 32% reduction in the initially measured interincisal distance at four years of post-RT follow-up [6]. Regrettably, radiation-induced TMJ disorders, including the RIT, usually progress slowly and subtly, often going unnoticed by the patient until the advanced stages [7].

RIT significantly diminishes a patient's quality of life and ability to carry out daily activities. It presents a complex challenge beyond

the immediate discomfort of restricted jaw movement. This disorder adversely affects essential functions such as eating, speaking, and maintaining oral hygiene, leading to nutritional deficiencies, weight loss, and increased susceptibility to oral infections. Difficulties with chewing and swallowing may necessitate modifications to a diet comprising softer foods, potentially resulting in inadequate nutrient intake and reduced overall well-being [8,9].

The TMJ comprises a complex structure integral to the jaw's movement and function. Its primary components consist of the mandibular condyle, articular disc, joint capsule, synovial fluid, and associated muscles and ligaments. Each of these components is essential for the proper functioning of the TMJ [10,11]. While the precise mechanism of radiation's impact on the TMJ remains incompletely elucidated, it is postulated that this occurrence may be attributable to radiation fibrosis, gradual reduction in vascularity, denervation atrophy of the joint muscles, and injury to the mandible and TMJ [12]. While it is recognized that RIT primarily results from muscle fibrosis and scarring around the TMJ, there is limited data on the specific changes to the TMJ following RT or chemo-RT. Therefore, this review aims to provide a comprehensive summary of the overall effects of RT on the TMJ and related structures, such as synovial fluid, in HNC patients. It also seeks to provide a comprehensive perspective on managing these effects by comparing studies in the relevant literature.

Anatomy and physiology of the temporomandibular joint and related structures

The TMJ is a unique joint with bilateral and diarthrodial characteristics, allowing for a wide range of movements. The coordinated actions of the two TMJs exhibit hinge-like movement in the sagittal plane and are capable of two global and three local degrees of freedom, thereby expanding their range of motion [13].

The mouth exhibits a diverse array of movements, encompassing hinge-like rotation for opening and closing, elliptical rotation for constrictive actions, vertical plane lateral rotation, sagittal plane anterior-posterior translations, transverse plane lateral translations, and superior-inferior translations between the articular disc and condyle surfaces [14]. The mandibular condyles serve as essential anatomical constituents of the TMJ, conforming to the curvature of the mandibular fossa, an element of the cranial base. This configuration notably augments the range of motion of the mandibular-cranial complex. Consequently, an optimally engineered fit between the mandibular condyle and the mandibular fossa can forestall ligamentous overextension or dislocation from the correct anatomical position during periods of stress [14,15].

The TMJ is a crucial cranial structure involved in numerous activities, such as chewing, swallowing, speaking, facial expressions, and breathing. When the TMJ is affected by Temporomandibular Disorder (TMD), individuals may experience pain and limitations in their ability to perform these activities. Notably, TMJ discomfort, a common symptom of TMD, is more frequently reported by women, with 25% of females and 9% of males noting persistent TMJ issues [16]. TMD encompasses a spectrum of conditions, including degenerative disorders stemming from internal joint problems with or without disc displacement, joint effusion without disc displacement, osteoarthritis, and less common conditions such as inflammatory arthritis, infection, trauma, and neoplasm [15,16].

Articular surfaces and articular disc

The articular disc of the TMJ is a biconcave fibrocartilage structure that may be categorized into three functional parts: the posterior band, intermediate zone, and anterior band [17]. The thick anterior and posterior bands occupy the area formed by the convex surface of the mandibular condyle. Their primary function is to ensure the structural stability of the disc [17]. The extracellular matrix of the disc mainly comprises collagen type I and elastin, with smaller amounts of collagen II and negligible amounts of type III, VI, IX, and XII [18]. Collagen type I is the main component, forming a crucial diagonal and side-to-side structure that is essential for withstanding stretching forces [19]. The distribution and alignment of collagen fibers vary depending on the location within the disc and the presence of any pathological conditions [20]. The intermediate zone of the disc is predominantly composed of large fibers that are typically aligned parallel to the disc's surfaces in the anteroposterior direction. These fibers have a mediolateral and craniocaudal orientation in relation to the surrounding fibers [21]. The fiber groups primarily oriented in a transverse direction are confined to the anterior and posterior bands. Upon reaching these bands, the intermediate zone fibers expand in a superior and inferior direction, with some of them forming a continuous connection with horizontally oriented fasciculi. Additionally, certain horizontally arranged fiber bundles at the inner and outer edges of the disc are connected with the vertically arranged fibers, creating a circular structure around the outer edge of the disk [22].

The key functions of articular cartilage include load transmission, shock absorption, and minimizing joint friction. The articular disc of the TMJ exhibits similar structural and functional characteristics to intraarticular discs in other joints [17]. However, its capacity for shock absorption and nutritional activity is relatively lower than that of other joint components. Furthermore, articular

surfaces are commonly affected by the complex mechanical loads resulting from the movements of the associated joint [17]. Articular surfaces are integral components of bones that contribute to joint formation, enabling joint movement and providing a damping function. Due to their specific roles, the anatomy and physiology of articular surfaces differ from other parts of the bone. The most notable structural feature of these surfaces is the presence of articular cartilage, an avascular type of connective tissue located exclusively on articular surfaces. Articular cartilage exhibits unique porosity and permeability compared to other connective tissues, making it distinct. Its environmental characteristics become prominent under conditions of nutritional activity [23].

Ligaments and muscles

The TMJ is enclosed by an articular capsule comprising the synovium, fibrous joint lining, and fibrous tissues known as the lateral temporomandibular ligament, sphenomandibular ligament, and stylomandibular ligament. The synovial membrane is situated in the upper compartment of the joint, separated from the lower compartment by a bi-laminated fibroblastic tissue. Within the upper compartment, the articular disc is present in three varieties based on its shape: bilaminar, biconcave, and intermediate. Furthermore, the bilaminar disc is subdivided into the posterior and anterior bands. The synovial joint has a relatively small surface area, leading to a higher cell concentration. It undergoes endochondral ossification and is referred to as secondary cartilage. The mandibular condylar surface contains a significant amount of type II collagen fibers. These interconnected fibers form an uneven network that contributes to the surface's regular histological appearances and gross aspects [10,22].

The masseter, temporalis, medial, and lateral pterygoid muscles are the primary muscles involved in mastication. During this process, the digastric, mylohyoid, geniohyoid, and platysma also act as secondary muscles. These muscles control the movement of the TMJ and are responsible for taking food into the mouth and breaking it down for digestion. They are paired muscles that connect to the lower jaw and facilitate its movement during chewing. The main functions of these muscles include raising and lowering the lower jaw, moving it forward, backward, and laterally, stabilizing it, and controlling the closure of the mouth [24]. The accessory muscles insert into the mandibular condyle and are not directly involved in moving the mandible. These muscles include the digastric, mylohyoid, geniohyoid, genioglossus, temporalis, and masseter. Some of these muscles, like the mylohyoid, geniohyoid, digastric, and stylohyoid, originate from the mandibular symphysis. They move downwards to elevate the hyoid bone, and when they work together, they can elevate the mandible and participate in functions such as phonation, swallowing, breathing, motor functions of the axial skull structures, and head movement with neck displacement. These muscles are closely related to the TMJ, and any changes in their position or muscle tone can lead to various joint pathologies.

Considering the anatomic and physiological features mentioned above, the masticatory apparatus serves as a complex network of variable but interconnected components that, when functioning in harmony, exert the best oral cavity functions. Therefore, any pathological changes, including those caused by high-dose ionizing radiation, may disrupt the structural integrity of either component of the masticatory apparatus, leading to restricted mouth opening, and RIT when resulting from RT, along with severe detriments to its associated functions.

The effect of RT on TMJ and synovial fluid

RT can impact the TMJ and the synovial fluid, providing lubrication and nutrients to the joint. These potential effects can be listed as follows (Table 1).

- **Inflammation:** RT can cause inflammation in the tissues surrounding the TMJ, which may lead to severe pain, swelling, and stiffness in the joint. The TMJ comprises complex cartilaginous tissue containing chondrocytes surrounded by a rich extracellular matrix (ECM) composed mainly of collagen fibers, proteoglycan, and water. Chondrocytes, residing within the ECM, are pivotal in regulating the synthesis and degradation of matrix proteins, thereby maintaining a stable state known as homeostasis. This process leads to a gradual turnover of matrix proteins [25]. The disruption of this delicate balance, as seen in a damaged TMJ, initiates a two-phase response. Initially, there are changes in the quantity and arrangement of the ECM, during which chondrocytes attempt to restore the damaged ECM. Subsequently, a progressive increase in degradation ensues, leading to an overall reduction in the ECM [26]. The degradation of articular cartilage is primarily governed by cytokines and growth factors, particularly tumor necrosis factor-alpha (TNF-alpha) and interleukin-1beta (IL-1beta), which regulate matrix metalloproteinases (MMPs) that influence matrix formation [27]. The consequences of this disruption, such as cartilage thinning in joints, pain, swelling, and erosion of subchondral bone, may occur following RT, underscoring the potential severity of ECM involvement in radiation-induced TMJ injury [28].
- **Fibrosis:** Radiation-induced fibrosis (RIF) may manifest in

the synovial membrane and adjacent soft tissues of the TMJ, leading to hypertrophy and constriction of the synovial membrane, resulting in restricted joint mobility and pain. RIF is further characterized by excessive fibroblast proliferation, infiltration of inflammatory cells, presence of atypical fibroblasts, and accumulation of a significant amount of extracellular matrix in the affected areas [29]. Although the precise mechanism of radiation's impact on the TMJ is not fully elucidated, it is postulated that fibrosis, primarily due to RT, is attributable to the gradual reduction in vascularity within the region, denervation atrophy of joint muscles, and the degeneration of the TMJ disc, surface, ligaments, and synovial fluid [30,31]. Moreover, heightened fibroblastic activity can cause adhesions, which may result in joint stiffness, restricted mobility, and enduring pain, significantly affecting the quality of life for patients following RT.

- **Reduced synovial fluid production:** RT can harm the synovial membrane and reduce the production of synovial fluid [32], which is crucial for lubricating the joint surfaces and minimizing friction during movement. Decreased synovial fluid output can lead to heightened friction between the joint surfaces, causing wear and tear, pain, and stiffness [33]. Boundary lubrication of the TMJ is provided by a surface-active phospholipid complexed with lubricin and hyaluronic acid, which facilitates the joint's load-bearing capacity [34,35]. Lubricin, a prevalent component in synovial fluid, is considered the lubricating molecule that enables smooth joint movement, particularly in the TMJ [36]. A study has documented that RT suppresses proteoglycan synthesis, particularly of lubricin, with resultant TMJ injury due to restricted TMJ movements and the loss of its capacity to resist deformation at higher levels of friction and force [37].
- **Joint degeneration:** Persistent inflammation, fibrosis, and decreased production of synovial fluid can result in degenerative alterations in the TMJ, such as osteoarthritis [38]. These alterations might manifest as joint pain, crepitus (grinding or popping sensations), and restricted range of motion [39]. The damage to the TMJ caused by RT is a complex process involving multiple factors. High-energy ionizing radiation can directly harm cells, leading to inflammation, fibrosis, and changes in blood vessels within the joint tissues. Additionally, radiation-induced DNA damage can impair the cells' ability to repair themselves, making the TMJ more susceptible to long-term chronic dysfunction and degeneration [3]. The central pathological process in osteoarthritis (OA) involves the degradation of articular cartilage, a resilient tissue that provides cushioning between bone ends within the joint. This degradation is attributed to an imbalance between anabolic and catabolic activities. Chondrocytes, the indigenous cells of cartilage, demonstrate heightened production of matrix-degrading enzymes, including matrix metalloproteinases (MMPs) and aggrecanases, resulting in the depletion of collagen and proteoglycans. Furthermore, diminished synthesis of extracellular matrix constituents exacerbates cartilage breakdown, perpetuating the destructive cycle [40]. While the precise pathogenic mechanism within the TMJ remains elusive, it is postulated that synovial inflammation ensues due to the mechanical stress, leading to the release of pro-inflammatory cytokines like interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), which contribute to cartilage degradation and pain sensitivity [41,42]. Additionally, it is hypothesized that synovial fibrosis develops, contributing to joint rigidity and restricted mobility. Consequently, the interplay between the synovium, cartilage, and subchondral bone potentially perpetuates the progression of arthritis and exacerbates tissue damage.
- **Risk of osteoradionecrosis of TMJ (TMJ-related ORN):** Extensive damage to the surrounding soft tissues, such as the synovial membrane, due to radiation can lead to the onset of osteoradionecrosis (ORN) despite its primary impact on bone tissue. This devastating complication is defined by bone degeneration and the potential exposure through the soft tissues in the mandible near the TMJ [43]. Unlike classical osteoradionecrosis (ORN), TMJ-related ORN potentially occurs due to radiation-induced damage to the blood vessels, cells, and structural components of the TMJ rather than the bony structures [44]. Exposure to high levels of ionizing radiation causes damage to the endothelial cells, formation of blood clots in small blood vessels, and reduced blood flow to the joint [45]. The TMJ is more likely to experience ischemia, necrosis, and secondary infection due to subsequent fibrosis, hypocellularity, and delayed wound healing [3,46]. Additionally, radiation-induced changes in bone metabolism and turnover lead to osteopenia, bone resorption, and eventually ORN in the mandibular condyle and other structures [46]. In summary, ORN formation in the TMJ occurs due to RT's inflammatory and fibroatrophic effects [47], similar to its impact on different bones, including the mandible (Figure 1).

Radiotherapy Effect	Factors	Mechanism	Results
Inflammation	TNF-alpha IL-1beta	Effects matrix metalloproteinases Influence matrix formation	Thinning in joint and cartilage, Pain, Swelling, Erosion of subchondral bone
Fibrosis	Fibroblasts Inflammatory cells with fibrotic effect	Presence of atypical fibroblasts Accumulation of a significant extracellular matrix	Adhesions form due to increased fibroblastic activity Stiffness in the TMJ, Limitation of movement in the jaw Persistent pain Quality of life is negatively affected
Reduced synovial fluid production	Lubricin	Suppression of proteoglycan synthesis Decreased synovial fluid	Heightened friction between the joint surfaces, causing wear and tear, pain, and stiffness Restricted TMJ movements and the loss of its capacity to resist deformation at higher levels of friction and force
Joint degeneration	Chondrocytes TNF-alpha IL-1beta	Depletion of collagen and proteoglycans Cartilage breakdown Diminished synthesis of extracellular matrix Synovial inflammation due to mechanical stress	Cartilage degradation Pain sensitivity Synovial fibrosis Joint rigidity Restricted jaw mobility Progression of arthritis and exacerbated tissue damage
Risk of osteoradionecrosis of TMJ -related ORN	Inflammatory cells with fibrotic effect Endothelial cells Inflammatory cells with hypoxic effect	Damage to the endothelial cells Formation of blood clots in small blood vessels Reduced blood flow to the joint Osteopenia Bone resorption	Bone degeneration and the potential exposure through the soft tissues in the mandible near the TMJ Presence of ORN in the mandibular condyle

Table 1: The effect of radiotherapy on temporomandibular joint and synovial fluid.

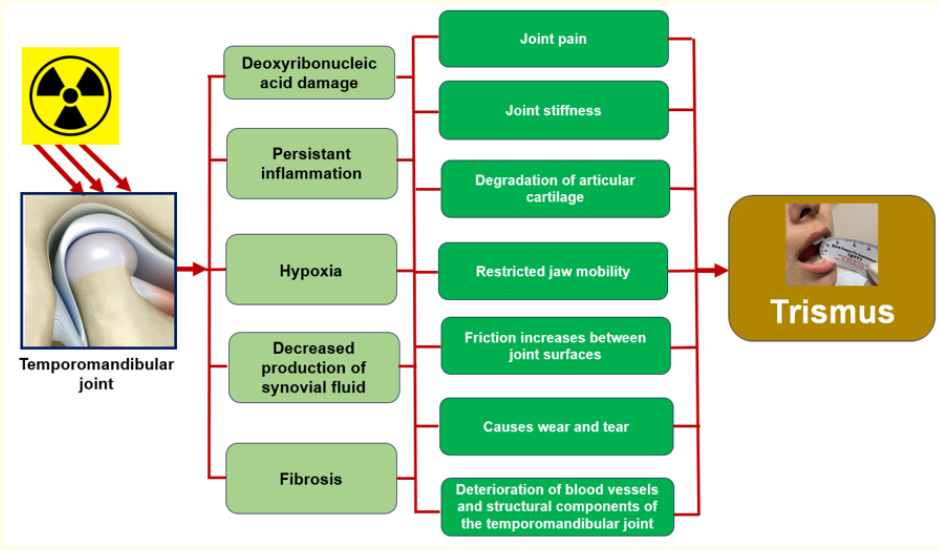

Figure 1: The mechanism of the effect of radiotherapy on temporomandibular joint.

Discussion

RT plays a pivotal role in the management of HNC patients, either used curatively or palliatively, as well as a standalone treatment option or in conjunction with other modalities. However, the unavoidable administration of high doses of RT on or near the TMJ presents specific challenges related to oral functions and life quality due to the proximity of certain HNCs to TMJs. Without a widely recognized definitive treatment option for RIT, currently, a comprehensive assessment of dosimetric parameters and their appropriate arrangements appears to be the most effective way to reduce the RIT prevalence and its harmful consequences to lower levels. However, this strategy may not be applicable in every HNC patients due to tumor control concerns and unpredictable individual hypersensitivities to ionizing radiation, emphasizing the significant need for further scholarly inquiry and exploration within this specialized subject of utmost relevance.

The radiation dose to the TMJ is estimated using dose-volume histograms created during treatment planning. Accurate delineation of the target volume and vital anatomical structures is of paramount importance during RT planning for HNCs situated close to the TMJ region. The TMJ, comprising the mandibular condyle and adjoining soft tissues, is susceptible to radiation-induced damage [48]. Radiation dosages directed at the TMJ may vary depending on factors such as tumor location and stage, as well as the therapeutic intent [49,50]. In curative scenarios, doses typically range from 60 to 70 Gray (Gy) administered over several weeks [51], with fractionation schedules tailored to optimize tumor control while minimizing early and late complications. Nevertheless, despite advancements in RT techniques, TMJ may still receive significant doses, especially when dealing with tumors or lymph nodes near the TMJ, such as the intra parotid and upper jugular lymph nodes [52].

Studies examining the impact of RT on articular, embryonic, or physeal cartilage have predominantly focused on the radiation-induced modifications in the synthesis and metabolism of the functional matrix [53,54]. A comprehensive understanding of the influence of radiation on articular cartilage is essential to ascertain its role in the development of arthropathy in humans following exposure. The main constituents of the cartilage matrix comprise proteoglycan (PG) polymers, specifically aggrecan and type-II collagen, which play a pivotal role in determining the mechanical properties of the tissue [55]. The covalently attached highly sulfated glycosaminoglycans (GAG) to the core protein of the PG possess fixed negative charges that contribute to the compressive stiffness by attracting water [56]. Radiation-induced cellular injury may weaken the cartilage at articular surfaces and increase the magnitude of joint erosion mainly through altered harmony between the matrix anabolism and catabolism, may contribute to overall joint erosion. Clinical evidence supports that, although it may not be directly associated with radiation exposure, the incidence of total joint replacement significantly increases in adults who have undergone cancer treatment [57]. Despite the absence of clearly defined mechanistic pathways, this evidence implies that alternative anti-cancer treatment modalities may also instigate or expedite TMJ degeneration, either on their own or in combination with RT. This rational assumption has recently been supported by a systematic review and meta-analysis conducted by Borges and colleagues [58]. This meta-analysis involved 8 studies with 1474 patients undergoing chemo-RT and 858 patients undergoing RT alone. According to the authors, chemo-RT significantly increased the prevalence of trismus compared to RT alone (Odds ratio: 2.55; $P = 0.0003$), underscoring the contributing significance of chemotherapy in the development of RIT.

Research regarding the impact of radiation-induced TMJ changes, particularly the correlation between radiation dose and its effect on the TMJ, masticatory apparatus, and jaws, is currently limited. In a study conducted by Somay., *et al*. [59] involving 51 patients with parotid cancer, it was revealed that a mean TMJ dose of ≥51.0 Gy was significantly associated with increased rates of RIT (36.8% versus 3.2% for doses < 51.0 Gy; $p < 0.001$). Although Steelman and Sokol [60] were unable to definitively establish a link between TMJ doses and the incidence of RIT in a cohort of 21 patients with nasopharyngeal cancers, the research conducted by Wollin [61] and colleagues demonstrated a direct correlation between TMJ doses exceeding 60-65 Gy and deteriorated TMJ functions, which aligns with the findings of Somay and colleagues [59]. Similar to the TMJ, the radiation doses received by the masticatory muscles and the masticatory apparatus as a block (excluding the TMJ) may also impact the radiation-induced trismus (RIT) rates. A study by Hague and colleagues demonstrated that higher mean radiation doses to the ipsilateral block, lateral pterygoid, and masseter muscles were significantly associated with deterioration in trismus [62]. Notably, all patients whose trismus worsened at 6 months received mean doses exceeding 40 Gy to the block. Therefore, the authors recommended limiting the dose to these structures to 40 Gy or less for tumors not invading the masticatory muscles, as this may improve RIT rates. Consequently, the current evidence suggests that every effort should be made to minimize TMJ and masticatory muscle doses to reduce the risk of RIT in HNC patients.

To minimize the adverse effects of RT or cheo-RT on the TMJ and synovial fluid, a variety of preventive and supportive measures can

be implemented. First, conducting a pretreatment assessment of TMJ function and health is crucial to establish a baseline evaluation and identify any preexisting conditions. Before starting treatment, TMJ functions, TMJ-related complaints, and MMOs should be documented for each patient. Regular assessment before, during, and after RT can help promptly identify any pathological changes in patients. Such a strategy may improve the affected patients' quality of life with appropriate precautions and well-selected treatments such as physical therapy, pharmacotherapy, or intra-articular injections, which may relieve TMJ symptoms and optimize joint function [11]. In addition, utilizing advanced RT techniques such as IMRT or proton therapy to minimize radiation exposure of surrounding healthy tissues can reduce the risk of degenerative and inflammatory changes by decreasing the TMJ and synovial fluid doses and, therefore, the risk of RIT [63]. Likewise, to safeguard the health of the TMJ during and after RT, it is imperative to impart regular patient education encompassing proper oral hygiene, tailored exercise regimens, nutritional guidance, and personal care practices. Patients should also receive continuous support from a multidisciplinary professional team [64]. TMJ dysfunctions can also manifest as a consequence of occlusion disorders, masticatory impairments, and enduring repercussions of RT-induced tooth loss [64]. Hence, collaborative efforts among radiation oncologists, oral and maxillofacial surgeons, dentists, and physiotherapists are essential for formulating individualized treatment plans and supportive care strategies. This coordinated approach will facilitate the development of preventive measures and complementary treatments.

Conclusion

In conclusion, RT significantly affects the anatomical structure and function of the TMJ, as well as the composition and function of synovial fluid. A comprehensive understanding of this fundamental knowledge on the complex influence of ionizing radiation on the TMJ and synovial fluid can help healthcare professionals better navigate treatment options, improving outcomes and overall well-being for patients receiving RT for HNCs. Consequently, further research endeavors are imperative to unravel the pathophysiology of radiation-induced TMJ dysfunction and to devise innovative therapeutic strategies to address this challenging complication.

Declarations

Availability of Data and Materials

Data cannot be shared publicly because the data is owned and saved by Baskent University Medical Faculty. Data are available from the Baskent University Institutional Data Access/Ethics Committee (contact via Baskent University Ethics Committee) for researchers who meet the criteria for access to confidential data: contact address, adanabaskent@baskent.edu.tr.

Competing Interests

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