

**A COMPREHENSIVE REVIEW OF THE PROS AND CONS OF
DEFINITIONS OF RADIATION-INDUCED TRISMUS**

ABSTRACT

Radiation therapy (RT) is the most common cause of cancer-related trismus. RT can lead to fibrosis and hypoxia in the temporomandibular joint ligaments, synovial fluid, and masticatory muscles. This makes it difficult for patients to move their jaws and eventually leads to restricted mouth opening. This devastating complication is called radiation-induced trismus (RIT), which occurs after RT in patients with head and neck cancers (HNC) and affects their daily routine functions such as eating, speaking, chewing, swallowing, and oral hygiene habits, as well as impairs their psychosocial communication and decreases their quality of life (QoL). The evaluation in RIT determination is basically performed by measuring the maximum mouth opening (MMO). Previous studies evaluating RIT have used many MMO cut-off values such as 40 mm, 35 mm, 30 mm, and 20 mm. The fact that no common and valid language is used to establish cut-off values means that the impact and prevalence of this serious complication are not fully revealed. Therefore, this present review aims to discuss the pros and cons by evaluating and comparing studies using the definitions established for RIT.

Keywords: radiotherapy, head and neck cancer, radiation-induced trismus, maximum mouth opening

INTRODUCTION

With about 600,000 new cases each year, head and neck cancers (HNC) rank as the sixth most common malignancy worldwide (1). Ninety percent of the histological types of HNC are squamous cell cancers (2). Although the median age of patients is roughly 60 years, a growing tendency of young-onset HNC in those younger than 45 years has been recorded globally, which may be attributable to an increase in the number of young-onset malignancies of the oral cavity and oropharynx (3,4). About 80% of HNC patients receive radiotherapy (RT). Moreover, definitive or postoperative RT has been linked to an increased incidence of long-term second main tumors in a variety of malignancies (5-7), adding to the already growing number of HNC patients. Despite significant advancements in RT planning and administration techniques, a sizeable portion of patients experience severe radiation-related complications (8). Trismus, dysphagia, xerostomia, dysgeusia, ageusia, dental disease, orofacial pain, oral infections, and osteoradionecrosis are some of these morbidities (9) (Figure 1). Reducing complications and maintaining quality of life (QoL) metrics has evolved into a crucial long-term goal for an increasing number of survivors as survival rates increased.

Despite its significant adverse consequences, there are few investigations into radiation-induced trismus (RIT). RIT is a catastrophic side effect of RT or concurrent chemoradiotherapy (C-CRT) that affects 5% to 69% of HNC patients, depending on the primary tumor type, its extension to neighboring tissues, and the stage of cancer (10). A maximum mouth opening (MMO) of ≤ 35 mm is commonly used as the RIT cutoff (11). It might occur three months after treatment or 12 to 48 months following RT or C-CRT. Regrettably, there is substantial disagreement in the literature about how to calculate MMO and, ultimately, RIT. This is due to the challenges associated with MMO measurement and RIT diagnosis, as well as a dearth of unambiguous, impartial, and universally accepted standards, which make it challenging to forecast, identify, and prevent this terrible

complication. This clinical picture is challenging in the absence of particular questionnaires to evaluate and describe the effects of this severe RIT-specific complication on the QoL of HNC patients.

Since age, gender, and race have a significant impact on both the MMO and the typical mouth-opening range, these definitions have been debated aggressively in earlier studies (12–15). For example, the typical MMO was determined to be 44.8 ± 9.4 mm in males and 39.2 ± 10.8 mm in women in a study of 299 individuals by Carlsson and Svardstrom et al (16). On the other hand, Agerberg found that MMO ranged from 42 to 75 mm in females and 44 to 77 mm in males (17). Determining the degree of restricted mouth opening in the diagnosis of trismus has proven difficult due to the ambiguity in establishing a normal mouth opening range, leading to the evolution of numerous trismus classifications. Consequently, the impact of a problem affecting HNC patients' QoL, such as RIT, is concealed, and the actions to be done to diagnose and overcome it are missed. Hence, the objective of this review is to comprehensively discuss the pros and cons of the current MMO measurement methodologies that were employed to assess RIT.

DEFINITIONS OF TRISMUS AND THEIR COMPARISONS

Trismus, or restricted mouth opening, can result from radiation-induced fibrosis following definitive or postoperative RT or tumor growth into the masticatory apparatus. Daily oral intake, dental care, social interactions, oncologic monitoring, and dental treatment could all be affected (18-22). In older investigations, several MMO cutoffs for trismus were developed according to the dental state of the individuals. For instance, the MMO cutoff was set at 35 mm for dentulous patients and 40 mm for edentulous patients in research by Louise Kent et al. in 40 HNC patients who had RT (23). However, Lindblom et al. (24) and Steiner et al. (25) classified trismus according to its severity and discovered various cutoff values, such as >35 mm for moderate trismus and 20 or 25 mm for severe trismus. Grading systems have also

been used to characterize and assess the severity of trismus, like grades 2, 3, and 4 for an MMO opening of 10 to 20 mm, 5 to 10 mm, and less than 5 mm, respectively (23).

In the absence of impartial and distinctive metric assessments, the MMO cut-off values for the trismus definition appear to have been chosen arbitrarily (26). Because of the multiplicity of cutoff points employed, the risk factors and effectiveness of trismus therapy cannot be systematically studied, and the research findings are complicated to comprehend. The broadly adopted trismus definition cut-off point for trismus definition in HNC patients is 35 mm or less (18,27-29). The restrictions that people with HNC described served as the foundation for this threshold in the most widely cited study by Dijkstra et al. (11). This definition's specificity and sensitivity scores were 71% and 98%, respectively. The MMOs were determined separately depending on the type of oncological treatment (no treatment, surgery only, RT only, or surgery and RT) in this study, which included 671 patients with HNCs. Patients were divided into three groups: dentulous, partially edentulous, and edentulous. They found that patients who received only RT had mouth-opening issues at a lower MMO (33 mm) than patients who only had surgery (37 mm) (11). The OraStretch® Range-of-Motion scale for patients with MMOs up to 52 mm and calipers for patients with MMOs greater than 52 mm were used for all of these measurements. However, measurements were carried out by a number of medical experts, so there was a chance for interobserver variations. Furthermore, the same measurement technique was used on patients who were dentulous, partially edentulous, and edentulous, and an average trismus cutoff metric was proposed for all patients rather than a specific cutoff for each situation. Therefore, the true differential impact of trismus on functionality and QoL in patients at the edge of the calculated cutoff value cannot be appropriately interpreted in comparison to the patients diagnosed with trismus. From a different perspective, failure to use a specific questionnaire

conjoined with MMO measurements to evaluate how this complication affects QoL will obscure the precise clinical picture of patients in the trismus group.

Weber et al. (18) employed a standardized 20-item QoL questionnaire based on the EORTC QoL questionnaire in their study of 101 patients with HNC who received surgery and/or RT or CCRT (H&N35). MMOs were assessed in this investigation using the Therabite® motion scale; according to the cut-off set in the Dijkstra et al. study, an MMO of less than 35 mm was termed trismus. Both MMO measurements and survey results demonstrated that patients with oral and pharyngeal cancers had eating (65%) and drinking (70%) problems owing to decreased mouth opening. Although the study's findings have a significant impact on the literature, one of its limitations is that patients with a mouth opening of 15 mm and one patient with a mouth opening of 35 mm were not fully specified, and patients with a mouth opening of less than 36 mm were assessed generally (18).

Thomas et al. (30) employed another RIT assessment technique in 150 patients with oropharyngeal cancer treated solely with RT. Patients were classified into three categories based on the severity of RIT using this system: Mild: MMO > 30 mm; moderate: MMO between 15–30 mm; severe: MMO < 15 mm. While such a rating system is more instructive for revealing how RIT affects patients' daily activities and QoL, it cannot be fully representative of all groups unless it is accompanied by a QoL questionnaire survey focused on assessing their health-related issues. The main advantage of this research over others is that it split the patients into groups, making the impact of RIT more visible and revealing the individual features of each trismus group.

In another study, Jen et al. (31) evaluated the prevalence of RT in relation to the dose of RT in 222 patients diagnosed with nasopharyngeal cancer. The patients were separated into two groups in this investigation: those who had RT in either 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. Nonetheless, the study's < 20 mm trismus cutoff is not generally used for HNC patients. This classification, which sets the cutoff value at 20 mm, leaves out patients in the trismus group who are above this cutoff value but below the normal mouth-opening limit and does not offer a thorough categorization of trismus occurrence rate. With such an approach, it may be challenging to establish the actual consequences of this complication since it is unclear at what dose and fractionation level the mouth opening falls below pretreatment levels.

Thirty-nine HNC patients who received definitive RT were the subjects of an investigation by Nyguen and colleagues representing the first of its kind research in such patient groups (32). The MMOs of these patients was defined as trismus if it was 40 mm or less, and RIT appeared in 30% of those who met this MMO cutoff. Dijkstra (11) modified the typical MMO values established between 40 and 50 mm for the group of healthy patients (33) to 36 mm for HNC patients. In this situation, it is unclear whether we should logically assess people with MMO between 36 mm and 40 mm in the trismus or the non-trismus group. As a result, this situation might affect the therapies given to patients following RT and might make patients less attentive to any necessary precautions. On the other hand, Buchbinder et al. (34), on the other hand, established 30 mm as the cutoff value of MMO in their analysis of 21 post-RT trismus patients diagnosed with oral cancer and separated the entire study population into two batches: trismus and non-trismus. The rate and severity of trismus, however, cannot be precisely assessed in this study because the pre-RT MMOs of these patients are unknown. Like Dijkstra et al. (11), Agarwal and colleagues utilized the MMO cutoff value of 35 mm and examined 30 study participants for RIT (36). If the cutoff is exact, this strategy should theoretically cover all patients with trismus. However, individuals with $\text{MMO} > 35$ mm will be regarded as healthy regardless of the decline in the affected individual's objective functioning and QoL status as opposed to pre-RT measurements. Such a definition will

undoubtedly impact the prevalence of RIT and underestimate the severity of the sequela in an artificial manner.

DISCUSSION

Trismus, or lockjaw, is typically caused by an ongoing tetanic spasm of the masticatory muscles. Trismus is a significant cause of morbidity in HNC patients receiving RT or CCRT. Additionally, due to weight loss brought on by inadequate nutrition, trismus may result in low tumor control rates and higher rates of cancer-related mortality in these patient groups. Although initially used to describe reduced mouth opening brought on by tetanus, it now refers to reduced mouth opening brought on by a broad range of etiologies, including the RT and CCRT (36). Trismus is divided into subgroups based on the principal anatomic site involved or the specific cause. Hence, while some specialists classify trismus based on intra- and extra-articular TMJ involvement (37), others rely on the etiology and use a comprehensive list of trismus categorizations that include infectious, traumatic, neurogenic, neoplastic, radiation-related, and many more (38).

The typical range of mouth opening is 40 to 60 mm (two to three finger breadths). Many experts believe that an MMO of less than 35 mm is trismus for cancer patients (38), although there may not be a one-size-fits-all solution. In the literature, there are numerous definitions and categorizations of trismus (Table 1). For example, when evaluating the incidence of RIT in 21 patients with nasopharyngeal cancer, Goldstein et al. classified the MMO into three categories: greater than 40 mm (normal), 30–39 mm, and 0–29 mm (39). According to the authors, a normal mouth opening is any MMO that is 40 mm or larger. The concept of trismus was made more reliable by the addition of MMO measurements taken during lateral and protrusive movements of the jaws. Following these additional measures, a mouth opening of more than 7 mm during lateral and protrusive motions was categorized as normal; 4–6 mm as category 2 (trismus); and 0–3 mm as category 3 (severe trismus). The

motion categories in both the lateral and protrusive MMOs were combined to create the mobility index. Due to the measurement of MMO during functional movements, this definition of compound trismus more clearly demonstrates the exact magnitude of the restriction of jaw mobility. However, some patients (MMO = 35–39 mm) who Goldstein classified as having trismus were given normal scores in the widely cited paper by Dijkstra et al. (11), creating a definitional inconsistency. Lindblom et al. (24) also employed a cutoff value of 35 mm for trismus diagnosis. The authors stressed the need of using a same cutoff measure for RIT classification across studies by pointing out that if they used 20 mm as the cutoff value, only 8% of their patients rather than the stated 43% would be categorized as having trismus. Trismus was defined by Steiner et al. (40) using an MMO cutoff of 35 mm, with an MMO of less than 25 mm indicating severe trismus. The authors did not, regrettably, consider the MMOs between 25 and 35 mm to have clinical significance in terms of the severity of trismus. Compared to Dijkstra's straightforward definition (11), this classification helps evaluate trismus and emphasize its severity; however, it is constrained in its ability to reveal the restriction of jaw movements because the amount of mouth opening determined does not match the data from Goldstein and colleagues' research (39). Furthermore, patients with MMOs of less than 20 mm are not classified, which makes it impossible to assess these patients. Thus, due to the exclusion of the group most adversely affected by RT in terms of trismus, the prevalence and importance of RIT were overestimated.

With a cutoff value for MMO between 30 and 40 mm, RIT is defined differently by various experts. The most widely accepted classification of trismus comes from Dijkstra et al. (11), who determined that an MMO of 35 mm or less in HNC patients qualifies as trismus. The most widely accepted classification of trismus is the study by Dijkstra et al, who considered an MMO of 35 mm or less in HNC patients to be trismus. Loorents et al. (41). and Scott et al. (42). selected an MMO cutoff value < 35 mm for trismus definition in their

studies. Additionally, the authors employed three different questionnaires, namely the University of Washington Quality of Life Scale (UWQOL) v4, the Liverpool Oral Rehabilitation Questionnaire (LORQ), and the performance status scale to illustrate the impact of this serious complication on patients QoL measures. Furthermore, the patients' MMOs were sorted into groups ranging from 20 mm to 45 mm at 4 mm intervals. Questionnaires were utilized to examine the clinic-patient connection and to discriminate between patients based on MMO, lack of chewing, the fullness of meals, and overall satisfaction with life. Nevertheless, failing to include patients with MMOs between 0 and 19 mm in this definition system may cause patients in the severe trismus stage to go unnoticed and prevent evaluation of their clinical picture.

Because Dijkstra et al. did not apply a graded definition when identifying patients as having trismus based on the 35-mm cutoff value, patients with 20-mm and 34-mm MMO were examined in the same condition, and the severity of this complication was not assessed individually for two patients (11). By adding quality-of-life surveys to this cutoff value, Loorents et al (41), although they did not use a graded classification, allowed the degree to which patients were at risk to be assessed at RIT according to the extent of MMO. In this study, a 5.2% decrease was observed at 6th. week of post-RT period MMOs compared with baseline measurements in the untreated control group. As a result, a straightforward RIT classification might not accurately depict the effects of trismus with different MMO restriction severity levels. Furthermore, a sizable portion of patients may have their diagnosis missed by ungraded classification methods. Dijkstra's reported specificity (true negative) rate of 71% (11), for instance, indicates that there is a 29 % chance of misdiagnosing trismus in patients who do not have it.

The cutoff value for trismus was set at 30 mm by Ozyar et al. (26) and Buchbinder et al. (43), but they did not employ a grading system. However, using a cutoff value of 35 mm

will demonstrate that patients in the group who have a normal mouth opening of 31–34 mm, as per Ozyar et al. (26) and Buchbinder et al. (43), have trismus as per the definitions of Dijkstra et al. (11) and Pauli et al. (44). Unfortunately, due to the wide variations in RIT frequency across reference studies, the findings of the available investigations may not accurately reflect the prevalence of this debilitating complication of RT in patients at risk. Scientifically, these huge discrepancies make it difficult to make valid comparisons between the results of the available studies and the impacts of RIT on the affected patients.

Another classification for trismus is the one used by Baraano et al. (45), which refers to an MMO of 20–35 mm. Studies like those of Dijkstra et al. that used a 35 mm cutoff are typically viewed as inferior to this classification (11). However, because it did not classify MMOs below 20 mm, this classification does not accurately reflect the prevalence of RIT. As opposed to studies with a single cutoff point, Thomas et al. classified trismus according to its severity, and this seems to be more steadfast in determining the incidence of RIT and the impact of RIT on patients' daily lives (30). Sadly, due to the lack of a set upper limit for MMOs for trismus, it may be challenging to estimate the incidence rate of MMOs up to 40–60 mm by classifying them into the mild trismus group.

Beyond the trismus cutoffs mentioned above, Jen et al. (31) and Nyguen et al. (32), respectively, proposed two additional cutoffs for the RIT definition. In their study assessing the prevalence of RIT in patients with nasopharyngeal carcinoma, Jen et al. accepted the MMO threshold of 20 mm for trismus (31). The prevalence of RIT may have decreased due to the authors' low threshold and acceptance of MMOs greater than 20 mm as normal mouth opening, leaving these patients unnoticed. The RIT rate might have been 5% instead of 17% in these patients if the cutoff value of 35 mm used by Dijkstra et al. (11) had been applied. Similarly, in a study of 39 patients presented by Nyguen et al., the incidence of RIT was calculated as 30% in patients treated with RT alone, with a cutoff value of 40 mm for trismus

(32). The incidence determined at 30% would have been much higher if cutoff values such as 35 mm, 30 mm, or 20 mm—frequently used by other researchers to determine trismus—had been used instead of this value. The planning for the prevention and treatment of RIT, which may have a significant positive impact on this patient group's QoL, may be misperceived as less critical, given the dissimilarities in prevalence rates.

The uncertainty in the multiple MMO values indicated above for trismus is due to the fact that a frequently used value has not yet been defined, and hence the rate of RIT fluctuates. In this respect, it may not be the best technique to assess RIT only on the decrease in MMO by employing a single cutoff criterion. Patients' daily activities, such as eating, drinking, speaking, chewing, and swallowing, as well as their social and psychological status, are impacted by every millimeter that the MMO shrinks. Staggering MMO to measure trismus severity, in addition to defining a uniform cutoff value, may be another option for determining the frequency of RIT and the real burden of this complication on patients. Performing MMO only based on measuring the interincisal gap and without evaluating the degree of MMO during lateral and protrusive mandibular motions may impede the exact decline of MMO and may not accurately represent the impact of this decrease on jaw functions and mobility. The inclusion of QoL surveys in studies, in addition to all of these measurements and evaluations, may aid in the development of new cutoffs for trismus assessment.

CONCLUSION

It seems that there is still no indisputable and universally welcomed MMO threshold for trismus when interpreting all of this research and comparisons collectively. According to the research, a novel, widespread, and accurate MMO cutoff value for trismus is needed, perhaps one that takes into account interincisal measurements in addition to mandibular protrusive and lateral MMO measurements. Furthermore, a single classification that categorizes trismus based on severity (likely a percentage change in MMO) and is backed by QoL survey findings

is urgently required. Only by clearly and thoroughly establishing the occurrence and impact of RIT, one of the most severe late consequences of RT, can treatments be planned to improve patients' QoL and avoid or mitigate this unpleasant issue. Future research addressing these concerns will yield crucial data that will guide preventative and treatment strategies in such patients.

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FIGURE LEGEND

Figure.1. Causes and mechanism of radiation-induced trismus

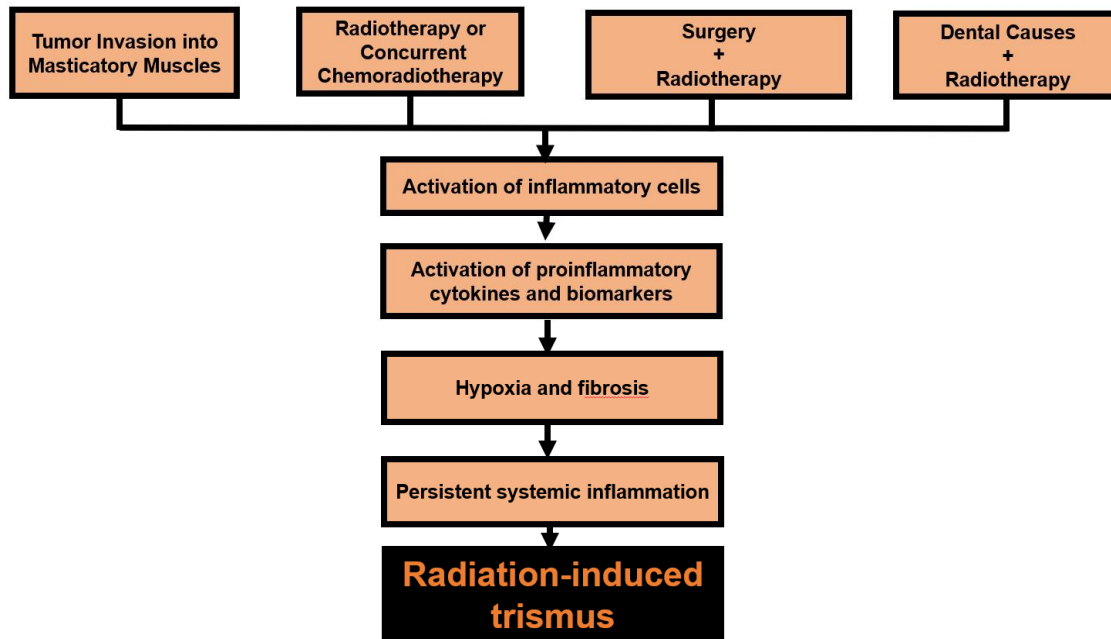
Author/Year	Definition	Pros	Cons
Nyguen et al (1988)	<ul style="list-style-type: none"> < 40 mm trismus 	<ul style="list-style-type: none"> One -step MMO measurement 	<ul style="list-style-type: none"> Increased prevalence of trismus due to high cut-off value Didn't use a QoL survey No Grading Not determine the limitation of jaw mobility Inadequate to emphasize the severity of trismus Not Determine the limitation of jaw daily activity
Thomas et al (1988)	<ul style="list-style-type: none"> MMO > 30 mm Mild MMO between 15–30 mm moderate MMO < 15 mm severe 	<ul style="list-style-type: none"> Grading Categorization Emphasize the severity of trismus 	<ul style="list-style-type: none"> MMO's upper limit for trismus is unclear Didn't use a QoL survey Not Determine the limitation of jaw daily activity Not determine the limitation of jaw mobility
Buchinder et al (1993)	<ul style="list-style-type: none"> ≤ 30 mm trismus 	<ul style="list-style-type: none"> One -step MMO measurement 	<ul style="list-style-type: none"> 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 (1999)	<ul style="list-style-type: none"> C-1; > 40 mm MMO-normal C-2; 30-39 mm MMO - trismus C-3; 0- 29 mm MMO - trismus 	<ul style="list-style-type: none"> Categorization Grading Determination of limitation of jaw mobility 	<ul style="list-style-type: none"> Inadequate to emphasize the severity of trismus Didn't use a QoL survey
Jen et al. (2002)	<ul style="list-style-type: none"> < 20 mm trismus 	<ul style="list-style-type: none"> One -step MMO measurement 	<ul style="list-style-type: none"> 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 (2005)	<ul style="list-style-type: none"> < 30mm trismus 	<ul style="list-style-type: none"> One -step MMO measurement 	<ul style="list-style-type: none"> 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. (2006)	<ul style="list-style-type: none"> ≤ 35 mm trismus 	<ul style="list-style-type: none"> One step measuring of MMO 	<ul style="list-style-type: none"> Didn't use a QoL survey No Grading Not determine the limitation of jaw mobility Inadequate to emphasize the severity of trismus
Scott et al. (2008)	<ul style="list-style-type: none"> ≤ 35mm trismus Grading MMO; 20-24 mm 25-29 mm 30-34 mm 35-39 mm 40-44 mm 45mm + 	<ul style="list-style-type: none"> Uses a QoL survey Emphasize the severity of trismus Grading Determination of limitation of jaw mobility Determination of limitation of jaw daily activity 	<ul style="list-style-type: none"> 0-19 mm MMO undefined
Barañano et al (2011)	<ul style="list-style-type: none"> 20-35 mm trismus 	<ul style="list-style-type: none"> Limiting MMO to determine trismus One -step MMO measurement 	<ul style="list-style-type: none"> 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 (2014)	<ul style="list-style-type: none"> ≤ 35 mm trismus 	<ul style="list-style-type: none"> One -step MMO measurement 	<ul style="list-style-type: none"> 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 (2014)	<ul style="list-style-type: none"> < 35mm trismus 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> No Grading
Lindblom et al (2014)	<ul style="list-style-type: none"> ≤ 35 mm trismus 	<ul style="list-style-type: none"> Uses a QoL survey Emphasize the severity of trismus One -step MMO measurement Determination of pain and limitation of jaw daily activity 	<ul style="list-style-type: none"> No grading
Steiner et al. (2015)	<ul style="list-style-type: none"> < 35 mm trismus < 25 mm severe trismus 	<ul style="list-style-type: none"> Grading Determination of limitation of jaw daily activity and jaw mobility Emphasize the severity of trismus 	<ul style="list-style-type: none"> 25 mm < MMO <35mm undefined Didn't use a QoL survey

Table 1. Pros and cons of the various definitions of radiation-induced trismus

Abbreviations: MMO: maximum mouth opening, mm; millimeter, QoL: quality-of life, C; category.

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Figure 1. Causes and mechanism of radiation-induced trismus



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