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RADIATION INDUCED TRISMUS: A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: Radiation induced trismus (RIT) called also "restricted mouth opening" is a well-known complication of head and neck (H&N) radiotherapy witch greatly affect functionality and quality of life (QoL) of patients. Its management is often difficult. The purpose of this review was mainly to identify risk factors and management strategies of this complication. Prevalence /incidence, physiopathology and impact on QoL, were also assessed. **Materials and methods:** Three databases were searched: PubMed, Cochrane library and Google scholar using combined MeSH terms and keywords in boolean equations (time period 2000 to 2018). All English or French articles that meet at least one of our research questions were included. The data were extracted according to a grid of analysis pre-established by the working group. **Results:** We reviewed 67 articles including 6 systematic reviews. Most of articles assessed management strategies or risk factors. Few studies have addressed the impact on QoL or physiopathology. **Conclusion:** Prevalence and incidence varied widely among studies. It may be attributed to lack of uniform criteria, visual assessment of RIT and retrospective study design. Newer radiation modalities may decrease the prevalence of RIT compared to conventional radiotherapy. Several risk factors have been identified. The modalities of radiotherapy (type, dose, and field) seem to be the most determining factor. No clear guideline recommendations could be made for the prevention or management of RIT. Although early rehabilitation combining mechanotherapy and specific physiotherapy exercises seems to be the most effective measure.

KEYWORDS: Trismus, Radiotherapy, Head and neck neoplasms, Risk factors, Treatment.

INTRODUCTION

Radiotherapy (RT) with or without surgery and/ or combined with chemotherapy is a standard treatment for patients with head and neck cancers (H&NC). The challenge is to optimize tumour control while reducing the morbidity and toxicity of radiation on surrounding healthy tissue.[1] Despite the advent of new radiotherapy techniques, irradiation is often associated with side effects such as "restricted mouth opening" called also trismus witch can significantly alters both functionality and patients' quality of life. Management of RIT is difficult given its pathophysiological complexity and absence of effective treatment.[2]

This systematic review represents a though evaluation of the literature to investigate especially risk factors and current approaches of management of RIT. Incidence or prevalence, physiopathology and the impact on QoL were also considered.

METHODOLOGY

Search strategy

A systematic literature search was completed with MEDLINE, Cochrane library and Google Scholar for articles published between January 1, 2000 and June 03, 2017. MeSH terms: 'trismus', 'radiotherapy', 'head and neck cancer' and 'fibrosis' were combined in Boolean querying. A more specific literature search was conducted for the keywords 'Limited mouth opening', 'Restricted mouth opening', 'Radiation fibrosis syndrome' and 'Radiation induced fibrosis' to determine if additional literature was not identified in the initial literature search.

Inclusion and exclusion criteria

Papers were selected for detailed review, only if contain at least one of the following data: risk factors of trismus, management strategies, incidence/prevalence, impact on QoL and physiopathology. No restrictions regarding study design were applied. Were excluded only articles written in languages other than English or French. This is further described in this monograph **(Fig. 1).**

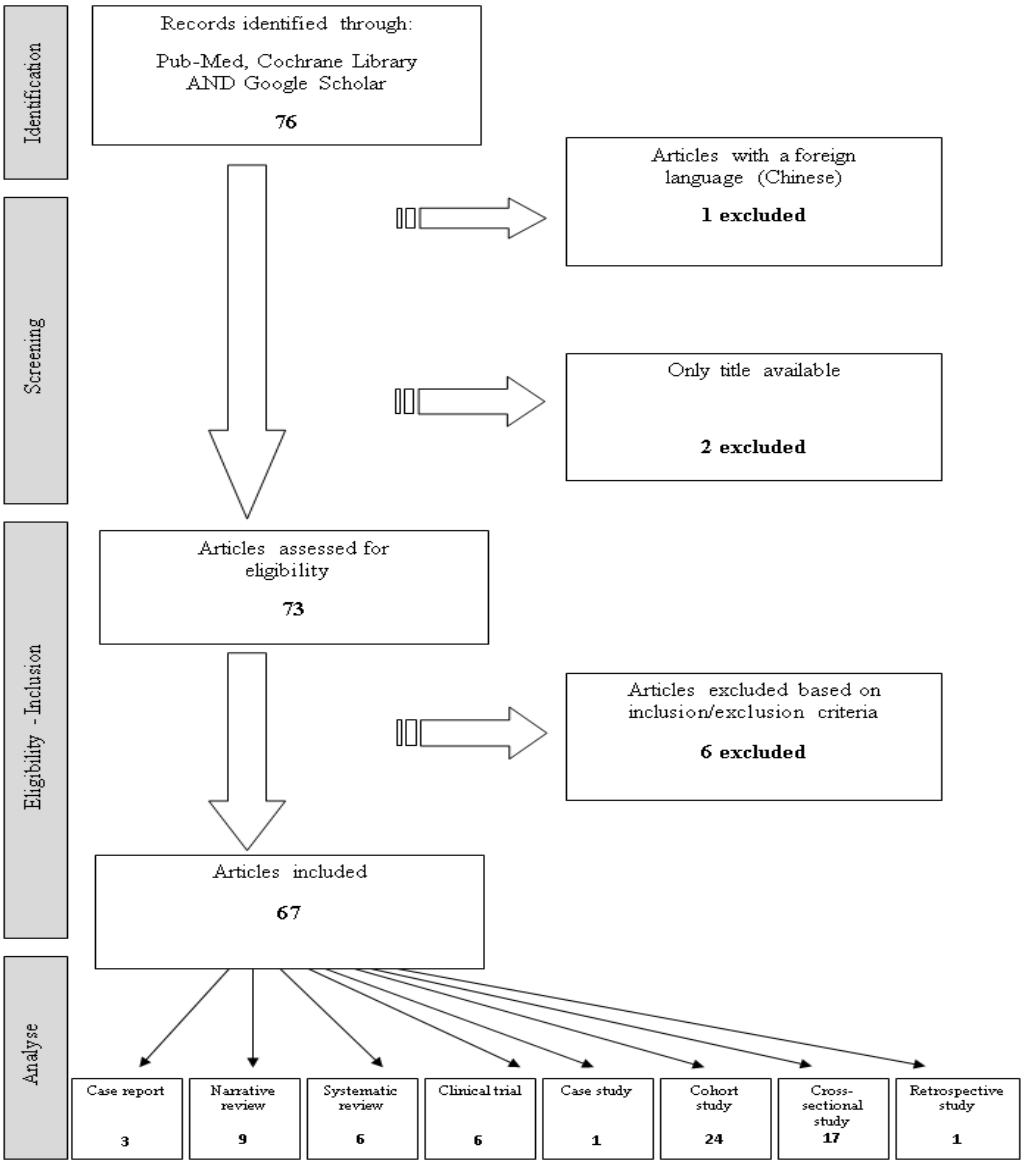

Figure 1: flowchart of article selection.

Data extraction

Articles met the inclusion criteria were read in full. Data were extracted according to a pre-established grid and summarizing in standardized tables.

RESULTS

A total of sixty seven (67) articles met the review criteria **(table 1).**[1-67] The following data were investigated:

1. Study design
2. Main purpose of the study
3. Original data (yes or no)
4. Characteristics of study population

5. Characteristics of tumour (location, TNM stage)
6. Type of radiotherapy
7. Other combined cancer therapy
8. Criteria for trismus
9. Prevalence /incidence of trismus
10. Trismus risk factors
11. Preventions and management strategies
12. Impact of trismus on QoL

Table 1: Types of study evaluated.

Type of study	Number of study (references)
Systematic review	6 (2-5, 1, 6)
Narrative review	9 (7-15)
Clinical trial	6 (16-21)
Cohort study	24 (22-45)
Cross-sectional study	17 (46-62)
Case study	1 (63)
Case report	3 (64-66)
Retrospective study	1 (67)

Most of articles assessed management strategies or risk factors of RIT (respectively thirty-three and twenty-six articles). Few studies have focused on the impact on QoL (six) or physiopathology (three). Twenty-three studies reported the incidence or the prevalence of trismus, but most of them (fourteen) have simply reported values. Nine original studies investigated the prevalence of trismus according to the type of radiotherapy used. Only one study compared the different tools for the subjective measures of trismus.

DISCUSSION

Measures of trismus[4,61]

Authors do not define trismus in the same way: it is a mouth opening less than 20 or 30 mm from some and 40 mm for others.[61] Moreover, they do not provide justification for these criteria.[4] Trismus was either described in subjective terms or measured. Repeated measurements performed in only few study and measurement instrument was were few times described in the studies.[4]

Physiopathology[5-7]

The physiopathological mechanism of RIT is poorly understood and seems to be complex. Authors have related RIT essentially to damage and fibrosis of the masticatory muscles[5-7] in

additionnal to scar tissue from radiation or surgery, vascular and nerve damage or a combination of these factors. Regardless of the immediate cause, loss of function and mandibular hypo-mobility will ultimately result in both muscle and temporo-mandibular joint (TMJ) degeneration.[5]

Incidence/prevalence

The prevalence of RIT varies widely from 5% to 79% **(table2)**. This wide range may be attributed to lack of uniform criteria defining trismus, visual assessment of trismus, heterogeneity of the studied population (such as differences in tumor site, type of treatment…), and retrospective study design.[3,6] Bensadoun et al[2] revealed a weighted prevalence for trismus of 25.4% for conventional RT and 5% for IMRT.

Table 2: Prevalence and incidence of "Radiation induced trismus" according to different authors.

Articles	Incidence	Prevalence	Prevalence according to the type of radiotherapy	
			Conventional radiotherapy	IMRT
Wang et al.2005[60]	5% to 16%	-	-	-
Bhrany et al.2007[16]	5% to 47%	-	-	-
Scott et al.2008[56]	-	5% to 38%	-	-
Melchers et al.2009[41]	-	5% to 38%	-	-
Stubblefield et al. 2010[53]	-	5% to 38%	-	-
Johnson et al. 2010[49]	42%	-	-	-
Bensadoun etal. 2010 [2]	-	-	25.4%	5%
Chen et al. 2011[23]	5.7%	-	-	-
Kamstra et al. 2013[29]	-	5% to 38%	-	-
Pauli et al. 2013[39]	9%* 28%**	-	25,4%	5%
Loorents et al.2014[19]	5% to 45%	-	25%	5%
Wetzels et al 2014[45]	-	39% to 79%	-	-
Steiner et al. 2015[57]	28.3%	-	-	-
Kamstra JI et al. 2015[27]	-	25% to 46%	-	-
Scherpenhuizen et al. 2015[6]	-	8% to 62%	-	-
Lee et al. 2015[50]	47.1%	-	-	-
Johnson J et al.2015[9]	42%	-	-	-
van der Geer et al. 2016[43]	36%	34.8%	-	-
Gebre-Medhin et al. 2016[46]	-	24%	-	-
Kamstra et al.2016[28]	-	5% to 46%	-	-
Ozdere et al.2016[64]	-	5% to 38%	-	-
Buglione et al.2016[8]	-	-	25.4%	5%
Pauli et al. 2016[37]	38 % to 42%	-	-	-

Risk factors

Type of irradiation[2,23,26,31,35,36,44,47]

The use of intensity-modulated RT (IMRT) seems to be associated with a less percentage and severity of RIT by saving or reducing doses received by healthy tissue especially masticator muscles and TJM.

Dose and volume of radiotherapy[2,8,10,13,23,31,43-47,49,52,55-57,59,61]

The prevalence of trismus increases with increasing doses of RT to mastication structures.

According to Stubblefield et al,[13] doses in excess of 60 Gy are more likely to cause trismus.

Bugilione et al[8] reported a dose of 70 Gy. However, the dose limit was setted by Rao et al[55] at 40 Gy for the ipsilateral masseter and at 64 Gy for the ipsilateral medial pterygoid muscle. For Teguth et al,[59] the probability of developing trismus is reported to increase 24% for every 10 Gy of additional radiation delivered to the medial pterygoid muscles. Several study[8,49,31] have concluded that: the larger the volume exposed to higher doses the higher the probability of functional damage.

Modalities of cancer therapies[4,30,36,61,69]

The increase in morbidity of cancer therapies is commonly associated with the multimodality of treatment. Van der Geer et al[43] reported that a longer overall treatment time of RT, whether patients receiving chemotherapy or not, leads to a higher risk of developing trismus. It could be assumed that patients with a longer overall treatment time of radiotherapy includes predominantly patients who received chemotherapy. Indeed, combined RT and Chemoyherapy is a more intensive and extensive approach, which would be expected to lead to more fibrosis and increase risk of trismus.

Steiner et al[57] and Bensadoun et al[2] confirmed these results and showed that combined modality treatment is associated with a higher incidence of trismus.

Primary tumor characteristics (Location stage and volume)[27,43,45,55,56]

The risk of trismus increases when the masticatory muscles are included in the irradiation field especially masseter and pterygoid muscle.[43,55] Kamstra et al[27] have demonstrated that several locations of tumor (such as oropharynx, nasopharynx and maxillary sinus), tumor stage T4 and higher target volume were risk factors for RIT. Wetzels et al[45] sowed that maxillary or mandibular tumor involvement are the highest contributing risk factors to

decreasing maximal mouth opening and the subsequent development of trismus after oral cancer treatment. According to their results, patients with tumor stage T4 have a small mouth opening by 8,8mm compared to those with T1 tumor and by 5, 6 mm compared to those with T2 tumor. Scott et al[56] reported that patients with T3-T4 tumors had significantly lower mouth opening than those with T1-T2 tumors. The values of mouth opening were respectively 24 and 35 mm.

Genotype[33]

Lyons et al[33] demonstrated that the TGF b1 genotype is likely to be an important predictor of the severity of post radiotherapy or chemo radiotherapy trismus. They concluded that the degree of RIT was related to the presence of the T allele at position 509 in the TGF-b1 gene.

Age and gender[27,31,43,45]

Kamstar et al[27] and Wetzels et al[45] have identified among trismus risk factors an advanced age. This can be explain by alteration of cell turnover with age. Lee et al[31] stated that women were significantly more likely to present with trismus than men. They attributed this result to the fact that women have lower mouth opening than men: (50.4 (5.9) mm) versus (53.8 (6.5) mm). They finally suggested developing separate criteria defining trismus in women.

Alcohol intake[10,27,31,45]

Lee et al[31] showed that those who do not drink alcohol are at particularly high risk of developing trismus. Contrary, those patients who consumed more than the weekly allowance of 40 units of alcohol for men and over 30 units for women had a significantly lower rate of trismus after treatment. Wetzels et al[45] have confirmed these findings: the difference in the amplitude of opening mouth between a non-consumer and one that consumes more than a drink per day was up to 3, 8 mm. Being intoxicated may reduce the feel of pain during mandibular movement, leading to wider opening of the mouth. Perhaps the alcohol also acts as a muscle relaxant and hinder the laying down of collagen.[31]

Impact on the quality of life[9,39,40,50,52,56,57,61]

Trismus interferes with many daily activities, such as speaking, eating, swallowing and maintaining oral hygiene. Consequently, it can lead to malnutrition, weight loss and difficulty with dental treatments, leading to tooth decay and osteradionecrosis. In addition, it may compromise tumour surveillance and can be particularly discomforting to patients. Trismus

affects not only the functional side but also the social, psychological and relational side. Patients complain of pain, muscular spasms and cramps that are associated with anxiety, insomnia, and depression.[39,52]

Based on this daily life interference and its psychiatric morbidity, several studies[9,39,52,61] have shown that trismus negatively affect health related quality of life (HRQL) and mental health. Johnson et al en 2012[9] have developed a trismus-specific self-administered questionnaire, the Gothenburg Trismus Questionnaire (GTQ), that showed good psychometric properties. They used the GTQ, the Short-Form 36 Health Survey (SF-36) and the Hospital Anxiety and Depression Scale (HADS) to measure the impact of trismus on HRQL and mental health in patients with H&NC. The results showed that trismus is associated with a significant impact on HRQL. They suggested that patients with trismus should be approached in a holistic way with respect for the underlying cause, treating not only the physical aspects of trismus but also addressing the patients' mental health.

Management measures[10]

Treatment of trismus can be conservative (with either medical or physical therapy) or surgical. Exercise therapy is the mainstay of treatment and exercise should start as soon as possible after treatment. The prevention of trismus, rather than its treatment, is the most important objective

Medical treatment[3,8,17,58]

Pentoxifylline appears to exert a modest therapeutic effect in patients with RIT.[3] Consequently, it was not advised in a recent consensus statement reported in 2016 by Buglione et al.[8]

However, use of botulinum toxin A seems to be beneficial. Stubblefield et al[58] and Hartl et al[17] have showed that it significantly improves pain, muscle cramps, and spasms (Oromandibular Dystonia) and consequently QoL of patients. Nevertheless, botulinum toxin did not improve trismus and modalities of its injection remain poorly defined in the literature (dose, rhythm, and site of injection)

Surgical treatment[16,42,65]

The principal technique is coronoidectomy. It involves the resection of the coronoid process to release mandibular motion. This technique is indicated in patients with severe RIT and

refractory to physical therapy or other treatment modalities. Resection of coronoid process can be uni or bilateral. In a prospective case series study, Brahny et al[16] have reported that, immediately after coronoidectomy, all of patients' interincisal distance increased at least 20 mm, with half improving 30 mm.

In a retrospective cohort study, Tasi and al[42] suggested a preventive combined surgery in which primary tumor resection should be associated to coronoidectomy and myotomy of all ipsilateral jaw closing muscles (temporal muscle insertion, masseter and medial pterygoid muscle). Their results showed that patient were more likely to have post-operative non-trismus.

Shamra and al[65] reported an innovative case report with use of superficial temporal fascia to cover the defect after bilateral coronoidectomy, myotomy and fibrous tissue dissection. They reported excellent results and no recurrence after a year of follow up.

However, for many authors surgery remains an invasive treatment and should be a last resort.

Physiotherapy rehabilitation

It is the mainstay treatment of RIT. Several studies have validated its efficiency.[6,21,24,28,29,34,37-41,54,63] Structured mandibular exercises aim to tone the atrophied muscles, give them back elasticity and thus improve amplitude of mouth opening. Many different stretching techniques were used in the therapeutic studies. [5] Choice of the technique is made according to the needs and the capacities of the patient. Therapeutic exercise modalities included: active range of motion exercises, dynamic bite openers, Therabite® device, Dynasplint® Trismus System, Engstrom® Jaw mobilizing device, homemade sledge-hammer device, tongue depressors, rubber plugs... Among all commercially available mechanical devices, the Therabite®[6,24,29,34,38-40,66] and the Dynasplint®[28,41] were most studied in the literature and seems to be particular effective in enhancement mouth opening.

Melchers et al[53] reported that patient adherence to exercise seems to be the most important factor in successful treatment. Pain, anxiety and the physiotherapist could influence adherence both positively and negatively. Hogdal et al[18] recommend that larger randomised clinical trials, with supervised training or developing strategies to improve adherence concerning self-care, are conducted.

Furthermore, it seems that the effect of exercises on mouth opening declines with a longer period of time between oncologic treatment and the start of exercises.[5] Kamstra et al[29] concluded that starting exercise therapy as soon as possible after (chemo) radiotherapy, improved the results of mouth opening exercises. Thus, most studies started exercises weeks or months after oncologic treatment.

The long-term effectiveness of physiotherapy in RIT has not been studied adequately and further research is needed. [5]

PREVENTIVE MEASURES

Pre-treatment[2,8,18,19,22,44,57]

Physiotherapy exercises, with or without mechanical device, appear to be useful in RIT management. Some authors[8,57] recommended that exercises should start as soon as possible after treatment preventively because such manoeuvres are far less effective in treating trismus once onset has occurred.[2,44]

However, findings reported by Ahlberg and al[22] showed that early exercises do not seem to provide additional beneficial effects in reduce trismus. Four years later, Hogdal and al[18] confirmed these results. Given study limitations, authors have nevertheless reported that results of their trial do not justify abandoning studies evaluating preventive interventions by physiotherapy exerice.

Loorent and al[19] in a prospective randomized study concluded that patients undergoing high dose RT do not need to be burdened with an intense prophylactic training programme during RT and up to 12 months after. Nevertheless measures of the amplitude of the mouth opening during RT and up to 12 months after, are recommended to identify a small risk group who are an exception and may need a training programme.

In total, it is still unclear, if exercises can prevent RIT. The type and frequency of exercises to recommend is also poorly defined, and therefore more studies should be conducted.

During treatment[8,10, 5,36,44,47,59]

Radiotherapic precautions: reduce radiation dose to the masticatory muscles and temporomandibular joint (without jeopardize the coverage of the planning target volume) seems to be the best preventive mesure to reduce the incidence of RIT.[8,36,59] In this context, IMRT seems to be particularly effective in reducing RIT.[35,44,47]

CONCLUSION

There is not uniform criteria defining RIT in literature. Its pathophysiology is poorly understood. Prevalence various widely among studies and it increases with doses of RT to mastication structures. The use of intensity-modulated RT seems to lower the incidence and severity of RTI. All studies reported that QoL is significantly impaired. Treatment of trismus can be conservative (with either medical or physical therapy) or surgical. Physiotherapy exercise is the mainstay of treatment and it should start as soon as possible after oncologic treatment. The prevention of trismus, rather than its treatment, is the most important objective. Further studies are required to fully understand the pathogenesis of RTI. Advances in trismus prevention and treatment are also needed to reduce morbidity and improve the QoL of H&NC patients.

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