Support Care Cancer (2010) 18:1033–1038
DOI 10.1007/s00520-010-0847-4

REVIEW ARTICLE

A systematic review of trismus induced by cancer therapies in head and neck cancer patients

Rene-Jean Bensadoun · Dorothea Riesenbeck · Peter B. Lockhart · Linda S. Elting · Fred K. L. Spijkervet · Mike T. Brennan · Trismus Section, Oral Care Study Group, Multinational Association for Supportive Care in Cancer (MASCC)/ International Society of Oral Oncology (ISOO)

Received: 5 October 2009 / Accepted: 18 February 2010 / Published online: 6 March 2010

Abstract
Purpose This systematic review represents a thorough evaluation of the literature to clarify the impact of cancer therapies on the prevalence, quality of life and economic impact, and management strategies for cancer-therapy-induced trismus.

Methods A systematic literature search was conducted with assistance from a research librarian in the databases MEDLINE/PubMed and EMBASE for articles published between January 1, 1990 and December 31, 2008. Each study was independently assessed by two reviewers. Taking into account predetermined quality measures, a weighted prevalence was calculated for the prevalence of trismus. The level of evidence, recommendation grade, and guideline (if possible) were given for published preventive and management strategies for trismus.
Results We reviewed a total of 22 published studies between 1990 and 2008. Most of them assessed the prevalence of this complication, and few focused on management. The weighted prevalence for trismus was 25.4% in patients who received conventional radiotherapy and 5% for the few intensity-modulated radiation therapy studies. No clear guideline recommendations could be made for the prevention or management of trismus.
Conclusions Newer radiation modalities may decrease the prevalence of trismus compared to conventional radiotherapy. Few studies have addressed the quality of life impact of trismus, and no studies were identified to assess the economic impact of trismus. The few preventive and management trials identified in the literature showed some promise, although larger, well-designed studies are required to appropriately assess these therapies before recommendations can be provided.

Keywords Cancer therapy · Trismus · Management strategies

R.-J. Bensadoun (✉)
Radiotherapy Department, Pôle Régional de Cancérologie,
CHU de Poitiers,
2 rue de la Milétrie, BP 577,
86021 Poitiers Cedex 9, France
e-mail: rene-jean.bensadoun@chu-poitiers.fr

D. Riesenbeck
Wildermannstr. 21,
45659 Recklinghausen, Germany
e-mail: d.riesenbeck@servitia.de

P. B. Lockhart · M. T. Brennan
Department of Oral Medicine, Carolinas Medical Center,
P. O. Box 32861, Charlotte, NC 28232, USA

P. B. Lockhart
e-mail: peter.lockhart@carolinas.org

M. T. Brennan
e-mail: mike.brennan@carolinas.org

L. S. Elting
Department of Biostatistics, The University of Texas M. D. Anderson Cancer Center,
P. O. Box 301402, 1515 Holcombe Blvd,
Houston, TX 77230-1402, USA
e-mail: lelting@mdanderson.org

F. K. L. Spijkervet
Department of Oral & Maxillofacial Surgery,
University Medical Center Groningen, University of Groningen,
Hanzeplein 1,
9700 RG Groningen, The Netherlands
e-mail: f.k.l.spijkervet@kchir.umcg.nl

Introduction

Trismus is defined as a tonic contraction of the muscles of mastication and results in a limited ability to open the

mouth [7]. Trismus has been associated with significant morbidity following radiotherapy (RT), with significant health implications, including reduced nutrition due to impaired mastication, difficulty in speaking, and compromised oral hygiene [7]. Limitations in jaw opening have been reported in 6% to 86% of patients having received RT to the temporomandibular joint and/or masseter/pterygoid muscles, with a frequency and severity that is somewhat unpredictable [12].

The loss of function and range of mandibular motion from RT appears to be related to damage and fibrosis to the muscles of mastication. Studies have demonstrated that an abnormal proliferation of fibroblasts is an important initial event in these reactions. Additionally, there may be scar tissue from radiation or surgery, nerve damage, or a combination of these factors. Regardless of the immediate cause, mandibular hypomobility will ultimately result in both muscle and temporomandibular joint degeneration. Studies have shown that muscles that fail to move through their range of motion for as little as 3 days begin to show signs of atrophy. Similarly, joints which are immobilized quickly begin to show degenerative changes in the joint, including thickening of synovial fluid and thinning of cartilage.

Radiation therapy involving the temporomandibular joint, the pterygoid muscles, or the masseter muscle is most likely to result in trismus [7]. The location of tumors related to this type of RT includes nasopharynx, oral cavity, oropharynx, base of tongue, salivary gland, or the maxilla or mandible. The prevalence of trismus increases with increasing doses of RT, and levels in excess of 60 Gy are more likely to cause trismus [24]. Patients who have been previously irradiated and who are being treated for a recurrence appear to be at higher risk of trismus than those who are receiving their first treatment [6, 27]. This suggests that the effects of radiation RT are cumulative, even over many years. Radiation-induced trismus may begin toward the end of RT or at any time during the subsequent 24 months. Limitations in opening often increase slowly over several weeks or months. The condition may worsen over time or remain the same, or the symptoms may reduce over time, even in the absence of treatment.

RT-induced oral complications are complex, dynamic pathobiological processes that lower the quality of life and predispose patients to significant clinical dysfunction. Limited mouth opening frequently results in reduced nutritional status. These patients may experience significant weight loss and nutritional deficits [11]. It is generally accepted that weight loss of more than 10% of initial body weight is considered significant. This is of particular importance at a time when the patient is recovering from surgery, chemotherapy, and/or RT. Additionally, it lowers the ability for "social eating" and thereby increases the risk of social isolation and decrease of quality of life in patients with head and neck cancer.

Limited mouth opening may also make proper mastication of food more difficult and results in compromised airway clearance. A normal act of swallowing requires an individual to first manipulate the food into a cohesive bolus. If the tongue cannot move properly, there may be post-swallow excess residue. The combination of compromised mastication, poor bolus organization, and increased residue has the potential to lead to aspiration of food.

Trismus is frequently overlooked, by patients and their providers, as they may assume that the reduction in jaw mobility is "normal" or that it will resolve on its own. Moreover, patients receiving RT or combined radiation and chemotherapy often require feeding tubes or limit their intake to mostly liquids during treatment. Thus, they may not realize the slow progressive onset of trismus, until they attempt to resume intake of soft or solid foods.

Finally, limited mouth opening can result in compromised oral hygiene. Patients who have received radiation involving the salivary glands must maintain excellent oral hygiene in order to prevent dental caries (cavities). Deficits in oral hygiene can aggravate mucosal and dental problems with the subsequent risk of mandibular osteoradionecrosis [20]. Also, the work of a dentist and other professional oral care measures, including surgery, can be made more difficult, which might even result in compromised oncological follow-up.

Historical considerations

This systematic review represents a search and evaluation of the literature appearing since the 1989 NIH Development Consensus Conference on the Oral Complications of Cancer Therapies and the publication of the National Cancer Institute (NCI) Monographs [28]. Our goal is to clarify the impact of newer cancer therapies on the incidence, nature, and severity of trismus.

Consensus from the 1989 NIH Development Consensus Conference on trismus can be summarized by:

- No agreed-upon pretreatment strategies to prevent or minimize trismus.

General consensus and directions for future research from the 1989 NIH Development Consensus Conference that may also apply to trismus can be summarized in:

- Establish baseline data with which all subsequent examinations can be compared.
- Identify risk factors for the development of oral complications.

Directions for future research from the 1989 NIH Development Consensus Conference applicable to trismus:

- Devise accurate, quantifiable, reproducible criteria for assessing and classifying oral complications of cancer therapy.
- Determine incidence and prevalence of oral complications related to different types of anticancer therapies and related risk factors.
- Study the mechanisms of cancer treatment injury to the hard and soft oral tissues at the molecular and cellular level and determine how these affect the oral environment.
- Develop radioprotective and chemoprotective agents.
- Determine the most effective strategies to ensure patient compliance with therapeutic regimens.

Progress in cancer treatment modalities in head and neck cancer since 1989 Since 1989, radiation techniques such as 3D conformal radiotherapy and intensity-modulated radiation therapy (IMRT) have been utilized in the treatment of head and neck cancer, with the hope that there would be a reduction in radiation damage to normal tissues.

Aims of this review

To extend on the 1989 NIH Development Consensus Conference on the Oral Complications of Cancer Therapies [28], the goals of this systematic review of trismus as an oral complication of cancer therapies were the following:

1. Determine the prevalence of trismus by cancer therapy regimen.
2. Determine the impact of trismus on quality of life.
3. Determine the economic impact of trismus.
4. Assess preventions and management strategies for trismus and determine the quality of recommendations for different treatment strategies.

Methodology

Search strategy and criteria for selecting articles

A systematic literature search was conducted for articles published between January 1, 1990 and December 31, 2008. The primary outcome was to trace all literature containing original data on incidence/prevalence of trismus as well as the impact on oral-health-related quality of life, economic burden, and management strategies for trismus in cancer patients undergoing head and neck surgery, radiotherapy, or combined treatment modalities.

Literature search utilized

A thorough literature search was completed with MEDLINE, CancerLit, EMBASE, Cochrane Library, and Best Evidence. This is further described in this monograph [1]. A more specific literature search was completed for the key words trismus and cancer to determine if additional literature was not identified in the initial literature search. Additional studies identified in the references of reviewed articles were also included in this review if they met our inclusion criteria.

Types of publications excluded

The search was limited to English language. Gender and age were not limited. The following publication types were eliminated by the review panel from the present systematic review: systematic and non-systematic reviews; studies not reporting actual data on trismus; studies reporting redundant data from previous publications; phase I and II studies, opinion papers, and case reports; articles published before 1990; and articles from the 1990 NCI Monographs [28].

Review methodology

Each article was independently evaluated by two reviewers (RJB, DR, PBL, or MTB) with pilot-tested collection forms. Trismus was assessed by the presence (Y/N), grade when available, or amount of opening (mm). Measures of quality of life (QOL) and economic variables were documented if available. Further data collected for each article such as type of study, blinding, presence of control group, scale validity, and samples size were used to determine the quality grading. Further details of this methodology can be seen in Brennan MT. et al. [1].

Results

Articles reviewed

We initially identified 43 articles from 1990 to 2008. A total of 22 articles met the review criteria (Table 1). Most of the studies reviewed simply reported the presence or absence of trismus and were not focused on the management of trismus. All studies evaluated trismus in head and neck (H & N) cancer patients receiving different modalities of RT. Nineteen reported late effects of conventional radiotherapy, 12 chemoradiation, and five brachytherapy in H & N cancer patients. Nine reported radiation-induced trismus in patients with nasopharyngeal or maxillary sinus cancer; seven oropharynx, oral cavity, or tonsil; and six with a mixture of different H & N cancer locations.

Table 1 Types of studies evaluated

Type of study	Number of studies (references)
Randomized controlled trial	0
Non-randomized clinical trial	3 [9, 10, 17]
Before and after study	2 [8, 22]
Cohort	17 [2, 3, 5, 6, 11–13, 15, 16, 18, 19, 21, 23–27]

Prevalence

The prevalence of trismus could be determined from 12 studies where trismus was appropriately assessed. The weighted prevalence in the conventional RT group was 25.4% but 5% for the few IMRT studies (Table 2). The trismus prevalence in studies of RT and CT was 30.7%.

Maximum vertical opening

Kent et al. examined the incidence of trismus in 16 patients treated with IMRT compared to 24 patients treated previously with conventional radiotherapy [12]. There was no significant difference in the maximum vertical dimension between the IMRT and the conventional RT groups, (38.8±9.0 vs 33.7±10.1 mm, respectively, p=0.11). Due to the small sample size of this study, the possibility of a type II error must not be overlooked.

Impact on quality of life

Kent et al. assessed differences in QOL for head and neck cancer patients with our without trismus, which were identified as difficulty with opening and difficulty with eating [12].

Economic impact

There were no studies evaluating the economic impact of trismus.

Treatment strategies

We found five therapeutic papers, which focus on various drugs or devices tested for the improvement of mouth opening, and/or physiotherapy [4, 9, 10, 17, 22]. These studies covered such activities as "gentle passive motion" beginning as soon as possible after radiation. We found no phase II or III studies testing therapeutic options for cancer-therapy-induced trismus in preventive or curative intent. One recent study was outside the review range (1990–2008), but was added to the treatment strategies review due to the potential impact for the field [17].

Prevention and management

Early treatment of trismus has the potential to prevent or minimize many of the consequences of this condition. If the clinical examination reveals the presence of limited mouth opening and diagnosis determines the condition due to be trismus, treatment should begin as soon as it is practical. As restriction becomes more severe and likely irreversible, the need for treatment becomes more urgent.

Over the years, clinicians have attempted to prevent or treat trismus with a wide array of appliances. These devices include cages that fit over the head, heavy springs that fit between the teeth, screws that are placed between the central incisors, and hydraulic bulbs placed between the teeth. These devices range widely in cost. Some, such as continuous passive motion devices, must be custom-made for each patient. Others are rented on a daily or weekly basis, at rates of up to several hundred dollars per week. The least expensive option is the use of tongue depressors, which has been used for many years to mobilize the jaw. A search of the literature, however, failed to reveal any studies that demonstrated a significant improvement in treating trismus with tongue depressors.

Active motion is movement driven by the musculature around the joint. Passive motion occurs when an external force is applied, causing movement of the joint in the absence of activity of the muscles around the joint.

An example of a device, which allows for the use of passive motion, is the "Therabite Jaw Motion Rehabilitation System." One report involving patient groups suggests some degree of efficacy [17], but the study was not randomized or controlled. The authors studied a population

Table 2 Weighted prevalence of trismus following radiation therapy for head and neck cancer

	Number of studies (reference)	Mean prevalence (%)	Standard error	95% Confidence interval
Conventional RT	10 [3, 5, 6, 12, 13, 15, 18, 21, 24, 27]	25.4	0.08	6.5–44.2
IMRT	2 [2, 11]	5.0	0.01	0.0–16.6
RT with chemotherapy	8 [2, 5, 6, 11, 12, 18, 21, 24]	30.7	0.09	8.3–53.0

of patients with radiation-induced trismus. Over a 10-week period, they compared the effectiveness of three different protocols to improve mandibular mobility. At the end of the study period, the group using the Therabite System had improved an average of more than 13 mm, by comparison with 5 mm in the tongue depressor group. A third group, using their fingers to force their mouth open, showed even less improvement. In another report, with a 16-week study period, it was also found that the use of tongue depressors was not helpful. One of the hypothesized benefits of the Therabite System is that it not only stretches the connective tissue that causes trismus but also allows for proper mobilization of the temporomandibular joint, thus addressing a secondary cause of pain and tightness [17]. This has not been proven as an evidence-based outcome.

Summary

- From the few studies that exist, IMRT may be associated with a less frequent prevalence of trismus. Further studies need to be conducted on trismus and IMRT to confirm this outcome.
- Concomitant CT and RT may be associated with a higher prevalence of trismus.
- Our systematic review failed to demonstrate any clear significant improvement of radiation-induced trismus from various local or systemic interventions.
- There may be some benefit from preventive and management strategies.
- Additional questions still remain
  - Impact of the increased total dose of RT on the prevalence of trismus
  - Impact of the altered fractionation schemes
  - Impact of concomitant chemotherapy or targeted medical treatments

Some therapeutic interventions seem to show some efficacy in decreasing the intensity of cancer treatment related trismus (pentoxifylline, botulinum toxin, exercise using Therabite® device for example). However, this proposed efficacy has to be confirmed by randomized controlled studies, which are lacking in this area.

Prevention strategies—level of evidence, recommendation grade, and guideline classification Pentoxifylline appears to exert a modest therapeutic effect in patients with radiation-induced trismus (level of evidence IV, recommendation grade C, and no guideline possible) [4].

Physiotherapy exercises appear to be useful in trismus management (level of evidence IV, recommendation grade B, and no guideline possible) [9].

Botulinum toxin injections seems to be effective in the improvement of pain scores and masticator spasms, but no improvement in trismus itself (level of evidence III, recommendation grade B, and no guideline possible) [10].

Therabite® System seems to be effective in the reduction of cancer-therapy-induced trismus (level of evidence III, recommendation grade B, and suggestion) [17].

Dynasplint® Trismus System seems to be effective in the reduction of contracture of the muscles of mastication (radiotherapy-induced trismus; level of evidence III, recommendation grade B, and no guideline possible) [22].

Recommendations for future research directions

Radiation oncology textbooks often fail to mention trismus as a sequela of RT in head and neck cancer patients. This contributes to a lack of recognition of the prevalence and significance of this condition. There has been an ongoing attempt by the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer to develop “late effects in normal tissue” morbidity scales, and the National Cancer Institute consensus conferences introduced the subjective, objective, management, and analysis classification for late toxicity. However, both are focused on major organ and dermatological injuries, and trismus is not addressed. This should be corrected in future revisions of these scales.

Considering the high prevalence of trismus in published studies and the QOL deficits associated with trismus, increased efforts for patient education, prevention, and early treatment options are warranted. Larger prospective trials that include the prevention and treatment of trismus are needed to improve management and to confirm the benefit of IMRT in the reduction of radiation-induced trismus and the QOL and economic impact of this common oral sequelae of RT.

Conflict of interest statement None to declare.

References

1. Brennan MT, Spijkervet FKL, Elting LS (2010) Methodology review. Support Care Cancer (in press)
2. Chao CK, Ozyigit G, Blanco AI, Thorstad WL, Deasy JO, Haughey BH, Spector GJ, Sessions DG (2004) Intensity-modulated radiation therapy for oropharyngeal carcinoma: impact of tumor volume. Int J Radiat Oncol Biol Phys 59:43–50
3. Chen AM, Bucci MK, Singer MI, Garcia J, Kaplan MJ, Chan AS, Phillips TL (2007) Intraoperative radiation therapy for recurrent head-and-neck cancer: the UCSF experience. Int J Radiat Oncol Biol Phys 67:122–129

4. Chua DT, Lo C, Yuen J, Foo YC (2001) A pilot study of pentoxifylline in the treatment of radiation-induced trismus. Am J Clin Oncol 24:366–369
5. Daoud J, Toumi N, Bouaziz M, Ghorbel A, Jlidi R, Drira MM, Frikha M (2003) Nasopharyngeal carcinoma in childhood and adolescence: analysis of a series of 32 patients treated with combined chemotherapy and radiotherapy. Eur J Cancer 39:2349–2354
6. Dijkstra PU, Huisman PM, Roodenburg JL (2006) Criteria for trismus in head and neck oncology. Int J Oral Maxillofac Surg 35:337–342
7. Dijkstra PU, Kalk WW, Roodenburg JL (2004) Trismus in head and neck oncology: a systematic review. Oral Oncol 40:879–889
8. Eisen MD, Weinstein GS, Chalian A, Machtay M, Kent K, Coia LR, Weber RS (2000) Morbidity after midline mandibulotomy and radiation therapy. Am J Otolaryngol 21:312–317
9. Grandi G, Silva ML, Streit C, Wagner JC (2007) A mobilization regimen to prevent mandibular hypomobility in irradiated patients: an analysis and comparison of two techniques. Med Oral Patol Oral Cir Bucal 12:E105–E109
10. Hartl DM, Cohen M, Juliéron M, Marandas P, Janot F, Bourhis J (2008) Botulinum toxin for radiation-induced facial pain and trismus. Otolaryngol Head Neck Surg 138:459–463
11. Hsiung CY, Huang EY, Ting HM, Huang HY (2008) Intensity-modulated radiotherapy for nasopharyngeal carcinoma: the reduction of radiation-induced trismus. Br J Radiol 81:809–814
12. Kent ML, Brennan MT, Noll JL, Fox PC, Burri SH, Hunter JC, Lockhart PB (2008) Radiation-induced trismus in head and neck cancer patients. Support Care Cancer 16:305–309
13. Keus RB, Pontvert D, Brunin F, Jaulerry BJP (1988) Result of irradiation in squamous cell carcinoma of the soft palate and uvula. Radiother Oncol 11:311–317
14. Laskin DM, Greene CS, Hylander WL (2006) Temporomandibular disorders: an evidence-based approach to diagnosis and treatment. Quintessence, Chicago
15. Le Scodan R, Pommier R, Ardiet JM, Montbarbon X, Malet C, Favrel V, Zrounba P, Poupart M, Céruse P, Ferlay C, Clippe S (2005) Exclusive brachytherapy for T1 and T2 squamous cell carcinomas of the velotonsillar area: results in 44 patients. Int J Radiat Oncol Biol Phys 63:441–448
16. Levendag P, Nijdam W, Noever I, Schmitz P, Van de Pol M, Sipkema D, Braat C, De Boer M, Jansen P (2004) Brachytherapy versus surgery in carcinoma of tonsillar fossa and/or soft palate: late adverse sequelae and performance status: can we be more selective and obtain better tissue sparing? Int J Radiat Oncol Biol Phys 59:713–724
17. Melchers LJ, Van Weert E, Beurskens CH, Reintsema H, Slagter AP, Roodenburg JL, Dijkstra PU (2009) Exercise adherence in patients with trismus due to head and neck oncology: a qualitative study into the use of the Therabite. Int J Oral Maxillofac Surg 38:947–954
18. Palazzi M, Guzzo M, Bossi P, Tomatis S, Cerrotta A, Cantú G, Locati LD, Licitra L (2004) Regionally advanced nasopharyngeal carcinoma: long-term outcome after sequential chemotherapy and radiotherapy. Tumori 90:60–65
19. Palazzi M, Guzzo M, Tomatis S, Cerrotta A, Potepan P, Quattrone P, Cantù G (2004) Improved outcome of nasopharyngeal carcinoma treated with conventional radiotherapy. Int J Radiat Oncol Biol Phys 60:1451–1458
20. Peterson DE et al. Systematic Review Osteoradionecrosis (2010) Support Care Cancer (in press)
21. Ozsaran Z, Yalman D, Baltalarli B, Anacak Y, Esassolak M, Haydaroğlu A (2003) Radiotherapy in maxillary sinus carcinomas: evaluation of 79 cases. Rhinology 41:44–48
22. Shulman DH, Shipman B, Willis FB (2008) Treating trismus with dynamic splinting: a cohort, case series. Adv Ther 25:9–15
23. Sultanem K, Shu HK, Xia P, Akazawa C, Quivey JM, Verhey LJ, Fu KK (2000) Three-dimensional intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: the University Of California—San Francisco experience. Int J Radiat Oncol Biol Phys 48:711–722
24. Teguh DN, Levendag PC, Voet P, van der Est H, Noever I, de Kruijf W, van Rooij P, Schmitz PI, Heijmen BJ (2008) Trismus in patients with oropharyngeal cancer: relationship with dose in structures of mastication apparatus. Head Neck 30:622–630
25. Wang CJ, Huang EY, Hsu HC, Chen HC, Fang FM, Hsiung CY (2005) The degree and time-course assessment of radiation-induced trismus occurring after radiotherapy for nasopharyngeal cancer. Laryngoscope 115:1458–1460
26. Wu Y, Hu WH, Xia YF, Ma J, Liu MZ, Cui NJ (2007) Quality of life of nasopharyngeal carcinoma survivors in Mainland China. Qual Life Res 16:65–74
27. Yeh SA, Tang Y, Lui CC, Huang YJ, Huang EY (2005) Treatment outcomes and late complications of 849 patients with nasopharyngeal carcinoma treated with radiotherapy alone. Int J Radiat Oncol Biol Phys 62:672–679
28. NCI (1990) National Institutes of Health Consensus Development Conference on Oral Complications of Cancer Therapies: Diagnosis, Prevention, and Treatment. Bethesda, Maryland, April 17–19, 1989. NCI Monogr 9:1–184