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Definitions of Radiation-induced Trismus in Head and Neck Cancer: Current Concepts and Controversies

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Abstract: Radiation-induced trismus is a devastating side effect of radiotherapy in patients with head and neck cancers. It hampers daily activities like eating, speaking, chewing, swallowing, and oral hygiene routines. Radiation-induced trismus also negatively affects social interactions, psychological wellbeing, and lowers the quality of life of patients. The most common method for determining radiation-induced trismus is to measure the ‘maximum mouth opening’. Different cut-off

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values for maximum mouth opening have been employed in studies that assessed radiation-induced trismus, including 40 mm, 35 mm, 30 mm, and 20 mm. The impact and prevalence of radiation-induced trismus are not fully understood because there is no common and reliable objective measure to determine cut-off values of maximum mouth opening. Additionally, regardless of the pretreatment measures, a standard cut-off is applied to all patients, where a change may be substantial for one patient but not necessarily for another. These discrepancies may cause certain patients' conditions to be overstated or understated, misdirecting their prophylactic or therapeutic interventions. This chapter highlights the current concepts and controversies of the definitions of radiation-induced trismus, and the possible challenges in managing radiation-induced trismus because of the varied definitions.

Keywords: definitions of trismus; head and neck cancer; maximum mouth opening; radiation-induced trismus in head and neck cancer; radiotherapy

INTRODUCTION

Head and neck cancers (HNC), which account for about 600,000 new cases annually and are the sixth most frequent malignancy in the world, can develop at any site in the head and neck region's specialized epithelium (1). Squamous cell cancers make up 90% of the histological types of HNC (2). Although the average patient age is around 60, a rising trend of young-onset HNC in individuals under the age of 45 years has been observed globally, which may be related to an increase in young-onset oropharyngeal and oral cancers (3, 4). Radiotherapy (RT), either for curative or palliative purposes, is administered to about 80% of HNC patients. Irradiation of the primary or secondary HNC, like any other tumor site, has been linked to an increase in the prevalence of secondary HNCs (5–7). A sizable proportion of patients suffer from severe radiation-related complications despite significant improvements in RT planning and delivery methods (8). Some of these morbidities include trismus (restricted mouth opening), dysphagia, xerostomia, dysgeusia, ageusia, dental diseases, orofacial pain, oral infections, and osteoradionecrosis (9) (Figure 1). As survival rates have increased, reducing complications and maintaining quality of life (QoL) metrics have become crucial long-term objectives for a growing number of survivors.

There are some studies into radiation-induced trismus (RIT), which contrast starkly with each other on the detrimental effects of RIT on almost all parameters of the QoL measures. Depending on the primary tumor type, its extension to the neighboring tissues, and the stage, RIT may emerge as a devastating complication of RT or concurrent chemoradiotherapy (C-CRT), affecting 5–69% of HNC patients (10). RIT may become apparent 3 to 48 months after RT or C-CRT. Sadly, there is disagreement in the literature about how to determine maximum mouth opening (MMO) and, consequently, RIT, even though an MMO of ≤ 35 mm is the commonly used metric to define RIT (11). This is mainly caused by the difficulties in predicting, recognizing, and preventing this terrible complication due to the challenges associated with MMO measurement and RIT diagnosis, as well as a lack of clear, unbiased, and

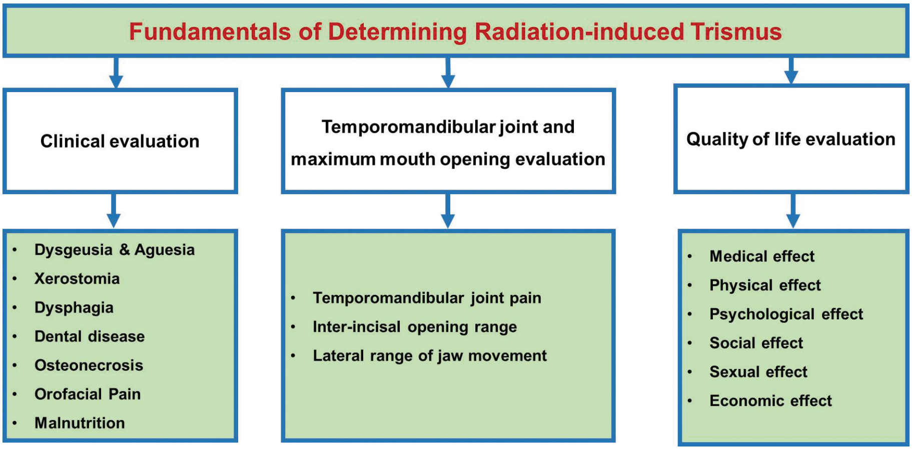

Figure 1. **Multiparametric evaluation of radiation-induced trismus and its consequences on affected patients.**

widely accepted standards. Because there are no specific questionnaires to assess and describe how this severe RIT-specific complication affects HNC patients' QoL, it is difficult to thoroughly interpret its actual impact on the affected patient's functionality and psychosocial status.

The MMO and the typical mouth opening range are significantly influenced by age, gender, and ethnicity. Therefore, RIT definitions have been hotly contested in past research (12–15). In a survey of 299 people, Carlsson and Svardstrom reported the average MMO to be 44.8 ± 9.4 mm in men and 39.2 ±10.8 mm in women (16). Agerberg, on the other hand, revealed that MMO varied from 44 to 77 mm in males and 42 to 75 mm in females (17). The degree of restricted mouth opening in the diagnosis of trismus has proven challenging because it is difficult to define a healthy mouth opening range. As a result, several trismus classifications have emerged. Consequently, the impacts of an issue like RIT, which impairs HNC patients' QoL, are obscured, and the required procedures for its identification and treatment are skipped. Thus, the primary purpose of this chapter is to comprehensively scrutinize the strengths and weaknesses of the current MMO measuring methodologies used to assess RIT in routine dentistry and radiation oncology clinics. This may aid in better evaluation and management of affected patients.

RADIATION-INDUCED TRISMUS: PATHOPHYSIOLOGY AND RISK FACTORS

Trismus affects up to 69% of HNC patients following oncological therapy, with RT being the most prominent determinant in its genesis and progression (10, 11). Although the entire mechanism is unknown, radiation-induced inflammation, endothelial injury, hypoxia, and fibrosis are thought to be the most important biological pathways leading to late devastating radiation-related side effects such as the RIT (9, 18). Double-strand DNA damage and the generation of reactive oxygen species cause radiation-induced cell damage in irradiated tissues (18). Enzymes associated with tissue injury increase oxidative stress in radiation-damaged tissues, causing tissue ischemia and vascular thrombosis. These events exacerbate local tissue damage and provoke the production of inflammatory cytokines and chemokines (19, 20). The typical outcome of this inflammatory process is hypoxia and irreversible radiation-induced fibrosis in the masticatory apparatus, which results in RIT (21). The likelihood of developing trismus increases significantly after irradiation of the temporomandibular joint (TMJ) and masticatory muscles (22, 23); prior surgery and concurrent chemotherapy are risk factors that also contribute. According to Wang et al. (24), the MMO declines rapidly in the first nine months following RT (mean: 2.4% per month), highlighting the severity of the RIT genesis process.

Although genetic factors may play a role, the most commonly cited risk factors for RIT include age, tobacco and alcohol use, poor oral health and daily oral care, tumor location in the oral cavity, larger tumor size, advanced tumor and nodal stage, presence of perineural invasion, prior surgery, the proximity of masticatory muscles to RT portal, restricted MMO before RT, non-IMRT techniques, RT volume, and mean masticatory apparatus dose (MAD) (25, 26). A well-known risk factor for RIT following RT or C-CRT is the advanced tumor stage, which may be connected to direct tumor invasion and perineural extension through the inferior alveolar nerve (27). Similar to this, higher radiation doses administered to the masticatory muscles, the TMJ, and associated ligaments during the treatment of specific tumors that call for higher radiation doses may cause fibrotic processes in the muscles, increase local inflammation, and possibly increase vascular occlusion, leading to hypoxia and ultimately RIT (27). Furthermore, it has been claimed that there is a relationship between MAD doses (particularly those exceeding 40 Gy) and increased RIT rates (28) (Figure 2).

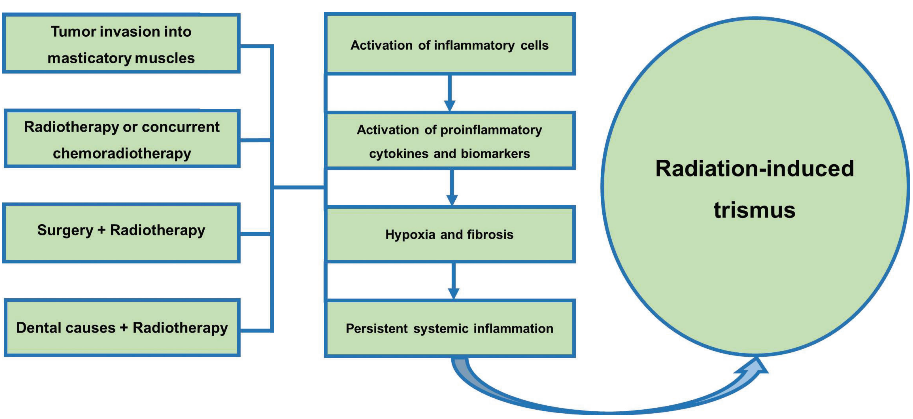

Figure 2. Summary of the etiology and pathogenesis of radiation-induced trismus.

METHODS FOR DETERMINATION OF RADIATION-INDUCED TRISMUS

Different approaches are used to determine trismus. MMO is frequently measured using traditional or calibrated calipers. Patients are instructed to maintain a neutral head posture throughout the procedure and to open their mouth as wide as they could (29). The "three-finger test" is an additional straightforward diagnostic procedure for identifying trismus. The patient is instructed to put three of his or her fingers in their mouth while the test is being conducted (30). Recently, single-use MMO measurement tools have also been adopted for sanitary reasons. One such single-use tool is Therabite®, which provides the most accurate measurement (31).

DEFINITIONS OF TRISMUS AND THEIR COMPARISONS

Trismus is among the most severe radiation-induced complications in HNC patients treated with RT or C-CRT. It can be caused by tumor growth in the masticatory apparatus or radiation-induced fibrosis after definitive or postoperative RT. RIT may impair social interactions, oncologic monitoring, dental care, and feeding habits (32–36). In earlier studies, several MMO cut-offs for trismus were developed based on the participants' dentition status. For example, in a study by Louise Kent et al. in 40 HNC patients who underwent RT, the MMO cut-off was set at 35 mm for dentulous patients and 40 mm for edentulous patients (33). Similarly, Lindblom et al. (22) used a cut-off value of 35 for trismus. In the discussion of the study, they stated that if they used 20 mm as the cut-off value, only 8% of their patients would be included in the trismus group and highlighted the importance of using a common cut-off value for RIT. Steiner et al. (37) used the 35-mm value as the RIT cut-off, and additionally defined any MMO < 25 mm as severe trismus, but did not assign the patients presenting with MMOs between 25 and 35 mm to any classification group. Grading systems have also been employed to evaluate the severity of trismus, such as grades 2, 3, and 4 for an MMO opening of 10–20 mm, 5–10 mm, and less than 5 mm, respectively (38). Nevertheless, the MMO cut-off values for the RIT definition appear to have been selected unsystematically (39, 40), as there are no objective and reliable metric assessments that contrast the pre-RT and post-RT MMO measures.

The use of variable RIT cut-offs prevents a comprehensive investigation of the risk factors and the relative efficacy of various RIT therapeutic strategies. The perplexing research findings are difficult to analyze. In HNC patients, 35 mm or less is the generally accepted MMO cut-off for the definition of trismus (32, 39–43). The MMO restrictions described by individuals with HNC formed the basis for the current RIT cut-off in the highly quoted study by Dijkstra and colleagues (11), with respective sensitivity and specificity values of 98% and 71%.

In a study by van der Geer et al. (44), which included 671 patients with HNCs, the MMOs were determined separately based on the type of oncological treatment (no treatment, surgery only, RT only, or post-surgical RT). Patients were divided into three groups: dentulous, partially edentulous, and edentulous. Patients who only received RT experienced mouth-opening issues at a lower MMO (33 mm) than patients who only underwent surgery (37 mm), according to their research. For measurements, the OraStretch® Range-of-Motion scale for patients with MMOs up to 52 mm and calipers for patients with MMOs >52 mm was used. However, because MMO measurements were performed by different medical experts, the risk of inter-observer variation cannot be ignored. Additionally, all patients who were dentulous, partially edentulous, and edentulous all underwent the same measurement procedure, and an average trismus cut-off metric rather than a particular cut-off for each circumstance was proposed for all patients. As a result, when compared to patients with trismus, the true differential impact of trismus on functionality and QoL cannot be accurately interpreted in patients with MMO measures very close to the calculated cut-off value, such as patients with an MMO of 36 or 37 mm. From a different angle, failure to use a specific questionnaire in conjunction with MMO measurements to assess how this complication affects QoL will obfuscate the actual clinical status of patients in the trismus group.

In their study of 101 patients with HNC who received surgery, RT, or C-CRT, Weber et al. (32) used a standardized 20-item QoL questionnaire based on the EORTC QoL questionnaire (H&N35). Using the Therabite® motion scale for MMO measurements and the cut-off determined by Dijkstra's study, any MMO of less than 35 mm was categorized as trismus. MMO measurements and survey results showed that patients with oropharyngeal cancers had difficulty eating (65%) and drinking (70%) due to more pronounced reductions in mouth opening measures. The study is constrained by the fact that patients with MMOs of less than 36 mm made up most of the study population, and patients with MMOs of 15 mm were not fully stipulated (32).

In 150 patients with oropharyngeal cancer who were only receiving RT, Thomas and colleagues (45) implemented another RIT assessment method. Patients were divided into three groups according to the severity of RIT: severe< MMO 15 mm; moderate, MMO between 15 and 30 mm; and mild, MMO > 30 mm. While such a scoring system is more informative for revealing how RIT affect patients' daily activities and QoL, it cannot fully represent all groups unless it is accompanied by a QoL questionnaire survey focused on assessing their health-related issues. The main superiority of this study over previous studies is the grouping of the patients, which makes the effects of RIT more obvious and reveals the distinctive characteristics of each group of trismus patients.

Jen and colleagues investigated the prevalence of RIT in 222 patients with nasopharyngeal cancers treated with RT (46). Patients in this study were divided into two groups based on whether they received RT in twice-daily or once-daily fractions. An MMO of 20 mm was deemed trismus, with its prevalence being determined as a function of the RT fractionation scheme. However, the 20-mm trismus cut-off used in this study was not the RIT threshold that is typically recommended for HNC patients in other studies. A classification that uses a cut-off value of 20 mm excludes patients with RIT whose MMO is above this value but below the normal limits and does not provide a trustworthy determination of RIT incidence rates. Furthermore, specifying the actual impacts of RIT may be difficult because it is unclear at what dose and fractionation the MMO fall below pretreatment levels.

Thirty-nine HNC patients who received definitive RT were the subjects of an investigation by Nyguen and colleagues (47). These patients' MMOs were categorized as trismus if they were 40 mm or less, and 30% of those who met this MMO cut-off had RIT. However, the so-called normal MMO values of 40 to 50 mm for the group of healthy persons were changed by Dijkstra and set at 36 mm for HNC patients (11, 48). But it is unclear in this case whether we should logically evaluate individuals with MMO between 36 mm and 40 mm in the non-trismus or the trismus group. As a result, these circumstances may impact the therapies provided to patients following RT, and patients may be less alert and willing to comply with any necessary precautions. In contrast, Buchbinder et al. (49) established 30 mm as the cut-off value of MMO in their analysis of 21 post-RT trismus patients diagnosed with oral cancer and divided the entire study population into two batches: trismus and non-trismus. However, because the pre-RT MMOs of these patients were not presented, it was impossible to accurately assess the rate and severity of trismus in this study. Agarwal and associates (50), who examined 30 study participants for RIT, used the same MMO cut-off value as Dijkstra et al. (11), which was 35 mm. Theoretically, this approach should encompass all trismus patients, but individuals with MMO > 35 mm will be considered healthy regardless of the decline in the affected person's objective functioning and QoL status compared to pre-RT measurements. Such a definition will undoubtedly affect the prevalence of RIT and artificially downplays the severity of the condition, despite its adverse consequences on the affected patient's QoL and productivity.

DISCUSSION

Despite the use of contemporary RT techniques, it is predicted that the incidence rates of trismus will rise quantitatively because of the tendency for longer survival times in patients with HNC in the era of modern RT, chemotherapy, targeted therapies, and immunotherapy. A persistent tetanic spasm of the masticatory muscles is a typical cause of trismus, also known as lockjaw. In HNC patients receiving RT or C-CRT, trismus is a significant cause of morbidity. Additionally, trismus may lead to low tumor control and higher rates of cancer-related mortality in these patient groups because of cachexia brought on by malnutrition. Although first used to describe reduced mouth opening brought on by tetanus, trismus currently describes reduced mouth opening brought on by various etiologies, including the RT and C-CRT (51). Depending on the primary anatomic site or the precise cause, trismus can be subdivided into various groups. Some medical professionals categorize trismus based on intra- and extra-articular TMJ involvement (52), whereas others rely on the etiology and use a comprehensive list of trismus categorizations that include infectious, traumatic, neurogenic, neoplastic, radiation-related, and many others (53).

RIT can compromise a patient's QoL and put their lives in danger. Additionally, RIT can hinder patients' daily activities and mood in the following areas: economically, socially, psychologically, and in terms of their sexual and physical health. In HNC patients, malnutrition status and weight loss are frequently linked to RIT (54), which can also result in exhaustion, weakness, inactivity, dissatisfaction with one's appearance, a depressive mood, and decreased survival, if cachexia is not prevented (55). Trismus may have more significant effects on jaw issues and restricted oral functions than it does on facial pain, taste loss, decreased salivation, and dry mouth (56–58). RIT can also impair a person's capacity to open their airways and chew nutrients. Earaches, headaches, jaw pain, difficulty in biting and chewing, cleaning teeth, swallowing nutrients, jaw pain, and cramps may manifest as additional physical symptoms of RIT (59). In HNC patients who have received RT, osteoradionecrosis and trismus are most likely the leading causes of halitosis (60), which can harm one's self-worth and personal relationships and even cause depression and social isolation (61). Halitosis undoubtedly affects the patient's sexuality, which contributes to social isolation (62).

The mouth opening typically measures between two and three fingerbreadths, or 40 to 60 mm. Although there might not be a one-size-fits-all definition, many experts acknowledge that an MMO of less than 35 mm is trismus for HNC patients (53). There are numerous RIT definitions and classifications in the trismus literature (Table 1). For instance, Goldstein et al. divided the MMO into three categories when assessing the incidence of RIT in 21 patients with nasopharyngeal cancer: greater than 40 mm (normal), 30–39 mm, and 0–29 mm, defined as trismus (63). However, the authors did not use specific classification terminologies for patients manifesting with MMOs of 30–39 mm or 0–29 mm. According to the authors, any MMO that was 40 mm or larger was considered normal. The inclusion of MMO

TABLE 1 Available studies on radiation-induced trismus and their comparative features

Author/year	Definition	Study Population	Properties
Nyguen et al. (46) (1988)	< 40 mm trismus	39 patients with HNC	One -step MMO measurement Increased prevalence of trismus due to high cut-off value Didn't use a QoL survey No Grading Not determine the limitation of jaw mobility Inadequate to emphasize the severity of trismus Not Determine the limitation of jaw daily activity
Thomas et al. (44) (1988)	MMO > 30 mm Mild MMO between 15–30 mm moderate MMO < 15 mm severe	150 patients with oropharyngeal CA	Grading Categorization Emphasize the severity of trismus MMO's upper limit for trismus is unclear Doesn't Use a QOL survey Not Determine the limitation of jaw daily activity Not determine the limitation of jaw mobility

(Continued)

TABLE 1 Available studies on radiation-induced trismus and their comparative features (*Continued*)

Author/year	Definition	Study Population	Properties
Bucbinder et al. (48) (1993)	≤ 30 mm trismus	21 patients with HNC	One -step MMO measurement Didn't Use a QoL survey No Grading Not determine the limitation of jaw mobility Inadequate to emphasize the severity of trismus Not Determine the limitation of jaw daily activity
Goldstein et al. (62) (1999)	C-1; > 40 mm MMO- normal C-2; 30-39 mm MMO -trismus C-3; 0- 29 mm MMO -trismus	58 patients with HNC	Categorization Grading Determination of limitation of jaw mobility Inadequate to emphasize the severity of trismus Didn't use a QoL survey
Jen et al. (45) (2002)	< 20 mm trismus	222 patients with NPC	One -step MMO measurement Decreased prevalence of trismus due to low cut-off value Didn't use a QoL survey No Grading Not determine the limitation of jaw mobility Inadequate to emphasize the severity of trismus Not Determine the limitation of jaw daily activity
Ozyar et al. (40) (2005)	< 30mm trismus	232 patients with NPC	One -step MMO measurement Didn't use a QoL survey No Grading Not determine the limitation of jaw mobility Inadequate to emphasize the severity of trismus No Determine the limitation of jaw daily activity
Dijkstra et al. (11) (2006)	≤ 35 mm trismus	89 patients with oral cavity or oropharynx CA	One step measuring of MMO Didn't use a QoL survey No Grading Not determine the limitation of jaw mobility Inadequate to emphasize the severity of trismus

(Continued)

TABLE 1 Available studies on radiation-induced trismus and their comparative features (*Continued*)

Author/year	Definition	Study Population	Properties
Scott et al. (56) (2008)	≤ 35mm trismus Grading MMO; 20–24 mm 25–29 mm 30–34 mm 35–39 mm 40–44 mm 45mm +	100 patients with oral cavity or oropharynx CA	Uses a QoL survey Emphasize the severity of trismus Grading Determination of limitation of jaw mobility Determination of limitation of jaw daily activity 0-19 mm MMO undefined
Barañano et al. (64) **pau** (2011)	20-35 mm trismus	100 patients with upper digestive tract CA	Limiting MMO to determine trismus One -step MMO measurement MMO <20mm undefined Didn't use a QoL survey Not determine the limitation of jaw mobility Inadequate to emphasize the severity of trismus Not Determine the limitation of jaw daily activity
Pauli et al. (55) (2014)	≤ 35 mm trismus	50 patients with HNC	One -step MMO measurement Didn't use a QoL survey No Grading Not determine the limitation of jaw mobility Inadequate to emphasize the severity of trismus Not Determine the limitation of jaw daily activity
Loorents et al. (39) (2014)	< 35mm trismus	66 patients with HNC	Uses a QoL survey Emphasize the severity of trismus Determination of limitation of jaw mobility Determination of limitation of jaw daily activity One -step MMO measurement No Grading
Lindblom et al. (22) (2014)	≤ 35 mm trismus	124 patients with HNC	Uses a QoL survey Emphasize the severity of trismus One -step MMO measurement Determination of pain and limitation of jaw daily activity No grading

(Continued)

TABLE 1 Available studies on radiation-induced trismus and their comparative features (*Continued*)

Author/year	Definition	Study Population	Properties
Steiner et al. (37) (2015)	< 35 mm trismus < 25 mm severe trismus	120 patients with HNC	Grading Determination of limitation of jaw daily activity and jaw mobility Emphasize the severity of trismus 25 mm < MMO <35mm undefined Didn't use a QoL survey

Abbreviations: CA:cancer; HNC: head and neck cancer; MMO: maximum mouth opening; QoL: quality of life

measurements obtained during lateral and protrusive movements of the jaws strengthened the validity of the concept of trismus. Combining the motion categories from the lateral and protrusive MMOs led to the creation of the mobility index. These additional measurements led to the classification of a mouth opening of more than 7 mm during lateral and protrusive motions as normal, 4-6 mm as trismus, and 0-3 mm as severe trismus. This definition of compound trismus more precisely demonstrates the degree of the restriction of jaw mobility because MMO was measured during functional movements. There is definitional inconsistency because some patients (MMO = 35–39 mm) whom Goldstein classified as having trismus received normal scores in the widely cited paper by Dijkstra et al. (11). A cut-off value of 35 mm was also used by Lindblom et al. (22) to diagnose trismus. By emphasizing that only 8% of their patients, as opposed to the claimed 43%, would be classified as having trismus if they used 20 mm as the cut-off value, the authors emphasized the importance of using the identical cut-off measure for RIT classification across studies. The authors did not, regrettably, consider the MMOs between 25 and 35 mm to have clinical significance in terms of the severity of trismus. This classification aids in evaluating trismus and emphasizing its severity compared to Dijkstra's simple definition (11); however, it is limited in its capacity to reveal the restriction of jaw movements because the amount of mouth opening determined does not correspond to the data from Goldstein and colleagues' research (62). Furthermore, patients with MMO of less than 20 mm are not classified, making assessment impossible in such patients. Because the group most negatively impacted by RT in terms of trismus was excluded, the prevalence and significance of RIT were overestimated.

Different experts have diverse definitions of RIT, with a cut-off value for MMO between 30- and 40 mm. Dijkstra et al. (11), who determined that an MMO of 35 mm or less in HNC patients qualifies as trismus, provided the most widely used definition. Like Dijkstra and colleagues (11), Loorents et al. (39), and Scott et al. (57) chose an MMO cut-off value of < 35 mm for the definition of trismus in their studies. The MMO of the patients were classified into groups ranging from 20 mm to 45 mm at 4 mm intervals. To show how this complication affected patients' QoL measures, the authors also used three different questionnaires: the University of Washington Quality of Life Scale (UWQOL) v4, the Liverpool Oral Rehabilitation Questionnaire (LORQ), and the performance status scale. The clinic-patient relationship was examined, and patients were partitioned according to MMO, lack of chewing, the fullness of meals, and general life satisfaction. However, failure to include patients with MMOs between 0 and 19 mm in this definition system may result in patients with severe trismus going unnoticed and preventing evaluation of their clinical manifestation status.

Due to the lack of grading criteria for trismus in Dijkstra et al.'s study, all patients with 20-mm and 34-mm MMO were examined in the same patient pool as if the effects of RIT were the same regardless of the actual MMOs. As a result, the authors were unable to evaluate the severity of RIT and its exact impact on the affected patients' lives and health status (11). Loorents et al. (39) assessed the severity of MMO by adding QoL surveys to this cut-off value without using a graded classification. In comparison to the untreated control group, the authors reported a 5.2% MMO decrease in the sixth week of the post-RT. Therefore, the effects of trismus with various MMO restriction severity levels might not be accurately depicted by a simple RIT classification. Furthermore, using ungraded classification techniques may result in a significant number of patients not receiving the correct diagnosis. For instance, based on Dijkstra's reported specificity rate of 71% (11), there is a 29% chance of misdiagnosing trismus in patients who do not have it. Unfortunately, these diagnostic errors may unnecessarily omit or require treatments for trismus.

Ozyar et al. (40) and Buchbinder et al. (49), who did not use a grading system, set the cut-off value for trismus at 30 mm. However, using a cut-off value of 35 mm will show that patients in the group who have a normal mouth opening of 31–34 mm, as per Ozyar et al. (40) and Buchbinder et al. (49) have trismus as per the definitions of Dijkstra et al. (11) and Pauli et al. (64). Due to the wide variations in RIT frequency across reference studies, the results of the current investigations may, sadly, not accurately reflect the true incidence rates of this debilitating complication in patients at risk. Scientifically speaking, it is difficult to compare the results of the available studies with the effects of RIT on the affected patients due to the vast differences in their definitions and associated shifts in incidence rates.

Baraano et al. (65) used a different classification for trismus, referring to an MMO of 20–35 mm. Studies that used a 35 mm cut-off, like those of Dijkstra et al., are typically thought to be inferior to this classification (11). This classification does not, however, accurately reflect the prevalence of RIT because it did not classify MMOs with less than 20 mm. Thomas et al. classified trismus according to its severity rather than using a single cut-off point in their studies, and this seems to be more reliable in determining the prevalence of RIT and how it affects patients' daily lives (45). Sadly, because there is no predetermined upper limit that is universally accepted for MMOs with trismus, it may be difficult to determine the actual incidence of MMOs in some patient groups, especially for patients whose MMOs are close to the definitional trismus limits.

Jen et al. (46) and Nyguen et al. (47) suggested two additional cut-offs for the RIT definition in addition to the above-mentioned trismus cut-offs. Jen et al. (46) accepted the MMO threshold of 20 mm for trismus in their study evaluating the prevalence of RIT in patients with nasopharyngeal carcinoma. Because the authors accepted MMOs larger than 20 mm as normal mouth openings and had a low threshold for RIT, these patients may have gone unnoticed, which may have reduced the prevalence of RIT. If Dijkstra and colleagues' cut-off value of 35 mm had been used, the RIT rate in these patients might have been 5% rather than 17% (11). Similar results were found in a study by Nyguen et al. on 39 patients, where the incidence of RIT was estimated to be 30% in patients receiving only RT, with a cut-off value of 40 mm for trismus (47). The incidence of 30% would have been much higher if cut-off values such as 35 mm, 30 mm, or 20 mm, which are frequently used by other researchers to determine trismus, had been used instead of this value. Given the differences in prevalence rates, it is possible that the prevention and treatment of RIT—which may have a significant positive impact on this patient group's QoL—will be underappreciated.

The incidence rates of RIT vary widely in the literature because, as was already mentioned, there is no established MMO cut-off for the diagnosis of trismus. As a result, the exact and reliable definition of trismus remains uncertain. In this sense, using a single cut-off criterion and basing the evaluation of RIT solely on the decline in MMO may not be the best approach. Every millimeter the MMO shrinks affects the patients' daily functions, including eating, drinking, speaking, chewing, and swallowing, as well as their social and psychological status. In addition to defining a uniform cut-off value, another option for determining the frequency of RIT and the true burden of this complication on patients is to stagger MMO to measure trismus severity. It may become difficult to determine the exact decline of MMO and the effects of this decline on jaw functions and mobility if MMO measurement is based solely on measuring the interincisal gap and without considering the degree of MMO during lateral and protrusive mandibular motions. Along with all these measurements and evaluations, incorporating QoL questionnaires into research may help define novel and distinct cut-offs for assessing trismus on an individual patient basis.

Overcoming the side effects of oncological treatment has become more crucial for improving patients' functionality and QoL because the addition of targeted agents and/or immunotherapy to the standard RT or CCRT has increased the survival rate of HNC patients (66). Previous studies have failed to reach a consensus on the best time to measure MMO to assess RIT (44, 67). The timing of MMO measurement could be crucial in determining the frequency and severity of RIT as it is an irreversible complication characterized by continued fibrosis and functional loss. To avoid or lessen the economic, social, and psychological burden of this complication, it is crucial to diagnose and treat it as soon as possible for professional groups like teachers, doctors, and bankers, who must have direct contact with people (68). To diagnose RIT, which may occur even after years of RT, and to treat it as soon as possible, it is crucial to establish unified time intervals for MMO measurement through studies with broad participation.

CONCLUSION

Despite the significant adverse effects of trismus on the patient's functionality and QoL, when interpreting all of this research and comparisons collectively, it appears that there is still no undisputed and widely acknowledged MMO threshold. Therefore, a novel, widely accepted, and precise MMO cut-off value for trismus is required, perhaps one that also considers interincisal measurements along with mandibular protrusive and lateral MMO measurements. Also, urgently needed is a single classification that groups trismus according to severity (likely as a percentage change in MMO) and is supported by QoL survey results. Treatments to enhance patients' QoL and prevent or lessen this unpleasant issue can only be planned once the occurrence and impact of RIT have been firmly established. These pressing challenges will be the subject of future, well-designed, large-cohort studies, which will yield crucial data that will guide preventive and treatment programs for such patients.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this manuscript.

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