Application of Manual Therapy for Dysphagia in Head and Neck Cancer Patients: A Preliminary National Survey of Treatment Trends and Adverse Events

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Gintas P Krisciunas, MPH, MA¹, Aneri Vakharia, BS¹, Cathy Lazarus, PhD², Stephanie Gomez Taborda, BS¹, Rosemary Martino, PhD³, Katherine Hutcheson, PhD⁴, Timothy McCulloch, MD⁵, and Susan E Langmore, PhD¹

Abstract

Background: Radiation-associated dysphagia is a common and debilitating consequence of treatment for head and neck cancer (HNC). Since commonly employed dysphagia therapy programs for HNC patients still lack authoritative efficacy, some speech-language pathologists (SLPs) have started employing manual therapy (MT) techniques in an attempt to prevent or rehabilitate dysphagia in this patient population. However, exceptionally little is known about the use of MT in this patient population.

Objectives: The purpose of this study was to describe practice patterns as well as the rate, type, and severity of adverse events associated with SLP provision of MT to HNC patients.

Methods: An Internet-based questionnaire geared toward SLPs who practice MT was developed and sent to SLPs practicing in the United States, 3 times, through 3 national listservs (American Speech Language Hearing Association [ASHA] Special Interest Division 13, ASHA Special Interest Division 3, and University of Iowa Voiceserv), over the course of 4 weeks.

Results: Of the 255 respondents, 116 (45.5%) performed MT on HNC patients. Of these 116 SLPs, 27.6% provided proactive MT during radiation, 62.1% provided 1 to 2 sessions per week, and 94.8% prescribed a MT home program. The rate, type, and severity of reported adverse events were similar between HNC and non-HNC patients.

Conclusion: This preliminary survey demonstrated that SLPs provide MT to HNC patients during and after cancer treatment, and that reported adverse events paralleled those experienced by noncancer patients. However, these results should be taken with caution, and a well-designed prospective study is needed to formally establish the safety and the preliminary efficacy of this novel clinical intervention.

Keywords

dysphagia, manual therapy, complementary and integrative medicine, head and neck cancer

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Introduction

Approximately 64% of patients treated with chemoradiation therapy (CRT) for head and neck cancer (HNC) develop swallowing problems.¹ Unless the patient has also had major surgery for their cancer, this dysphagia is most often caused by an excessive production of extracellular matrix proteins (fibrosis), which stiffens the connective tissue and entraps the surrounding muscles and peripheral nerves.^{2–4} Muscle entrapment impedes muscle contractile forces and restricts structural ¹Department of Otolaryngology, Boston University Medical Center, Boston, Massachusetts

²Department of Otolaryngology, Icahn School of Medicine at Mount Sinai, New York, New York

³Department of Otolaryngology, University of Toronto, Toronto, Ontario, Canada

⁴Department of Head & Neck Surgery, University of Texas MD Anderson Cancer Center, Houston, Texas

⁵Department of Otolaryngology, University of Wisconsin, Madison, Wisconsin

Corresponding Author:

Aneri Vakharia, Boston University Medical Center, BCD Building, 800 Harrison Avenue, Boston, MA 02218, USA. Email: aneriv@bu.edu

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (http://www.creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us. sagepub.com/en-us/nam/open-access-at-sage). movement, which results in an inability to completely clear a bolus through the pharynx. As a result, HNC patients who suffer from dysphagia are at high risk for aspiration pneumonia, can become nutritionally compromised, may require drastic diet alterations, and often experience significant decreases in quality of life.^{5–7} The long term implication of this fibrosis-associated dysphagia is especially problematic for HNC patients with human papillomavirus-mediated tumors who tend to be younger and who often have many years of productive and disease-free life.^{8,9}

Two common approaches are used to treat fibrosisassociated dysphagia. Approximately half of speechlanguage pathologists (SLPs) practicing in the United States first see patients reactively, only if dysphagia develops after completion of CRT.¹⁰ The other half of SLPs try to intervene proactively, during radiation therapy, in an attempt to prevent or mitigate the severity of a fibrosis-associated dysphagia. In either scenario, compensatory techniques (eg, postural changes, diet modifications, swallow maneuvers)^{11,12} and swallow or nonswallow exercises (eg, tongue exercises, effortful swallow, Mendelsohn maneuver)^{13,14} are prescribed in an attempt to make swallowing safer and to strengthen the muscles associated with swallowing. Unfortunately, compensatory techniques do not rehabilitate the patient's swallow,^{15,16} and swallow exercises and nonswallow exercises have conflicting reports of efficacy in the HNC population.^{17–21}

In the absence of research that authoritatively demonstrates the efficacy of traditional dysphagia therapy in this patient population, SLPs have started looking for novel interventions-or novel applications of existing interventions-that may benefit HNC patients. One untested intervention that may mitigate fibrosisassociated dysphagia by modulating the wound healing process is MT. MT represents a broad range of techniques that generally include passive and active stretching, light and deep soft tissue mobilization, and joint manipulation. MT techniques have been shown to prevent contractile tension from scars, increase tissue and muscle extensibility, promote joint range of motion,²²⁻²⁴ attenuate acute toxicities such as pain,^{25–27} and reduce inflammation.^{28–30} By extension, since fibrosisassociated dysphagia is caused by an abnormal wound healing response characterized by excessive inflammation followed by marked scar tissue deposition and anatomic immobility,31-34 it makes sense that MT techniques may be useful in treating fibrosis-associated dysphagia in the HNC patient population.

Since SLPs already employ a form of MT called Laryngeal Manipulation³⁵ for voice disorders as well as stretching protocols to ameliorate neck or jaw stiffness in HNC patients, the application of new types and timing of MT techniques is unsurprising. To date, only 1

article has been published about the use of MT during radiation therapy for HNC.³⁶ An interdisciplinary team developed a HNC and dysphagia specific multimodality MT program that was administered to 5 HNC patients during radiation therapy. It was reported that the patients experienced decreased levels of throat pain after each MT session and were without any adverse events. However, it was a small case series that did not include functional outcomes, so the application of MT for HNC patients as a means to prevent and treat dysphagia remains unexplored.

As MT techniques are seen as a possible means to prevent or mitigate fibrosis-associated dysphagia in the HNC patient population, increasing numbers of patients and clinicians are seeking this treatment in the hopes of realizing some therapeutic benefit. However, very little is known about SLP MT practice patterns or about the safety of using manual therapies (MT) on HNC patients during or after radiation therapy. Accordingly, the purpose of this exploratory survey was to query SLPs who perform MT on HNC patients about their practice patterns as well as the rate, type, and severity of adverse events associated with treating this patient population.

Methods

Questionnaire Development

An Internet-based questionnaire was collaboratively developed by a group of expert clinicians located at various academic teaching hospitals distributed throughout the United States and Canada. Repeated iterative survey pilot testing, discussion, and revision established the content validity of the questionnaire. The questionnaire went through 6 iterations before all experts agreed on the questions and content. Face validity of the questionnaire was tested using a group of 10 external unaffiliated clinicians. The feedback from these unaffiliated clinicians was incorporated into the questionnaire design. The final questionnaire contained a total of 26 questions, but contained branching logic so that respondents were only asked questions that were relevant to their practice. This survey was approved as an exempt research study by the Institutional Review Board.

Questionnaire Content

The final questions (see Supplementary Material) represented 4 broad topics of interest. The first entailed limited clinician demographics that allowed the research team to understand how experienced the responding clinicians were (years of practice, HNC caseload, board-certified specialist in swallowing or not, MT training they received, years practicing MT).

The second topic of interest entailed patient and MT details: what patient populations they used MT with (HNC, voice, globus, etc), what anatomic areas they applied MT to (neck, jaw, face, chest, abdomen, back, etc), and what types of MT they used in their clinical practice (general "MT," massage therapy, myofascial release therapy). For specificity, "MT" was described as hands-on passive and active stretching, light and deep soft tissue mobilization to increase tissue extensibility, and joint manipulation (which includes laryngeal manipulation). Myofascial release was defined as applying gentle sustained pressure into the myofascial connective tissue. Massage therapy was described as rubbing, palpating, and kneading muscles and joints at various patient-centered intensities. We purposely excluded lymphedema therapy since its purpose is different than that of the other MT techniques. Collectively, these techniques were called MT, and all references to MT in this article refer to any/all of these treatment modalities in collective.

The third topic of interest concerned the type and severity of any adverse events patients experienced as a result of their MT program. Clinicians were separately asked about adverse events experienced by HNC versus non-HNC patients so that the adverse event profiles could be compared.

The fourth topic of interest pertained to the clinical application of MT in the HNC patient population. More specifically, responding clinicians were asked when they perform MT on HNC patients (during/after radiation therapy), how often they perform MT on patients, and whether they teach patients a self-administered home program.

Study Design/Survey Administration

To allow for confidential and unbiased responses, especially with respect to reporting adverse events experienced as a result of MT provision, the survey responses were collected anonymously. Because the research involved an anonymous survey, it was determined to be exempt under 45 CFR 46.101(b) category 2 by the lead institution's Institutional Review Board, so informed consent was not needed.

The questionnaire was administered using the SurveyMonkey[®] online interface (SurveyMonkey.com) between July 17, 2016 and August 15, 2016. It was sent approximately once per week but on different days and times to maximize the response rate. Each week the questionnaire was sent to 3 e-mail listservs; the American Speech Language Hearing Association (ASHA) Special Interest Division 13, the ASHA Special Interest Division 3, and the University of Iowa Voiceserv. Special Interest Division 13 includes SLPs with a special interest in swallowing and swallowing

disorders, so it would likely include a number of clinicians who treat HNC patients with MT. The Special Interest Division 3 and the University of Iowa Voiceserv listservs include members with an interest in voice and voice disorders that would include SLPs who use MT for disorders such as muscle tension dysphonia and who may also use such techniques on HNC patients. The 3 listservs represent a total of approximately 13,500 SLPs. However, it is likely that a significant proportion of those SLPs subscribed to more than one of those listservs, so the total number of unique SLPs is unknown. As an exploratory survey of a novel and previously undescribed clinical intervention, the number of respondents was expected to be low and the results were to be analyzed descriptively.

Results

A total of 255 responses were collected. Of the 255 responses, 101 respondents did not practice MT and 154 did employ MT in their clinical practice. The 255 respondents' basic demographic data are presented in Table 1.

Of the 101 respondents who did not practice MT, the majority cited that they did not practice MT due to a lack of training (n = 88, 87.1%). Only 4% (n = 4) suggested they did not think performing such therapies were useful or effective, and 2% (n = 2) believed that SLPs should not perform therapies. Roughly 18% (n = 18) of these 101 respondents specified "other reasons" for

Table I. Clinical Demographics of Survey Respondents ($n = 25$
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Demographics	Do Perform MT (n = 154) No. (%)	Do Not Perform MT (n = 101) No. (%)
Years practicing in sp	eech pathology	
0-4 years	19 (12.3)	12 (11.9)
5–10 years	22 (14.3)	29 (28.7)
>10 years	113 (73.4)	60 (59.4)
Number of new HNC	C patients per month	
I–5 patients	108 (70.1)	70 (69.3)
6-10 patients	20 (13.0)	9 (8.9)
>10 patients	26 (16.9)	22 (21.8)
Years performing MT		
0-4 years	78 (50.7)	NA
5–10 years	39 (25.3)	NA
>10 years	37 (24.0)	NA
BCS-S certified	. ,	
Yes	19 (12.3)	22 (21.8)
No	135 (87.7)	79 (78.2)

Abbreviations: BCS-S, Board Certified Specialist in Swallowing and swallowing disorders; HNC, head and neck cancer; MT, manual therapy; NA, not applicable. not employing MT such as appointment time constraints, lack of proficiency, and that physical therapists (PTs) and occupational therapists already perform these types of therapies.

The other 154 respondents reported that they did employ MT in their practice. The majority of SLPs received MT training through a continuing education course (n = 123, 79.9%) and/or through "on-the-job training" through their colleagues (n = 81, 52.6%). Only 10.4% (n = 16) received training through formal certification. The majority of these clinicians (n = 96, 62.3%) did not receive MT training that was specific to HNC patients. Most respondents (n = 78, 50.7%) had been performing MT for 4 years or less, 25.3% (n = 39) had 5 to 10 years of experience, and roughly 24% (n = 37) reported using MT for more than 10 years. The overwhelming majority performed MT on both HNC patients (n = 116; 75.3%) and on non-HNC patients (n = 141; 91.6%).

Of the 116 SLPs who perform MT on HNC patients, 1.7% (n = 2) perform MT only during radiation therapy, 25.9% (n = 30) provide MT during and after radiation therapy, and roughly 31% (n = 36) provide MT only after completion of radiation therapy. The remaining SLPs (n = 48, 41.4%) perform MT in a reactive manner, only once a patient complained of dysphagia and/or after tissue sensitivity has subsided. The majority of the 116 clinicians provided MT to HNC patients 1 to 2 times a week (n = 72, 62.1%). The remaining clinicians were divided between providing MT less than once a week (n=25, 21.5%) and 3 to 5 times per week (n = 17, 14.7%). Almost all of these SLPs (n = 110, 110, 110)94.8%) teach their HNC patients MT techniques that are to be self-administered at home. The majority of SLPs recommended that patients self-administer MT at home 6 or more times per week (n = 69, 62.7%), followed by 3 to 5 times per week (n = 37, 33.6%) (Table 2).

The vast majority (n = 111, 95.7%) of those who performed MT on HNC patients reported no adverse events associated with this treatment. Of the 5 respondents who reported adverse events while performing MT, there were 2 incidences of lightheadedness and of pain, and 1 incidence of loss of consciousness and of adverse skin reaction. In comparison, of the 141 surveyed SLPs who provide MT to non-HNC patients (globus, muscle tension dysphonia, etc), the exact same percent 95.7% (n = 135) reported no adverse events. Of the 6 respondents who reported adverse events with the non-HNC patient population, the events included 2 incidences of pain, light-headedness, and dizziness, and 1 incidence of nausea (Table 3).

Discussion

To date, other than a single case series describing the application of a dysphagia-centric MT program with

Table 2. Timing and Frequency of MT Provision With HNC Patients (n = || 16).

Timing and Frequency of MT	No. (%)
When MT is performed	
During radiation therapy only	2 (1.7)
After radiation therapy only	36 (31.0)
During and after radiation therapy	30 (25.9)
In a reactive manner	35 (30.2)
Another time point	13 (11.2)
Times per week patients are seen in clinic	for MT
Less than once per week	25 (21.5)
I–2 times per week	72 (62.1)
3–5 times per week	17 (14.7)
More than 5 times per week	2 (1.7)
Times per week clinicians instruct MT be	practiced at home
None: do not recommend	6 (5.2)
I–2 times per week	4 (3.4)
3–5 times per week	37 (31.9)
>6 times per week	47 (40.5)
Other frequency ^a	22 (19.0)

Abbreviation: MT, manual therapy.

^aAll respondents indicated 7 day per week or greater frequency.

 Table 3. Adverse Events Reported for HNC Versus

 Non-HNC Patients.

Adverse events reported for HNC patients ^a	Adverse events reported for Non-HNC patients ^b
Pain $(n = 2)$	Pain $(n = 2)$
Light headedness $(n = 2)$	Light headedness $(n = 2)$
Loss of consciousness $(n = 1)$	Dizziness $(n = 2)$
Adverse skin reaction $(n = 1)$	Nausea $(n = 1)$

Abbreviation: HNC, head and neck cancer.

^aFive respondents (out of 116 respondents) reported a total of 6 adverse events.

 $^{\mathrm{b}}\text{Six}$ respondents (out of 141 non-HNC respondents) reported a total of 7 adverse events.

5 patients during RT,³⁶ there are no published reports describing the use of MT to treat dysphagia in the HNC patient population. Although the number of SLPs who reported using MT with HNC patients (n = 116) was small in proportion to the total number of clinicians surveyed, it was a greater number than expected since so little is known or published about MT application in this patient population. However, given that traditionally employed dysphagia therapies still lack demonstrable efficacy when applied either proactively or reactively in the HNC patient population,^{18,19,21,37} it makes sense that clinicians are seeking and experimenting with new and potentially promising treatment modalities.

The use of MT in the HNC population also has a biomolecular rationale. For patients afflicted with

fibrosis and radiation-associated dysphagia, excessive inflammation (or an inability to modulate that inflammation) ultimately leads to an aberrant wound healing process that results in constitutive production of collagen.^{34,38,39} The unregulated production of fibrotic tissue ultimately occludes deep connective tissues, muscles, and obliterates the microvasculature.^{31–33,39,40} Importantly, this generalized understanding suggests that if local inflammation and fibroblast activity can be modulated enough to prevent the switch from normal to abnormal wound healing, then fibrosis and the associated dysphagia may also be mitigated.

Interestingly, preliminary evidence from pre-clinical models and from other disciplines suggests that MT may in fact mitigate inflammation and fibroblast activity. Massage and spinal manipulative therapy have been shown to reduce a number of inflammatory cytokines including NFkB, HSP27, TNF-a, and IL-6 in human studies.^{30,41} In vitro and preclinical animal models have demonstrated that passive stretch and myofascial release can reduce scar tissue formation, increase muscle regeneration, and attenuate the inflammatory response to injury.⁴²⁻⁴⁴ Furthermore, MT techniques are an integral part of proactive burn management performed by PTs to prevent contractures, or contractile tension, caused by the aberrant scarring process.²² These interventions begin as soon as the patient is able to tolerate them, often with the support of pain medication.²³ Since RT for HNC is similar to a prolonged and compounded burn,³² similar protocols offered to HNC patients during RT, within patient tolerance, may also be effective. Although none of the existent literature is specific to radiation therapy for HNC, it can be inferred that there is an untested rationale for employing MT protocols in this patient population.

Given the tenuous evidence for traditionally employed dysphagia therapy coupled with a biomolecular rationale for the use of MT with the HNC patient population, it makes sense that MT is becoming a more sought after treatment for fibrosis-associated dysphagia. This survey revealed that twice as many SLPs started performing MT in the last 4 years as compared to 5 to 10 years ago or 10+ years ago, suggesting there is a surge in interest in these techniques. Since the majority of surveyed SLPs have been practicing clinicians for more than 10 years, it may be the case that more seasoned SLPs are actively seeking MT training after working in the field for a number of years. This would make sense if SLPs experience varying degrees or inconsistent success in treating dysphagia with traditional swallowing therapy and were actively pursuing additional training in techniques such as MT.

With regard to treatment protocols, the frequency of MT provision was quite high with the majority of clinicians recommending 1 to 2 clinical treatment sessions per week and a self-administered home program 6 to 7

times per week. This suggests that the majority of SLPs who employ MT believe that continual rather than punctuated treatment provides the greatest benefit. For patients undergoing RT for HNC who receive daily fractions of radiation, attempting to mitigate the daily insult to tissues with daily MT therapy is also logical from a biomolecular standpoint.

This survey is the also the first to report the rate and general severity of MT associated adverse events experienced by HNC patients. The results of this preliminary survey revealed that the reported rate and general severity of adverse events experienced by HNC patients was the same as those experienced by non-HNC patients. This was somewhat surprising since many clinicians assume that the fragile state of HNC patients and their high rates of skin toxicity would predispose them to higher rates of adverse events associated with MT. However, this assumption neglects the fact that MT programs are meant to be tailored to each patient. In the authors' collective experience with MT provision to HNC patients, if a patient is experiencing increased pain or adverse effects of radiation therapy in one or more parts of their neck, then the MT program is adjusted accordingly. The goal is to increase pliability, reduce contractile forces, modulate inflammation, and reduce hypoxia, but not at the expense of patient safety or undue pain. This contention is supported by published descriptions of clinical experience, clinical research, and a literature review that demonstrate the ability of MT techniques to decrease pain in various patient groups.^{26,27,36}

In this survey, 3 of the 6 reported adverse events experienced by HNC patients were dizziness, lightheadedness, or loss of consciousness. For 1 of these 3 events, a respondent specified that the light-headedness experienced was due to carotid compression. It is possible that the other 2 similar adverse events were also due to carotid compression, and one might question whether the clinicians performing MT on these patients were novice providers. This may also suggest that properly designed protocols and/or training could reduce the risk of adverse events. Given that the rate of dizziness or lightheadedness events was similar between HNC and non-HNC patients, it is likely that proper training in MT techniques is the best way to avoid these events irrespective of the patient population being treated. Importantly, the results of this survey reaffirm our own clinical experience, and suggest that if MT is provided to HNC patients by adequately trained clinicians, then it may not be any more dangerous than if applied to patients who suffer from globus or muscle tension dysphonia.

Limitations

A relatively small sample size is a limitation of this study. Given the novelty of MT application in HNC patients, we anticipated a low response rate. This inherently limits our understanding of outcomes such as the true rate and severity of adverse events and how rates may differ among patients who receive MT at different times (during vs after RT) and intensities (duration/ frequency/modality). The number, type, and severity of the adverse events reported may be higher than what was reported and may have been influenced by recall bias or by unwillingness to report adverse events. Although we tried to minimize fear of reporting adverse events by designing a completely anonymous survey, SLPs who experienced high rates of adverse events while performing MT in the HNC population may have been reluctant to respond to the survey or to be completely candid in their responses. Such confounders can only be attenuated with a well-designed prospective clinical trial. We also do not know the true extent to which MT is performed in this patient population, although this was not a question that we attempted to answer in this study. It is likely that some SLPs who provide MT to HNC patients and who subscribe to the 3 listservs did not participate in the survey. It is also likely that a number of SLPs who perform MT on HNC patients do not subscribe to any of the 3 listservs, and alternative methods of identifying those clinicians are needed to achieve a maximally representative sample. In either scenario, the SLPs that were not captured in this survey may be fundamentally different in unmeasured ways than those who answered the survey, which would lead to selection bias. Finally, the survey was only implemented to SLPs in the United States and did not include other countries where complimentary and integrative therapies such as MT may be

Next studies. The goal of this study was to determine how SLPs employ MT to HNC patients and to assess the safety of MT in this patient population, especially if employed proactively during radiation therapy. However, this is a very preliminary study of a novel application of MT, so the results should be interpreted with caution. Future prospective studies are needed to authoritatively assess the number, type, and severity of adverse events associated with performing MT during RT in HNC patients. We hope that this survey will inform a future phase 2/3 clinical trial that can rigorously test the safety and preliminary efficacy of this therapeutic intervention. Doing so would allow the medical community to either start employing a proven and safe intervention or avoid widespread use of an ineffective or unsafe treatment.

employed with varying levels of frequency or expertise.

Conclusion

This preliminary survey study indicated that the SLPs who employ MT for dysphagia in HNC patients most often recommend 1 to 2 clinical treatment sessions per week with a self-administered home program 6 to 7 times per week. The timing of MT administration was variable and may be recommended either during or after RT. The type, severity, and number of reported adverse events experienced by HNC patients versus non-HNC patients were similar. A phase 2/3 clinical trial that formally tests safety and preliminary efficacy should be conducted so that objective evidence can guide the use of this therapy before it becomes overly popular with a high-risk patient population.

Declaration of Conflicting Interests

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Supplemental material

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References

- Francis DO, Weymuller EA, Parvathaneni U, Merati AL, Yueh B, et al. Dysphagia, stricture, and pneumonia in head and neck cancer patients: does treatment modality matter? *Ann Otol Rhinol Laryngol.* 2010;119(6):391–397.
- 2. Fajardo LF. The pathology of ionizing radiation as defined by morphologic patterns. *Acta Oncol.* 2005;44(1):13–22.
- 3. Gramley F, Lorenzen J, Koellensperger E, Kettering K, Weiss C, Munzel T. Atrial fibrosis and atrial fibrillation: the role of the TGF-beta1 signaling pathway. *Int J Cardiol.* 2010;143(3):405–413.
- Johns MM, Kolachala V, Berg E, Muller S, Creighton FX, Branski RC. Radiation fibrosis of the vocal fold: from man to mouse. *Laryngoscope*. 2012;122 Suppl 5:S107–S125.
- Campbell BH, Spinelli K, Marbella AM, Myers KB, Kuhn JC, Layde PM. Aspiration, weight loss, and quality of life in head and neck cancer survivors. *Arch Otolaryngol Head Neck Surg.* 2004;130(9):1100–1103.
- Connor NP, Cohen SB, Kammer RE, et al. Impact of conventional radiotherapy on health-related quality of life and critical functions of the head and neck. *Int J Radiat Oncol Biol Phys.* 2006;65(4):1051–1062.
- Nguyen NP, Frank C, Moltz CC, et al. Impact of dysphagia on quality of life after treatment of head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* 2005;61(3):772–778.
- Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med. 2010;363(1):24–35.
- Elrefaey S., Massaro MA, Chiocca S, Chiesa F, Ansarin M. HPV in oropharyngeal cancer: the basics to know in clinical practice. *Acta Otorhinolaryngologica Italica*. 2014;34(5):299–309.

- Krisciunas GP, Sokoloff W, Stepas K, Langmore SE. Survey of usual practice: dysphagia therapy in head and neck cancer patients. *Dysphagia*. 2012;27(4):538–549.
- Logemann JA, Rademaker AW, Pauloski BR, Kahrilas PJ. Effects of postural change on aspiration in head and neck surgical patients. *Otolaryngol Head Neck Surg.* 1994;110(2):222–227.
- Logemann JA, Gensler G, Robbins J, et al. A randomized study of three interventions for aspiration of thin liquids in patients with dementia or Parkinson's disease. J Speech Lang Hear Res. 2008;51(1):173–183.
- Lazarus C. Tongue strength and exercise in healthy individuals and in head and neck cancer patients. *Semin Speech Lang.* 2006;27(4):260–267.
- Hoffman MR, Mielens JD, Ciucci MR, Jones CA, Jiang JJ, McCulloch TM. High-resolution manometry of pharyngeal swallow pressure events associated with effortful swallow and the Mendelsohn maneuver. *Dysphagia*. 2012;27(3):418–426.
- Nguyen NP, Moltz CC, Frank C, et al. Dysphagia severity following chemoradiation and postoperative radiation for head and neck cancer. *Eur J Radiol.* 2006;59(3):453–459.
- Pauloski BR. Rehabilitation of dysphagia following head and neck cancer. *Phys Med Rehabil Clin N Am*. 2008;19(4):889–928, x.
- 17. Ahlberg A, Engstrom T, Nikolaidis P, et al. Early self-care rehabilitation of head and neck cancer patients. *Acta Otolaryngol.* 2011;131(5):552-561.
- Perry A, Lee SH, Cotton S, Kennedy C. Therapeutic exercises for affecting post-treatment swallowing in people treated for advanced-stage head and neck cancers. *Cochrane Database Syst Rev.* 2016(8):CD011112.
- Greco E, Simic T, Ringash J, Tomlinson G, Inamoto Y, Martino R. Dysphagia treatment for patients with head and neck cancer treated with radiotherapy: a metaanalysis review. *Int J Radiat Oncol Biol Phys.* 2018; 101(2):4221–444.
- Langmore SE, Pisegna JM. Efficacy of exercises to rehabilitate dysphagia: a critique of the literature. *Int J Speech Lang Pathol.* 2015;17(3):222–229.
- McCabe D, Ashford J, Wheeler-Hegland K, et al. Evidence-based systematic review: oropharyngeal dysphagia behavioral treatments. Part IV—Impact of dysphagia treatment on individuals' postcancer treatments. *J Rehabil Res Dev.* 2009;46(2):205–214.
- 22. Clinton S, Kinler E, Pariser G, Nuss D, Physical therapy management of a manual laborer following a modified radical neck dissection. *Rehabil Oncol.* 2007;25(2):3–11.
- Procter F. Rehabilitation of the burn patient. *Indian J Plast Surg.* 2010;43(Suppl):S101–S113.
- Anthonissen M, Daly D, Janssens T, Van den Kerckhove E. The effects of conservative treatments on burn scars: a systematic review. *Burns*. 2016;42(3):508–518.
- 25. Martins DF, Mazzardo-Martins L, Cidral-Filho FJ, Gadotti VM, Santos AR. Peripheral and spinal activation of cannabinoid receptors by joint mobilization alleviates

postoperative pain in mice. *Neuroscience*. 2013;255:110–121.

- Bialosky JE, Bishop MD, Price DD, Robinson ME, George SZ. The mechanisms of manual therapy in the treatment of musculoskeletal pain: a comprehensive model. *Man Ther.* 2009;14(5):531–538.
- Degenhardt BF, Darmani NA, Johnson JC, et al. Role of osteopathic manipulative treatment in altering pain biomarkers: a pilot study. J Am Osteopath Assoc. 2007;107(9):387–400.
- Corey SM, Vizzard MA. Bouffard NA, Badger GJ, Langevin HM. Stretching of the back improves gait, mechanical sensitivity and connective tissue inflammation in a rodent model. *PLoS One*. 2012;7(1):e29831.
- 29. Berrueta L, Muskaj I, Olenich S, et al. Stretching impacts inflammation resolution in connective tissue. *J Cell Physiol*. 2016;231(7):1621–1627.
- Crane JD, Ogborn DI, Cupido C, et al. Massage therapy attenuates inflammatory signaling after exercise-induced muscle damage. *Sci Transl Med.* 2012;4(119):119ra13.
- Darby IA, Hewitson TD. Fibroblast differentiation in wound healing and fibrosis. *Int Rev Cytol.* 2007;257:143–179.
- Denham JW, Hauer-Jensen M. The radiotherapeutic injury-a complex 'wound'. *Radiother Oncol.* 2002;63(2):129–145.
- Wynn TA. Cellular and molecular mechanisms of fibrosis. J Pathol. 2008;214(2):199–210.
- Yarnold J, Brotons MC. Pathogenetic mechanisms in radiation fibrosis. *Radiother Oncol.* 2010;97(1):149–161.
- 35. Rubin JS, Lieberman J, Harris TM. Laryngeal manipulation. *Otolaryngol Clin North Am.* 2000;33(5):1017–1034.
- Krisciunas GP, Golan H, Marinko LN, Pearson W, Jalisi S, Langmore SE. A novel manual therapy programme during radiation therapy for head and neck cancer—our clinical experience with five patients. *Clin Otolaryngol*. 2016;41(4):425–431.
- Langmore SE, McCulloch TM, Krisciunas GP, et al. Efficacy of electrical stimulation and exercise for dysphagia in patients with head and neck cancer: a randomized clinical trial. *Head Neck*. 2016;38 Suppl 1:E1221–E1231.
- Westbury CB, Yarnold JR. Radiation fibrosis-current clinical and therapeutic perspectives. *Clin Oncol (R Coll Radiol)*. 2012;24(10):657–672.
- 39. Haydont V, Riser BL, Aigueperse J, Vozenin-Brotons MC. Specific signals involved in the long-term maintenance of radiation-induced fibrogenic differentiation: a role for CCN2 and low concentration of TGF-beta1. Am J Physiol Cell Physiol. 2008;294(6):C1332–C1341.
- Gojniczek K, Jurzak M, Garncarczyk A. The role of connective tissue growth factor (CTGF) in fibroproliferative processes and tissues fibrosis. *Adv Cell Biol.* 2008;1(1):1–17.
- Teodorczyk-Injeyan JA, Injeyan HS, Ruegg R. Spinal manipulative therapy reduces inflammatory cytokines but not substance P production in normal subjects. *J Manipulative Physiol Ther.* 2006;29(1):14–21.
- 42. Hwang JH, Ra YJ, Lee KM, Lee JY, Ghil SH. Therapeutic effect of passive mobilization exercise on improvement of

muscle regeneration and prevention of fibrosis after laceration injury of rat. *Arch Phys Med Rehabil*. 2006;87(1):20–26.

43. Keylock KT, Vieira VJ, Wallig MA, DiPietro LA, Schrementi M, Woods JA. Exercise accelerates cutaneous wound healing and decreases wound inflammation in aged mice. Am J Physiol Regul Integr Comp Physiol. 2008;294(1):R179–R184.

44. Meltzer KR, Cao TV, Schad JF, King H, Stoll ST, Standley PR. In vitro modeling of repetitive motion injury and myofascial release. *J Bodyw Mov Ther*. 2010;14(2):162–171.