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*Man*ual *T*herapy for Fibrosis-Related *L*ate *E*ffect Dysphagia in Head and Neck Cancer Survivors: The Pilot MANTLE trial

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Abstract

Introduction: Late dysphagia that develops or persists years after head and neck cancer (HNC) is a disabling survivorship issue. Fibrosis is thought to stiffen connective tissues and compress peripheral nerve tracts, thereby contributing to diminished strength, flexibility, and in some cases denervation of swallowing muscles. Manual therapy (MT) is used in cancer survivors for pain and other indications, but it is unknown if increasing blood flow, flexibility, and cervical range of motion (CROM) in the head and neck may improve late dysphagia.

Methods and Analysis: MANTLE is an NCI-funded prospective single-arm pilot trial evaluating the feasibility, safety, and therapeutic potential of MT in patients with late dysphagia after radiation therapy (RT) for HNC. Disease-free survivors ≥2 years after curative-intent RT for HNC with at least moderate dysphagia and ≥2 CTCAE v4.0 fibrosis are eligible. The target sample size is 24 participants who begin the MANTLE program. MANTLE is delivered in 10 MT sessions over 6 weeks with an accompanying home exercise program (HEP). Patients then transition to a 6-week post-washout period during which they complete the HEP and then return for a final post-washout evaluation. Feasibility (primary endpoint) and safety will be examined. Serial assessments include cervical range of motion, modified barium swallow (MBS) studies, quantitative magnetic resonance imaging (MRI), electromyography (optional), and patient-reported outcomes (PROs) as secondary, tertiary, and exploratory endpoints.

Ethics and dissemination: The research protocol and informed consent document was approved by the Institutional Review Board at the University of Texas MD Anderson Cancer Center. Findings will be disseminated through peer-reviewed publication that will be made publicly available on PubMed Central upon acceptance for publication, in compliance with NIH public access policy.

Trial registration: NCT03612531 US National Library of Medicine ClinicalTrials.gov, Registered 26 July 2018; https://clinicaltrials.gov/ct2/show/NCT03612531

Keywords: Head and neck cancer, speech pathology, radiation oncology

Article Summary

- MANTLE is a pilot, single arm feasibility trial of manual therapy for late radiation-associated dysphagia.
- Feasibility is the primary endpoint, as measured by therapy completion rate.
- Secondary endpoints examine functional, physical, and patient-reported outcomes.
- Strengths of this study include examination of a novel therapy for an often refractory condition with comprehensive outcome measures.

Introduction

Dysphagia is a priority issue for head and neck cancer (HNC) survivors. While noteworthy as a driver of quality of life (QOL) (1), chronic, persistent, or late dysphagia is also a serious health problem in long-term survivorship. Even in modern practice, chronic aspiration (airway entry of liquids or food) is a life-threatening manifestation of dysphagia afflicting up to 30% of survivors treated with definitive radiotherapy (RT) or chemoradiotherapy (CRT) (2). HNC survivors treated with CRT are 2.7 times more likely to develop aspiration pneumonia than non-cancer controls, and aspiration pneumonia confers a 42% increased risk of mortality among survivors(3).

There is a rapidly growing pool of HNC survivors at risk for late dysphagia. Almost half of HNCs are now human papillomavirus (HPV)-driven oropharyngeal cancers, the incidence of which is expected to increase through at least 2030(4). The vast majority of this fast-growing, large subgroup of HNC survivors has been treated with curative RT at doses of 60 Gray (Gy) or more to the pharyngeal axis sufficient to induce chronic or late radiation-associated dysphagia (RAD)(5-7). Distinct from tobacco-related HNC, HPV-associated HNC is diagnosed younger (median: 54 years)(8) with excellent two- and five-year survival probability of 95%(9) and 79%(10), respectively. For these reasons, modern HNC survivors with HPV-attributable oropharyngeal cancer have the potential to live many active years (even decades) with toxicities of RT.

While many survivors initially recover functional swallowing after acute effects of radiation resolve, an important subset develops debilitating persistent or late RAD. It is estimated 30 to 40% treated with current treatment regimens that prescribe 66-72 Gy radiotherapy develop chronic RAD, and a highly burdened subset progress significantly over subsequent years(7, 11).

Late-radiation associated dysphagia (late-RAD)(12-14) is a particularly challenging, typically progressive form of refractory dysphagia that manifests years into survivorship (median latency: 8 years, cumulative incidence 8% at 7-years survival) after a period of reasonable functional recovery(15). As the era of HPV-associated oropharyngeal cancer survivorship matures, the number of late-RAD cases grows. Late-RAD is among the most difficult late-effect conditions to manage in HNC survivors, associated with a cascade of functional decline. Late lower cranial neuropathies (LCNP) are highly prevalent in survivors with late-RAD, 48 to 83% in the investigators' prior work, and increase the likelihood of lifelong feeding tube dependence due to refractory aspiration(5, 12, 16). Despite standard therapies such as swallowing exercises with or without cervical esophageal dilation, 66% of late-RAD cases in the investigators' published case series became chronically feeding tube dependent in late survivorship at a median age of 64 years (9 years after cancer cure)(14, 17). The QOL and health implications of becoming feeding tube dependent for life at this active age are staggering(14). Recent work highlights the gravity of this among cancer patients who ranked feeding tube dependence as one of the top six outcomes of their cancer that they perceive to be worse than death(18).

Therapy success in survivors with RAD is time dependent. Work from our group and others suggest particularly disappointing responses in survivors who begin swallowing therapy more than 2 years after completing curative RT (19, 20). For instance, in the investigators' published case series of late-RAD, oral diet scores were observed to significantly deteriorate (p=0.002) over a median follow-up of 10 months in the late post-RT period, despite standard swallowing exercise therapies with or without esophageal dilation. Likewise, in secondary analysis an NCI-funded multi-site swallowing therapy trial among 117 survivors with chronic and late RAD, response to swallowing therapy was time dependent. QOL and diet scores improved most among those who started therapy <1 year after RT, with little improvement evident among those who started therapy more than 2 years post RT(21).

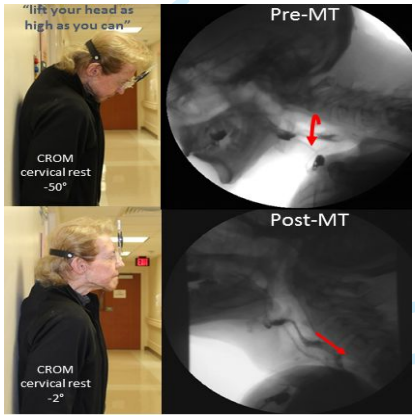
Clinical experience supports that survivors with late-RAD almost universally present with palpable, high-grade fibrosis. Fibrosis is thought to compress peripheral nerve tracts, thereby contributing to denervation of critical swallowing muscles(22). Largely considered irreversible and potentially progressive, these normal tissue changes disrupt the intricate sensorimotor processes required to simultaneously close the airway, open the esophagus, and push a bolus through the pharynx for successful swallowing. With mature fibrosis, late-RAD coexists with other problems including impaired cervical range of motion (CROM) and abnormal cervical posture(23). Broad manifestations of radiation injury have been referred to as radiation fibrosis syndrome with progressive myelo-radiculo-plexo-neuro-myopathic changes resulting in a host of functional challenges including cervicalgia and head drop syndrome(24). A recent cross-sectional analysis of musculoskeletal impairment in 29 long-term HNC survivors reported 89% had abnormal cervical posture with significant deviation in cervical extension relative to normative ranges (z-score: 0.63, $p<0.001$). Postural and CROM impairments significantly correlated with patient-reported outcome (PRO) measures of shoulder and jaw function, but swallowing associations were not reported.(23) There are, however, emerging data to support a correlation between cervical posture and swallowing. Better CROM and skin pliability (as a clinical marker of cervical fibrosis) associated significantly with swallowing safety per penetration-aspiration scale (PAS) scores from videofluoroscopic swallowing evaluations in survivors with chronic RAD, however, in this secondary analysis of clinical trial data, change in cervical posture or pliability did not associate with change in swallowing function after swallowing therapy(25).

Cervical posture is empirically a critical background factor facilitating safe swallowing. That is, when swallowing with forward head posture (“head drop”), the path of least resistance for any residual bolus in the pharynx is forward into the airway. This might contribute to gravity-assisted aspiration (GASP), whereby post-swallow residue enters the airway more easily when the resting head posture is forward.

Indeed, GASP is a regular clinical observation in the investigators' practice. In contrast, with normal upright cervical posture, residual bolus may dwell posteriorly in the pharynx waiting to be safely cleared into the esophagus on a subsequent swallow.

Adjusting the swallow environment by normalizing cervical posture, as shown in *Figure 1*, is often overlooked as a therapeutic target for late-RAD. Normalizing cervical extension and posture is the initial goal in the proposed MT program in this trial. Integration of this goal focused on priming or optimizing the swallow environment prior to mobilizing intrinsic swallowing musculature represents a novel element of our proposed MT swallow therapy program, called MANTLE (*Man*ual *T*herapy for Fibrosis-Related *L*ate *E*ffect Dysphagia).

[INSERT FIGURE 1, **Cervical extension and aspiration improved in case example after manual therapy**]



Preliminary unpublished clinical data from the investigators detect an average 11-degree improvement in a fibrosis-related endpoint of cervical extension after a single session of MT ($p<0.001$), and notable qualitative remarks about functional gains after MT in clinical practice (e.g., "that's the first time I've felt myself swallow in years"). These early observations helped motivate the development of the MANTLE therapy program and this trial. Acknowledging the typically progressive and refractory nature of late

fibrotic effects, it is critical to understand the durability of improved CROM and whether this translates to better swallowing function.

Objectives:

Therefore, the pilot MANTLE trial proposes to study a novel, adjunctive MT program in patients with fibrosis-related late-RAD with the following objectives:

1) To determine the feasibility and safety of MANTLE as a program of treatment for fibrosis-related dysphagia in HNC survivors
2) To estimate effect size, dose-response (number of treatment sessions to normalized cervical range of motion), and durability of MANTLE for improving cervical range of motion in HNC survivors with fibrosis-related late dysphagia
3) To examine functional outcomes after MANTLE in HNC survivors with fibrosis-related late effects and their association with change in dysphagia grade, cervical extension, and other cofactors.

Methods

Study Design

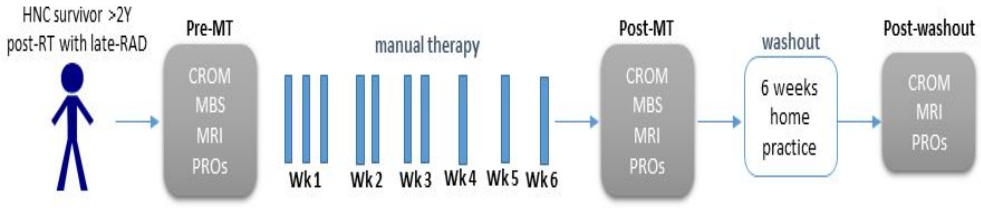
MANTLE is a single-institution, prospective single-arm pilot trial of MT in patients with late dysphagia after head and neck RT. Clinical schedules in the Section of Speech Pathology and Audiology at the University of Texas MD Anderson Cancer Center (Houston, Texas, USA) are screened to identify eligible patients referred for post-radiation swallow assessment. The investigators will enroll consecutive patients who meet eligibility and give written informed consent. Target enrollment is 24 participants who start the MANTLE program, with up to 32 participants enrolled during screening. The first

participant enrolled August 6, 2018; trial completion is projected to occur in April 2021. MT is delivered according to a standard protocol for 6 weeks followed by a 6 week wash-out period. Feasibility and safety will be examined. Serial assessments also include CROM, imaging, and PROs. The trial schema is depicted in *Figure 2*.

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312). The principles of informed consent in the current edition of the Declaration of Helsinki will be implemented before any protocol-specific procedures or interactions are carried out. Informed consent will be obtained, in accordance with 21 CFR 50.25. The written consent document will embody the elements of informed consent, as described in the Declaration of Helsinki and will also comply with local regulations of the Institutional Review Board (IRB) of MDACC.

Protocol amendments impacting eligibility, outcome, and/or analysis will submitted for IRB approval, communicated through the institutional electronic protocol system to all relevant investigators, and updated in trial registration.

[INSERT FIGURE 2, **MANTLE trial schema.**]



Inclusion criteria:

1) Age ≥ 18 years

2) Late DIGEST grade ≥2 dysphagia on Modified Barium Swallow (MBS) ≥2 years after curative-intent radiotherapy for head and neck cancer

3) Grade ≥2 CTCAE v4.0 fibrosis

4) Willing and able to return for 10 sessions that taper in frequency over 6 weeks of therapy

Exclusion criteria:

1) Active recurrent or second primary head and neck, central nervous system, or thoracic cancer at time of enrollment

2) Active osteoradionecrosis or other non-healing wounds (e.g., fistula, ulcer, soft tissue necrosis) in MT regions of interest at time of enrollment

3) History of subtotal or total glossectomy or total laryngectomy

4) Functionally limiting cardiac, pulmonary, or neuromuscular disease

5) Current tracheostomy

Treatment

MT is commonly used in cancer survivors after RT and in the cervical region for pain and other indications.(26-28) The proposed MT program was developed by dysphagia-specialized speech pathologists (SLP) dually licensed in massage therapy (HM) and certified in lymphedema therapy (CLT) (HM, CPB, KS) and summarized using the TIDieR template(29).

The MANTLE program added hierarchical goals for cervical extension, lateral flexion, and rotation to the goals of a published swallowing-focused MT program developed jointly by speech pathologists and a head and neck anatomist.(26) MANTLE conceptualizes and sequences the mobilization targets from superficial to deep as detailed in Table 1. Normalized cervical extension can be conceptualized as

restoring the typical "head-drop" post-RT fibrotic cervical posture to its natural, upright swallowing-optimized state as shown in *Figure 1*. Lateral flexion and cervical rotation are subsequently targeted to prime the tissues to access deeper swallowing regions-of-interest (ROIs) including the tongue, pharynx, and larynx as summarized in *Table 1*. Building on Level I evidence from patients with non-cancer cervical pathology (i.e., benign neck pain), the proposed MANTLE program combines myofascial release (MFR) and massage with range of motion (ROM) exercise to iteratively mobilize swallowing-related ROIs.(30-32)

Table 1. Manual Therapy Program for Late Effect Dysphagia (MANTLE Program)

Functional Goal	**Region Of Interest (ROI)**	**MT Techniques**
Improve **cervical extension**	Upper/mid back and circumferential neck	1. Myofascial release (MFR): separating soft tissue layers, reduce tension between structures 2. Massage: increase vascularity and mobility by manipulation of muscular attachments and muscle bellies 3. Passive range of motion (PROM): clinician-directed joint and soft tissue mobilization without active muscle contraction (after tissue softening) 4. Active Assist Range of Motion (AAROM)/Active Range of Motion (AROM): clinician supported soft tissue and joint mobilization with patient assisted muscle contraction transitioning to patient-independent muscle contraction 5. Strengthen: cervical and laryngeal ROM against resistance 6. Post strengthening repeat PROM/AROM
Improve **lateral flexion** and **cervical rotation**	Bilateral neck	
Improve **movement in muscles involved in deglutition**	Anterior neck/oral cavity[3]: prioritized in order of severity of patient-specific deficits: oral cavity, oropharynx, larynx, pharynx	

In the MANTLE trial, a trained SLP performs the late-RAD MT program. Patients are seen for 10 sessions over 6 weeks with titrating intensity (Week 1: 3 sessions, Weeks 2-3: 2 sessions weekly, Weeks 4-6: 1 session weekly). The 10 sessions performed by the SLP in clinic include soft tissue mobilization and instruction on a cervical stretching/strengthening home exercise program (HEP). After the 10 sessions (over 6 weeks), the patient then transitions to exclusive home practice of the HEP using a standardized clinical handout but without clinician assistance for a 6 week wash-out period.

Subject registration

All adult men and women scheduled for routine clinical MBS at MDACC are considered for participation in this study without regard to race, gender, or socioeconomic status. Central registration is used for tracking study accrual and eligibility. Registration procedures include the following:

- Interested patients are given an explanation of the study to include potential risks and benefits by the principal investigator, co-investigator, or other designated medical personnel.
- Investigator or other trained, designated personnel obtain signed informed consent before any study-specific procedures are performed.
- The subject is seen and evaluated by the principal investigator, co-investigator, or designee prior to enrollment. Screening assessments are performed.
- The principal investigator, co-investigator or designee evaluate eligibility based on inclusion/exclusion criteria stated in this protocol.

Screening evaluations

Patients are evaluated by the speech pathologist and referring physician or advanced practice provider in the interdisciplinary head and neck cancer program. Medical history, oral motor examination, and

oropharyngeal swallow function are recorded. The electronic medical record is reviewed for relevant history pertaining to eligibility criteria.

Study evaluations

Table 2: Summary of Treatment Evaluations

Table 2. Schedule of Evaluation Procedures for MANTLE Trial

Assessment	Method	Domain	Endpoints	Scale	Pre-MT	During-MT	Post-MT	Post-washout
CROM	Goniometer Assessment (clinic)	Cervical range of motion	Cervical extension, lateral flexion, rotation	Continuous	X	X[a]	X	X
MBS	Fluoroscopy	Dysphagia severity grade	DIGEST[26]	Ordinal: 0 (best), 4 (worst)	X		X	
		Swallow kinematics	CASM[27]	Continuous	X		X	
Lymphedema/fibrosis rating	Clinician grading (physical exam)	Severity of lymphedema/fibrosis	CTCAE fibrosis, HN-LEF	Ordinal	X	X[d]	X	X
MIO	Therabite ruler (clinic)	Mouth opening	mm interincisal opening	Continuous	X		X	X
LROM	Therabite ruler (clinic)	Lingual range of motion	Tongue protrusion, lateralization, elevation	Continuous	X		X	X
MDADI[28]	PRO (20-item)	Swallowing-related QOL	Composite, Global, &	Continuous: 20 (worst), 100 (best)	X		X	X

			subscale scores					
MDASI-HN[29]	PRO (31-item)[b]	Symptom burden	Symptom severity, symptom interference	Continuous: 0 (best), 10 (worst)	X	X[c]	X	X
LSIDS-H&N	PRO (64-item)	Lymphedema/fibrosis specific symptoms	Symptom severity associated with lymphedema and fibrosis		X		X	X
PSS-HN[31]	Interview (3-item)	Functional status	Diet, Eating, Speech subscales	Ordinal: 0 (worst), 100 (best)	X	X[d]	X	X
MRI	Imaging	Soft tissue kinetics	T1 signal intensity	Continuous	X		X	X
(Optional)EMG (tongue) EMG+NCS (trap)	Electromyography	Innervation	4-point denervation potentials grade	Ordinal	X		X	

Abbreviations: MBS, modified barium **swallow, EMG, electromyography, DIGEST, Dynamic Imaging Grade of Swallowing Toxicity, CASM, Computational Analysis of Swallowing Mechanics, CROM, Cervical Range of** Motion, MDADI, MD Anderson Dysphagia Inventory, MDASI, MD Anderson Symptom Inventory, PSS-HN, Performance Status Scale Head and Neck Cancer. [a]CROM collected at each MT visit. [b]28-item MDASI-HN with 3 special interest items. [c]MDASI collected bi-weekly during MT. [d]collected at mid-point of MT.

Outcomes are assessed according to the schedule outlined in Table 2. To facilitate retention, all patient-completed questionnaires may be completed by paper or electronic means (i.e., via REDCap), and data collection procedures are aligned with clinical visits (33, 34). Outcome data will be collected from all

participants; regardless of deviations from the therapy protocol. Details of data collection procedures follow.

Cervical Range of Motion: A goniometer measures CROM (degrees) to assess active cervical spine ROM. Five core CROM measures include cervical extension, sagittal plane at rest, lateral flexion (left/right), coronal plane at rest, and lateral rotation (left/right). The primary CROM measure of interest is cervical extension. Cervical extension measures are highly reliable (ICC=.90). Average extension measures in healthy adults aged 60 to 69 range from 57 degrees in males (SD: 10.5) to 65 degrees in females (SD: 13.3). Cervical extension measures decrease by approximately 5 degrees for each decade of life.(35) Lingual and jaw range of motion are also measured per published methods(36, 37).

Lymphedema/Fibrosis Grading: Clinician-grading of lymphedema/fibrosis is conducted according to the published Head and Neck-Lymphedema Fibrosis (HN-LEF)(38, 39), Common Terminology Criteria for Adverse Events (CTCAE) (40), and MD Anderson adaptation of the Foeldi lymphedema rating(41), per physical examination of the patient. Clinical grading is a brief assessment that can be completed in <15 minutes using all 3 complementary sets of grading methods.

Modified Barium Swallow (MBS) Studies: Digital videos from clinical MBS will be scored by a trained speech pathologist blinded to the patient, study, and follow-up interval using methods including the *Dynamic Imaging Grade for Swallowing Toxicity (DIGEST)*(42) and *Computational Analysis of Swallowing Mechanics (CASM)* (43, 44).

MRI: Multiparametric, serial MRI are acquired with a 1.5 T to 3.0T GE Discovery 750 MRI scanner (GE Healthcare, Wisconsin, USA) using laterally placed 6-element flex coils centered on the base of tongue

region. Feasibility and optimization of this MRI paradigm have been described by the investigative team(45), with particular emphasis on immobilization using dedicated H&N coils and a flat insert table with an indexed base plate. Multiparametric imaging will be performed longitudinally (pre-, post-MT, and post-washout). *Table 3* summarizes candidate acquisitions for this study. Our primary candidate imaging biomarker of MANTLE-related soft-tissue change is normalized $\Delta T1_{normalized}$ signal intensity, as we have previously published this parameter's relevance as a dose-dependent soft tissue anatomic imaging biomarker of fibrosis.(46) ROI delineation will be done using the investigators' published method and will include, among our published library of 72 normal structures, the following swallowing-relevant OARs: mylohyoid, geniohyoid, and constrictors.

Table 3. Candidate quantitative imaging parameters selected for MANTLE trial

Acquisition type	Imaging parameter/biomarkers	Tissue injury correlate
T1-pre/post contrast	T1 intensity, T1/R1, T1-rho	Radiation associated fibrosis
T2/T2* Map	T2 contrast, T2*	Radiation associated edema
DTI	Muscle fiber tractography and fractional anisotropy	Muscle/nerve fiber/tumor microstructure, directionality tracts
DCE	Perfusion parameters (K_{trans}, K_{ep})	Tissue perfusion/ Microvessel permeability

Optional Intramuscular electromyography (EMG) and nerve conduction study (NCS) assess insertional activity in the tongue (XII nerve) as a marker of denervation(47). EMG recordings are conducted by a neurologist trained in clinical neurophysiology and denervation potentials graded per:

0 None

1 Persistent, single trains of potentials in at least 2 areas

2 Moderate number of potentials in 3 or more areas

3 Many potentials in all areas

4 Full interference pattern of potentials

EMG and nerve conduction studies will also be taken in the trapezius muscle (XI nerve), as the region is easily accessible for non-invasive EMG with NCS and represents a muscle within the irradiated field with lower cranial nerve innervation. Both quantitative and qualitative EMG will be assessed. NCS will be assessed quantitatively, with waveforms generated from which we acquire amplitude, latency, and conduction velocity(48). Optional EMG will not be conducted if platelets <50,000.

M.D. Anderson Dysphagia Inventory (MDADI) is a written questionnaire to evaluate dysphagia-specific QOL in H&N cancer patients.(49) The 20-item MDADI questionnaire quantifies an individual's global, physical, emotional, and functional perceptions of his or her swallowing ability. In an internal validation in 100 patients with HNC, concurrent validity was found to be moderate by comparison with the Performance Status Scale for Head and Neck Cancer Patients (Spearman correlation, 0.47-0.61). Correlation with the physical functional subscale (Spearman correlation, 0.40) and emotional subscale of SF-36 (36-Item Short Form Survey) (Spearman correlation, 0.36) demonstrated convergent and divergent validity, respectively, of the MDADI. Test-retest reliability (physical, 0.86; emotional, 0.88; functional, 0.88) and internal consistency reliability (overall Cronbach's alpha, 0.96) were sound.

M.D. Anderson Symptom Inventory for Head and Neck Cancer (MDASI-HN) is a patient-reported outcome questionnaire designed to measure severity or burden of systemic and head and neck (HN) specific symptoms and their interference with or effect on patients' daily functioning. This 28-item multi-symptom inventory includes 13 core items ("systemic symptoms": pain, fatigue, sleep, *etc*.), nine

HN-specific items ("local symptoms": dry mouth, mucus, shortness of breath, taste, *etc*.), and six interference items (activity, work, relations, *etc*.). The core MDASI items have been validated for use in cancer patient populations regardless of the specific diagnosis or type of therapy and thus can be used to compare overall burden of disease between different types of cancer(50). The HN-specific items were validated internally with regard to construct and concurrent validity in HN cancer patients.(51, 52) Internal consistency reliability is high in the core, HN-specific, and interference items (Cronbach's alphas of 0.72-0.92). Validated linguistic translations (Chinese, French, German, Greek, Italian, Spanish, and Turkish) of the MDASI-HN may be administered to non-English speaking participants.

Lymphedema Symptom Intensity and Distress Survey – Head and Neck (LSIDS-H&N) (53) is a 64-item instrument designed to assess lymphedema symptoms in head and neck cancer patients. Survey items were selected to address six domains (head and neck-specific functioning, systemic symptoms, psychosocial issues, altered sensation symptoms, neck-shoulder musculoskeletal/skin symptoms, and miscellaneous symptoms) identified by an expert panel. Preliminary testing of LSIDS-H&N demonstrated both feasibility and readability.

Performance Status Scale for Head and Neck Cancer Patients (PSS-HN) is a clinician-rated instrument rated by a semi-structured interview consisting of three questions: normalcy of diet, public eating, and understandability of speech.(54) The PSS-HN has been psychometrically validated and recommended by the National Comprehensive Cancer Network for measurement of swallowing and speech performance in patients with HNC.

Adherence Logs standard clinical adherence logs are given to track adherence to the HEP performed throughout the entire MANTLE trial.

Follow-up intervals

Post-MT and post-wash out evaluations (specified in *Table 2*) will be conducted immediately after the 6 week training period with an allowable window of 2 weeks.

Safety and Feasibility

Safety and Feasibility of MT: Feasibility of MANTLE will be assessed by estimating program completion rates, sources of attrition, and adherence (i.e., clinical attendance, and adherence to home exercise program). Process evaluation checklists will be completed after each session to examine fidelity to the MANTLE treatment program, and patients will be asked to log their home practice using a study-specific adherence form. AEs are also assessed and recorded. Cervical MT is a safe therapy in many populations. Risk of serious adverse events is estimated to be 6 in 10 million[42,43]. Serious AEs relate to cardiovascular risk and are more common when providing a thrust manipulation technique that is employed in this protocol. Mild AEs, while still rare (estimated 1% to 2% of patients), are more common and can include local discomfort, headache, lightheadedness, falls, and fatigue. SAEs were not encountered in our preliminary retrospective review of patients receiving MT.

Data Management

The data is maintained in an institutionally approved electronic data capture system with an integrated codebook. Data management adheres to institutional guidelines and policies for maintaining confidentiality to protect PHI from public viewing by safeguarding storage and disposal of documents containing PHI and computer workstations and databases that access PHI. Data validation will include missing data reports range checks for data values, and logic checks for plausible relationships. The PI, statistician, and data manager will have access to the final trial dataset.

Monitoring

The trial will monitored by the Office of Protocol Research at the MD Anderson Cancer Center subject to independent audit by MD Anderson's Internal Audit Department in accordance with the Texas Internal Audit Act and the University of Texas System Board of Regents and the Internal Audity Activity Charter. Adverse events will be recorded by the study team. The IRB will be notified of any related grade three or greater adverse events and provided data to permit a safety review of the study treatment. The IRB may request additional meetings or safety reports as deemed necessary.

Patient and Public Involvement

The investigators did not formally engage a patient or public stakeholder team in trial development or recruitment strategies. Study data will be disseminated via peer-reviewed publication made publicly available through PubMed Central, and shared with participants through this medium.

Statistical Considerations

Statistical analysis and sample size justification

The primary objective of MANTLE is to determine feasibility based on the program completion rate. Investigators planned to enroll 24 patients and estimated an attrition rate of 20% to achieve a final sample size of 19 participants. Program completion rate is estimated from the participants who start the MANTLE program after screening procedures excluding screen failures and those who withdrawal before therapy starts. Note, the final protocol was amended to account for unanticipated prolonged treatment interruption or delay due to the institutional suspension of live clinical services and clinical research in response to the COVID-19 pandemic. For that reason, investigators increased maximum accrual to 32 participants and will cease enrollment after 24 participants start treatment without any

COVID-19-related interruptions. The primary analysis will include the 24 participants who started MT and who did not experience the COVID-19-related interruption of study participation. Any study withdrawals or interruptions in study participation for reasons other than COVID interruptions will be part of this feasibility analysis. In addition, as a sensitivity analysis, all available data, including any data collected from the participants interrupted by the COVID-19 research suspension, will be analyzed in a stratified manner.

For analysis of the **primary objective** to determine the feasibility and safety of the MANTLE program, a completion rate of 75% will be considered the benchmark of feasibility. Completion rate will be defined by completion of the 6-week clinical MANTLE program without withdrawing and attending a minimum of 2 sessions plus the post-treatment assessment. Session attendance will be monitored separately to assess adherence and fidelity. We will summarize fidelity and adherence to the standard MANTLE protocol using quantitative and qualitative methods. Adverse events will be tabulated.

For analysis of the **secondary objective**, we chose cervical extension as the primary CROM measure of interest and as the direct treatment target due to our preliminary data suggesting significant improvements after MT in patients with fibrosis-related late effects (1 session mean Δ: 11%; $p<0.001$) as well as our conjectured relevance of CROM to swallowing safety. Cervical extension CROM measures are also highly reproducible (ICC=.90) and are taken each standard MT session as part of routine clinical appointments to direct therapy. For this analysis, we will use simple descriptive statistics to first summarize baseline, post-MT1, and post-MT2 (after the six week wash-out period of exclusive home therapy) CROM measures for each anatomic plane. We will compare baseline to post-MT1 CROM measures using a one-sided paired *t*-test. With 24 patients and conservatively estimating an attrition rate of 20% based on our prior experience, the final sample size of 19 patients will provide 80% power to

detect an effect size of d = 0.593, which corresponds to a $\Delta CROM_{baseline\text{-}post\text{-}MT}$ of 10.68 degrees (assuming the SD = 18 per our pilot data in HNC). To determine whether cervical extension normalizes within 10 sessions of clinician-administered MT, post-MT CROM raw scores will be converted to *z*-scores based on age- and sex-specific norms to estimate the proportion of participants with post-MT cervical extension scores that fall within 2 SDs of normative values. To examine the durability of response, we will normalize post-MT2 CROM measures to determine the percentage of participants who maintain or improve (*z*-score ≥ post-MT score – 2 SDs) post-wash-out. For the expected proportion of 80% who maintain or improve CROM, the 95% CI will extend 15% from the observed proportion. The number of MT sessions before normalization of CROM will be tabulated. In exploratory analysis, we will plot CROM measures across time and will consider using linear mixed models to account for repeated outcome measures with adjustment for clinicodemographic covariates.

For the analysis of our **tertiary objective** , we will conduct a stepwise multivariable analysis to explore covariant swallow morphometrics associated with change in dysphagia grade and cervical extension after MT using the published CASM method. Swallow coordinates from all frames of pre- and post-MT MBS studies and covariates (time, bolus type, $DIGEST_{pre}$, ΔDIGEST, age, sex, tumor site, surgery, ΔCROM, $CROM_{post}$) will be specified in MorphoJ, an integrated morphometric software program, for stepwise analysis: 1) canonical variate analysis (CVA) to identify and rank covariates associated with swallow morphometric changes in patients improved/stable dysphagia (ΔDIGEST), 2) *post hoc* discriminant function analysis will be conducted next to visualize treatment-specific eigenvectors of swallowing muscle motion differences by covariates of interest from CVA (e.g., pre-post MT), and 3) morphometric regression to estimate post-RT eigenvectors associated with change in swallow severity per DIGEST and pre-post MT conditions. For CVA of k variables (12 coordinates motion) in G groups (DIGEST, MT), the total sample size must be larger than [(2k-4) + (G-1)],(55) requiring 21 patients.

Exploratory analyses

Secondary endpoints of MDADI, MDASI-HN, lingual and jaw ROM, lymphedema/fibrosis staging, lingual and jaw ROM, PSS-HN, and MRI parameters will be assessed according to their distributions (continuous: paired *t*-test or non-parametric Wilcoxon signed-rank test, ordinal: rank-invariant). Effect sizes, such as Cohen's *d*, with 95% confidence intervals will be calculated for each endpoint and interpreted. Exploratory analyses and correlative questions will be considered for hypothesis-generating purposes only.

Discussion

The highly focused long-term objective of the MANTLE trial is to improve swallowing function in some of the worst dysphagia presentations in HNC survivorship - that is, those with severe late-RAD we have shown to be often treatment refractory. The focus on late-RAD represents a departure from most therapy trials for RAD that suffer from population heterogeneity as a consequence of enrolling both early and late-RAD patients jointly, where the pathophysiology and trajectory of dysphagia almost certainly differs. By explicitly studying manual therapy (MT) effects solely in late (>2 years) post-radiated survivors, this line of research offers specificity of target in examining the therapeutic potential of this common treatment modality. The endpoints are thoughtfully constructed to estimate effect sizes of various avenues of clinical benefit including mobility, functional change, QOL, and physical swallowing change. Any functional benefit for those with late-RAD could be meaningful as this represents a high burden, growing survivor population with disappointingly limited therapy options in current practice.

MANTLE was designed as a pilot study because we are trialing a new therapy intended for expansion to larger, confirmatory trials of efficacy or effectiveness in our program of research on radiation associated

dysphagia. With the results of this pilot investigation, we expect to demonstrate that the novel MANTLE program is feasible and safe to examine in a larger program of research. Furthermore, we expect to estimate effect sizes achieved in secondary endpoints that will be necessary for power calculations in future trials of efficacy or effectiveness. The diverse outcomes panel was selected specifically to understand which data collection procedures (i.e., functional measures, questionnaires, imaging) may be sensitive to possible changes with MT and merit inclusion in future, larger studies.

Strengths and Limitations

The ideal dosing of MT for this indication is unknown. The dosing schedule is based on prior clinical experience as well as the MT evidence base. Published cervical MT programs vary in intensity from 4+ sessions over 2-7 weeks in populations with neck/shoulder dysfunction (30-32) to 12 sessions over 4 weeks in non-HNC populations with fibrosis-related late effects in other body regions(56). The MANTLE program is designed with 10 sessions over 6 weeks of clinician-directed MT simultaneous with the implementation of cervical HEP. Relative to other cervical MT programs in the literature, this represents a fairly intense manual therapy schedule to match the known pathophysiology and duration of injury of the target population with late-RAD. The MANTLE therapy schedule is intentionally titrated using a scaffold approach in therapy schedule to offer more frequent upfront soft tissue manipulation while transitioning the patient to the independence of a HEP for maintenance. The investigators acknowledge that the therapy schedule developed for the MANTLE protocol may require further refinement as the results mature; however, 10 sessions over 6 weeks were judged by the investigators to represent a time interval during which therapy response should be detectable. Future directions of this trial might include adjusting the dosing of MT and HEP to achieve similar results.

The aims and outcome measures are thoughtfully constructed to provide pilot data regarding the

feasibility/safety (Aim 1), dose and durability (Aim 2), and functional translation (Aim 3) of MANTLE as an adjunctive therapeutic modality for late-RAD. Upon completion of Aim 1, we expect to show a therapy completion rate of 75% as a marker of feasibility. For Aim 2, we expect to demonstrate that cervical range of motion can normalize within 10 sessions of MANTLE in at least 80% of HNC survivors with late-RAD. Aim 3 will provide effect sizes estimates of swallowing function changes after MANTLE. In this pilot trial, we expect to observe attrition <25%, adherence >60%, no therapy-related grade ≥3 adverse events, and sufficient power to estimate Cohen's *d* effect size ≥0.50 for the primary secondary endpoint of interest CROM.

Exploring functional endpoints of the therapeutic trial, we expect to also evaluate mechanism of functional change in swallowing (per DIGEST), muscle motion parameters (per CASM) associated with functional swallowing improvements (per DIGEST) using radiographic MBS studies. The post-MANTLE MBS is conducted immediately following 6 weeks of MT. Even healthy individuals may require 8 to 12 weeks to see functional improvement with stretching and strengthening (57, 58). As such, the post-MANTLE MBS after just 6 weeks of therapy may be earlier than maximal benefit is achieved. Nonetheless, at 6 weeks, any change detected on MBS could be more directly attributed to the MANTLE therapy prior to the wash-out period and may reflect stimulability in the tissue.

The final data collection is 12 weeks after starting MANTLE. While long-term follow-up of dysphagia progression after MANTLE is not feasible in the timeframe of this pilot trial, any positive changes in CROM, patient-reported outcomes, soft tissue (per MRI), or radiographic or perceived swallowing function is likely meaningful because late-RAD is currently considered a treatment refractory toxicity syndrome.

Future Directions

If proven safe and feasible, future studies will need to address/investigate efficacy, effectiveness, sustainability of therapeutic gains, ideal schedules, frequency and combination of MT techniques, and best matching of mobility focused MT with direct functional therapies. For instance, might MANTLE prime the patient with late-RAD to achieve better functional gains during a bolus driven paradigm like the McNeil Dysphagia Therapy Program? Future considerations should also include remote practice as it is rapidly expanding in the era of the COVID pandemic. With this in mind, it will become even more important to understand the outcome of the cervical HEP alone (without soft tissue manipulation as it is used in MANTLE) among patients with RAD who may not be able to access in-person clinical services for soft tissue manipulation. We believe that the proposed MANTLE trial could provide pilot data that might justify practice-changing clinical trials for the growing number of HNC survivors who have no proven options to manage late-RAD

Declarations

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Author contributions

All listed co-authors read and approved the manuscript, and performed the following:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of trial concept and data;

2. Drafting the work or revising it critically for important intellectual content;

3. Final approval of the version to be published;

4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Specific individual contributions in addition to all criteria above are listed as follows:

KH- Principal Investigator; Corresponding/primary author; conceived, coordinated, and directed all study activities, responsible for data collection, project integrity, manuscript content and editorial oversight and correspondence; direct oversight of study personnel.

SB – Operationalization and refinement of data collection procedure, primary trial manager.

KH, HM, CPB, KS, KW, SYL, CDF - Direct patient care provision, direct outcomes assessment and development and refinement of clinical data collection procedures.

CW- Developed statistical analysis plan.

CDF, JW - Responsible for programmatic and infrastructure oversight for MRI analysis and DICOM segmentation; direct and final oversight of MRI data collection; direct oversight of trainee personnel.

SYL - Direct and final oversight of surgical data collection.

KW – Direct and final oversight of EMG data collection.

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Ethics and Consent to Participate

The research protocol and informed consent document was approved by the Institutional Review Board at the University of Texas MD Anderson Cancer Center. The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312). The MANTLE research protocol was activated July 12, 2018 after IRB approval. The trial was prospectively registered with ClinicalTrials.gov on July 26, 2018 and first posted on ClinicalTrials.gov August 2, 2018 prior to enrollment of the first study participant on Aug 6, 2018 with projected study completion date in April, 2021.

Consent for publication: all authors provide consent for publication.

Competing interests: the authors declare no competing interests:

Availability of data and materials: not applicable

Figure Legends

Figure 1. Cervical extension and aspiration improved in case example after manual therapy.

Exemplar case before (top) and after (bottom) single session of MT 18 years post-treatment, surgery and radiotherapy for head and neck cancer. Note red arrows on modified barium swallow study depicting residual bolus in pharynx directed anteriorly toward airway with neck dropped (top), and directed posteriorly toward esophagus with cervical extension normalized (bottom).

Figure 2. MANTLE trial schema.

Abbreviations: HNC, head and neck cancer; RT, radiotherapy; RAD, radiation associated dysphagia; MT, manual therapy; CROM, cervical range of motion; MBS, modified barium swallow; MRI, magnetic resonance imaging; PROs, patient reported outcomes

References (Vancouver)

1. Hunter KU. Toxicities affecting quality of life after chemo-IMRT of oropharyngeal cancer: prospective study of patient-reported, observer-rated, and objective outcomes. Int J Radiat Oncol Biol Phys. 2013;85.

2. Eisbruch A, Kim HM, Feng FY, Lyden TH, Haxer MJ, Feng M, et al. Chemo-IMRT of oropharyngeal cancer aiming to reduce dysphagia: swallowing organs late complication probabilities and dosimetric correlates. Int J Radiat Oncol Biol Phys. 2011;81(3):e93-9.

3. Xu B, Boero IJ, Hwang L, Le QT, Moiseenko V, Sanghvi PR, et al. Aspiration pneumonia after concurrent chemoradiotherapy for head and neck cancer. Cancer. 2015;121(8):1303-11.

4. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol. 2011;29(32):4294-301.

5. Awan MJ. Late radiation-associated dysphagia (late-RAD) with lower cranial neuropathy after oropharyngeal radiotherapy: a preliminary dosimetric comparison. Oral Oncol. 2014;50.

6. M. D. Anderson Head Neck Cancer Symptom Working Group. Beyond mean pharyngeal constrictor dose for beam path toxicity in non-target swallowing muscles: Dose-volume correlates of chronic radiation-associated dysphagia (RAD) after oropharyngeal intensity modulated radiotherapy. Radiother Oncol. 2016;118(2):304-14.

7. Kamal M, Mohamed ASR, Volpe S, Zaveri J, Barrow MP, Gunn GB, et al. Radiotherapy dose-volume parameters predict videofluoroscopy-detected dysphagia per DIGEST after IMRT for oropharyngeal cancer: Results of a prospective registry. Radiother Oncol. 2018;128(3):442-51.

8. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tan PF, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. The New England journal of medicine. 2010;363(1):24-35.

9. Fakhry C, Westra WH, Li S, Cmelak A, Ridge JA, Pinto H, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst. 2008;100(4):261-9.

10. Weinberger PM, Yu Z, Haffty BG, Kowalski D, Harigopal M, Brandsma J, et al. Molecular classification identifies a subset of human papillomavirus--associated oropharyngeal cancers with favorable prognosis. J Clin Oncol. 2006;24(5):736-47.

11. Caudell JJ, Schaner PE, Meredith RF, Locher JL, Nabell LM, Carroll WR, et al. Factors associated with long-term dysphagia after definitive radiotherapy for locally advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2009;73(2):410-5.

12. Hutcheson KA, Lewin JS, Barringer DA, Lisec A, Gunn GB, Moore MW, et al. Late dysphagia after radiotherapy-based treatment of head and neck cancer. Cancer. 2012;118(23):5793-9.

13. Awan MJ, Mohamed AS, Lewin JS, Baron CA, Gunn GB, Rosenthal DI, et al. Late radiation-associated dysphagia (late-RAD) with lower cranial neuropathy after oropharyngeal radiotherapy: a preliminary dosimetric comparison. Oral Oncol. 2014;50(8):746-52.

14. Hutcheson KA. Late radiation-associated dysphagia (RAD) in head and neck cancer survivors. Perspectives on Swallowing and Swallowing Disorders (Dysphagia), 22 (2), 61–72. 2013.

15. Hutcheson KA, Yuk M, Hubbard R, Gunn GB, Fuller CD, Lai SY, et al. Delayed lower cranial neuropathy after oropharyngeal intensity-modulated radiotherapy: A cohort analysis and literature review. Head Neck. 2017.

16. Aggarwal P, Zaveri JS, Goepfert RP, Shi Q, Du XL, Swartz M, et al. Swallowing-related outcomes associated with late lower cranial neuropathy in long-term oropharyngeal cancer survivors: cross-sectional survey analysis. Head & neck. 2019;41(11):3880-94.

17. Hutcheson KA. Late Radiation-Associated Dysphagia (RAD) in Head and Neck Cancer Survivors. Perspectives on Swallowing and Swallowing Disorders (Dysphagia). 2013;22(2):11.

18. Rubin EB, Buehler AE, Halpern SD. States worse than death among hospitalized patients with serious illnesses. JAMA internal medicine. 2016;176(10):1557-9.

19. Langmore SE, McCulloch TM, Krisciunas GP, Lazarus CL, Van Daele DJ, Pauloski BR, 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:E1221-31.

20. Hutcheson KA, Kelly S, Weber RS, Lewin JS. Offering more for persistent dysphagia after head and neck cancer: The evolution of boot camp swallowing therapy. Combined Otolaryngology Spring Meeting; Boston, MA2015.

21. Van Daele DJ, Langmore SE, Krisciunas GP, Lazarus CL, Pauloski BR, McCulloch TM, et al. The impact of time after radiation treatment on dysphagia in patients with head and neck cancer enrolled in a swallowing therapy program. Head & neck. 2019;41(3):606-14.

22. Hutcheson KA, Yuk MM, Holsinger FC, Gunn GB, Lewin JS. Late radiation-associated dysphagia (late-RAD) with lower cranial neuropathy in long-term oropharyngeal cancer survivors: Video case reports. Head Neck. 2014.

23. Ghiam MK, Mannion K, Dietrich MS, Stevens KL, Gilbert J, Murphy BA. Assessment of musculoskeletal impairment in head and neck cancer patients. Support Care Cancer. 2017.

24. Stubblefield MD. Radiation fibrosis syndrome: neuromuscular and musculoskeletal complications in cancer survivors. PM & R : the journal of injury, function, and rehabilitation. 2011;3(11):1041-54.

25. Silbergleit AK, Schultz L, Krisciunas G, Langmore S. Association of Neck Range of Motion and Skin Caliper Measures on Dysphagia Outcomes in Head and Neck Cancer and Effects of Neck Stretches and Swallowing Exercises. Dysphagia. 2020;35(2):360-8.

26. 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):425-31.

27. Gross AR, Hoving JL, Haines TA, Goldsmith CH, Kay T, Aker P, et al. A Cochrane review of manipulation and mobilization for mechanical neck disorders. Spine (Phila Pa 1976). 2004;29(14):1541-8.

28. Gross AR, Kay T, Hondras M, Goldsmith C, Haines T, Peloso P, et al. Manual therapy for mechanical neck disorders: a systematic review. Manual therapy. 2002;7(3):131-49.

29. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ. 2014;348:g1687.

30. Page MJ, Green S, Kramer S, Johnston RV, McBain B, Chau M, et al. Manual therapy and exercise for adhesive capsulitis (frozen shoulder). Cochrane Database Syst Rev. 2014(8):Cd011275.

31. Camargo PR, Alburquerque-Sendin F, Avila MA, Haik MN, Vieira A, Salvini TF. Effects of Stretching and Strengthening Exercises, With and Without Manual Therapy, on Scapular Kinematics, Function, and Pain in Individuals With Shoulder Impingement: A Randomized Controlled Trial. J Orthop Sports Phys Ther. 2015;45(12):984-97.

32. Trott CA, Ruiz Aguila ME, Leaver AM. The clinical significance of immediate symptom responses to manual therapy treatment for neck pain: observational secondary data analysis of a randomized trial. Manual therapy. 2014;19(6):549-54.

33. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. Journal of Biomedical Informatics. 2009;42(2):377-81.

34. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. Journal of Biomedical Informatics. 2019;95:103208.

35. Youdas JW, Garrett TR, Suman VJ, Bogard CL, Hallman HO, Carey JR. Normal range of motion of the cervical spine: an initial goniometric study. Phys Ther. 1992;72:770-.

36. Dijkstra PU, Huisman PM, Roodenburg JL. Criteria for trismus in head and neck oncology. Int J Oral Maxillofac Surg. 2006;35(4):337-42.

37. Lazarus CL, Husaini H, Jacobson AS, Mojica JK, Buchbinder D, Okay D, et al. Development of a new lingual range-of-motion assessment scale: normative data in surgically treated oral cancer patients. Dysphagia. 2014;29(4):489-99.

38. Deng J, Ridner SH, Wells N, Dietrich MS, Murphy BA. Development and preliminary testing of head and neck cancer related external lymphedema and fibrosis assessment criteria. European journal of oncology nursing : the official journal of European Oncology Nursing Society. 2015;19(1):75-80.

39. Deng J, Dietrich MS, Ridner SH, Fleischer AC, Wells N, Murphy BA. Preliminary evaluation of reliability and validity of head and neck external lymphedema and fibrosis assessment criteria. European journal of oncology nursing : the official journal of European Oncology Nursing Society. 2016;22:63-70.

40. Common Terminology Criteria for Adverse Events (CTCAE). v4.03 ed. Bethesda, MD: National Institutes of Health, National Cancer Institute, Department of Health and Human Services; 2010.

41. Lewin JS, Hutcheson KA, Barringer DA, Smith BG. Preliminary experience with head and neck lymphedema and swallowing function in patients treated for head and neck cancer. Perspectives on Swallowing and Swallowing Disorders Dysphagia. 2010;19:45-52.

42. Rosenbek JC, Robbins JA, Roecker EB, Coyle JL, Wood JL. A penetration-aspiration scale. Dysphagia. 1996;11(2):93-8.

43. Schwertner RW, Garand KL, Pearson WG, Jr. A Novel Imaging Analysis Method for Capturing Pharyngeal Constriction During Swallowing. Journal of imaging science. 2016;1(1).

44. Pearson WG, Jr., Taylor BK, Blair J, Martin-Harris B. Computational analysis of swallowing mechanics underlying impaired epiglottic inversion. Laryngoscope. 2016;126(8):1854-8.

45. Ding Y, Mohamed AS, Yang J, Colen RR, Frank SJ, Wang J, et al. Prospective observer and software-based assessment of magnetic resonance imaging quality in head and neck cancer: Should standard positioning and immobilization be required for radiation therapy applications? Pract Radiat Oncol. 2015;5(4):e299-308.

46. Messer JA, Mohamed AS, Hutcheson KA, Ding Y, Lewin JS, Wang J, et al. Magnetic resonance imaging of swallowing-related structures in nasopharyngeal carcinoma patients receiving IMRT: Longitudinal dose-response characterization of quantitative signal kinetics. Radiother Oncol. 2016;118(2):315-22.

47. Perlman AL, Palmer PM, McCulloch TM, Vandaele DJ. Electromyographic activity from human laryngeal, pharyngeal, and submental muscles during swallowing. Journal of applied physiology (Bethesda, Md : 1985). 1999;86(5):1663-9.

48. Preston DC, Barbara E. Shapiro. Electromyography and Neuromuscular Disorders: Clinical-Electrophysiologic Correlations. 3rd ed: Saunders; 2013 2013.

49. Chen AY, Frankowski R, Bishop-Leone J, Hebert T, Leyk S, Lewin J, et al. The development and validation of a dysphagia-specific quality-of-life questionnaire for patients with head and neck cancer: the M. D. Anderson dysphagia inventory. Arch Otolaryngol Head Neck Surg. 2001;127(7):870-6.

50. Cleeland CS, Mendoza TR, Wang XS, Chou C, Harle MT, Morrissey M, et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. Cancer. 2000;89(7):1634-46.

51. Rosenthal DI, Mendoza TR, Chambers MS, Asper JA, Gning I, Kies MS, et al. Measuring head and neck cancer symptom burden: the development and validation of the M. D. Anderson symptom inventory, head and neck module. Head Neck. 2007;29(10):923-31.

52. Rosenthal DI, Mendoza TR, Fuller CD, Hutcheson KA, Wang XS, Hanna EY, et al. Patterns of symptom burden during radiotherapy or concurrent chemoradiotherapy for head and neck cancer: a prospective analysis using the University of Texas MD Anderson Cancer Center Symptom Inventory-Head and Neck Module. Cancer. 2014;120(13):1975-84.

53. Deng J, Ridner SH, Murphy BA, Dietrich MS. Preliminary development of a lymphedema symptom assessment scale for patients with head and neck cancer. Support Care Cancer. 2012;20(8):1911-8.

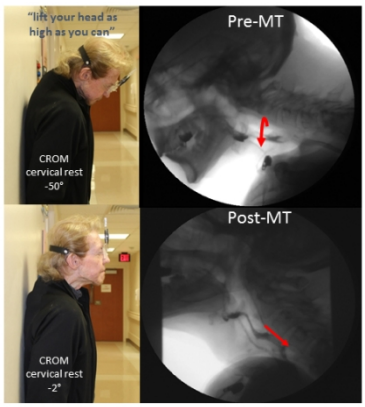
54. List MA, Ritter-Sterr C, Lansky SB. A performance status scale for head and neck cancer patients. Cancer. 1990;66(3):564-9.

55. Webster MA, Sheets HD. A practical introduction to landmark-based geometric morphometrics. Quantitative Method Paleobio. 2010;16:168-88.

56. Cho Y, Do J, Jung S, Kwon O, Jeon JY. Effects of a physical therapy program combined with manual lymphatic drainage on shoulder function, quality of life, lymphedema incidence, and pain in breast cancer patients with axillary web syndrome following axillary dissection. Support Care Cancer. 2016;24(5):2047-57.

57. Jones DA, Rutherford OM. Human muscle strength training: the effects of three different regimens and the nature of the resultant changes. J Physiol. 1987;391:1-11.

58. Seo MW, Jung HC, Song JK, Kim HB. Effect of 8 weeks of pre-season training on body composition, physical fitness, anaerobic capacity, and isokinetic muscle strength in male and female collegiate taekwondo athletes. J Exerc Rehabil. 2015;11(2):101-7.



Exemplar case pre- and post 1 session of MT 18 years post surgery and radiation for HNC. Note red arrows on modified barium swallow study depicting residual bolus in pharynx directed anteriorly toward airway with neck dropped (top), and directed posteriorly toward esophagus with cervical extension normalized (bottom)

Cervical extension and aspiration improved in case example after manual therapy

MANTLE trial schema

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*Man*ual *T*herapy for Fibrosis-Related *L*ate *E*ffect Dysphagia in Head and Neck Cancer Survivors: The Pilot MANTLE trial

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*Man*ual *T*herapy for Fibrosis-Related *L*ate *E*ffect Dysphagia in Head and Neck Cancer Survivors: The Pilot MANTLE trial

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Abstract

Introduction: Late dysphagia that develops or persists years after head and neck cancer (HNC) is a disabling survivorship issue. Fibrosis is thought to stiffen connective tissues and compress peripheral nerve tracts, thereby contributing to diminished strength, flexibility, and in some cases denervation of swallowing muscles. Manual therapy (MT) is used in cancer survivors for pain and other indications, but it is unknown if increasing blood flow, flexibility, and cervical range of motion (CROM) in the head and neck may improve late dysphagia.

Methods and Analysis: MANTLE is an NCI-funded prospective single-arm pilot trial evaluating the feasibility, safety, and therapeutic potential of MT in patients with late dysphagia after radiation therapy (RT) for HNC. Disease-free survivors ≥2 years after curative-intent RT for HNC with at least moderate dysphagia and ≥2 CTCAE v4.0 fibrosis are eligible. The target sample size is 24 participants who begin the MANTLE program. MANTLE is delivered in 10 MT sessions over 6 weeks with an accompanying home exercise program (HEP). Patients then transition to a 6-week post-washout period during which they complete the HEP and then return for a final post-washout evaluation. Feasibility (primary endpoint) and safety will be examined. Serial assessments include cervical range of motion, modified barium swallow (MBS) studies, quantitative magnetic resonance imaging (MRI), electromyography (optional), and patient-reported outcomes (PROs) as secondary, tertiary, and exploratory endpoints.

Ethics and dissemination: The research protocol and informed consent document was approved by the Institutional Review Board at the University of Texas MD Anderson Cancer Center. Findings will be disseminated through peer-reviewed publication that will be made publicly available on PubMed Central upon acceptance for publication, in compliance with NIH public access policy.

Trial registration: NCT03612531 US National Library of Medicine ClinicalTrials.gov, Registered 26 July 2018; https://clinicaltrials.gov/ct2/show/NCT03612531

Keywords: Head and neck cancer, speech pathology, radiation oncology

Article Summary (including strengths and limitations of study)

- MANTLE is a pilot, single arm feasibility trial of manual therapy for late radiation-associated dysphagia.
- Feasibility is the primary endpoint, as measured by therapy completion rate.
- Secondary endpoints examine functional, physical, and patient-reported outcomes.
- Strengths and limitations of this study: strengths include examination of a novel therapy for an often refractory condition with comprehensive outcome measures.
- Strengths and limitations of this study: limitations include pilot nature of the trial without a control group or lead-in and lack of cervical posture measures.

Introduction

Dysphagia is a priority issue for head and neck cancer (HNC) survivors. While noteworthy as a driver of quality of life (QOL) (1), chronic, persistent, or late dysphagia is also a serious health problem in long-term survivorship. Even in modern practice, chronic aspiration (airway entry of liquids or food) is a life-threatening manifestation of dysphagia afflicting up to 30% of survivors treated with definitive radiotherapy (RT) or chemoradiotherapy (CRT) (2). HNC survivors treated with CRT are 2.7 times more likely to develop aspiration pneumonia than non-cancer controls, and aspiration pneumonia confers a 42% increased risk of mortality among survivors(3).

There is a rapidly growing pool of HNC survivors at risk for late dysphagia. Almost half of HNCs are now human papillomavirus (HPV)-driven oropharyngeal cancers, the incidence of which is expected to increase through at least 2030(4). The vast majority of this fast-growing, large subgroup of HNC survivors has been treated with curative RT at doses of 60 Gray (Gy) or more to the pharyngeal axis sufficient to induce chronic or late radiation-associated dysphagia (RAD)(5-7). Distinct from tobacco-related HNC, HPV-associated HNC is diagnosed younger (median: 54 years)(8) with excellent two- and five-year survival probability of 95%(9) and 79%(10), respectively. For these reasons, modern HNC survivors with HPV-attributable oropharyngeal cancer have the potential to live many active years (even decades) with toxicities of RT.

While many survivors initially recover functional swallowing after acute effects of radiation resolve, an important subset develops debilitating persistent or late RAD. It is estimated 30 to 40% treated with current treatment regimens that prescribe 66-72 Gy radiotherapy develop chronic RAD, and a highly burdened subset progress significantly over subsequent years(7, 11).

Late-radiation associated dysphagia (late-RAD)(12-14) is a particularly challenging, typically progressive form of refractory dysphagia that manifests years into survivorship (median latency: 8 years, cumulative incidence 8% at 7-years survival) after a period of reasonable functional recovery(15). As the era of HPV-associated oropharyngeal cancer survivorship matures, the number of late-RAD cases grows. Late-RAD is among the most difficult late-effect conditions to manage in HNC survivors, associated with a cascade of functional decline. Late lower cranial neuropathies (LCNP) are highly prevalent in survivors with late-RAD, 48 to 83% in the investigators' prior work, and increase the likelihood of lifelong feeding tube dependence due to refractory aspiration(5, 12, 16). Despite standard therapies such as swallowing exercises with or without cervical esophageal dilation, 66% of late-RAD cases in the investigators' published case series became chronically feeding tube dependent in late survivorship at a median age of 64 years (9 years after cancer cure)(14, 17). The QOL and health implications of becoming feeding tube dependent for life at this active age are staggering(14). Recent work highlights the gravity of this among cancer patients who ranked feeding tube dependence as one of the top six outcomes of their cancer that they perceive to be worse than death(18).

Therapy success in survivors with RAD is time dependent. Work from our group and others suggest particularly disappointing responses in survivors who begin swallowing therapy more than 2 years after completing curative RT (19, 20). For instance, in the investigators' published case series of late-RAD, oral diet scores were observed to significantly deteriorate over a median follow-up of 10 months in the late post-RT period, despite standard swallowing exercise therapies with or without esophageal dilation. Likewise, in secondary analysis an NCI-funded multi-site swallowing therapy trial among 117 survivors with chronic and late RAD, response to swallowing therapy was time dependent. QOL and diet scores improved most among those who started therapy <1 year after RT, with little improvement evident among those who started therapy more than 2 years post RT(21).

Clinical experience supports that survivors with late-RAD almost universally present with palpable, high-grade fibrosis. Fibrosis is thought to compress peripheral nerve tracts, thereby contributing to denervation of critical swallowing muscles(22). Largely considered irreversible and potentially progressive, these normal tissue changes disrupt the intricate sensorimotor processes required to simultaneously close the airway, open the esophagus, and push a bolus through the pharynx for successful swallowing. With mature fibrosis, late-RAD coexists with other problems including impaired cervical range of motion (CROM) and abnormal cervical posture(23). Broad manifestations of radiation injury have been referred to as radiation fibrosis syndrome (RFS) with progressive myelo-radiculo-plexo-neuro-myopathic changes resulting in a host of functional challenges including cervicalgia and head drop syndrome(24). A recent cross-sectional analysis of musculoskeletal impairment in 29 long-term HNC survivors reported 89% had abnormal cervical posture with significant deviation in cervical extension relative to normative ranges (z-score: 0.63, $p<0.001$). Postural and CROM impairments significantly correlated with patient-reported outcome (PRO) measures of shoulder and jaw function, but swallowing associations were not reported.(23) There are, however, emerging data to support a correlation between cervical biomechanics and swallowing. Better CROM and skin pliability (as a clinical marker of cervical fibrosis) associated significantly with swallowing safety per penetration-aspiration scale (PAS) scores from videofluoroscopic swallowing evaluations in survivors with chronic RAD, however, in this secondary analysis of clinical trial data, change in cervical ROM or pliability did not associate with change in swallowing function after swallowing therapy(25).

In long-term HNC survivors with late-RAD, circumferential cervical muscles can demonstrate reduced capacity for contraction and appropriate ROM due to RFS, which can result in a head drop position. Anterior and lateral cervical muscles are typically shortened and firm to touch due to progressive fibrotic tissue sclerosis. As a result of fibrotic cervical flexors, cervical extensors are overstretched and can

become weak and atrophied over time (24, 26).

Cervical posture is empirically a critical background factor facilitating safe swallowing. That is, when swallowing in a head drop position, the path of least resistance for any residual bolus in the pharynx is down into the airway. This might contribute to gravity-assisted aspiration (GASP), whereby post-swallow residue enters the airway more easily when the resting head posture is dropped. Indeed, GASP is a regular clinical observation in the investigators' practice. In contrast, with more normal upright cervical posture, residual bolus may dwell posteriorly in the pharynx waiting to be safely cleared into the esophagus on a subsequent swallow as shown as proof of concept in exemplar case in Figure 1. Adjusting the swallow environment by improving cervical posture, as shown in *Figure 1*, is often overlooked as a therapeutic target for late-RAD. For these reasons and clinically recognizing the high prevalence of forward head drop co-occurring with late-RAD, neutralizing cervical posture by improving upper and lower cervical extension is the initial goal in the proposed MT program in this trial. Integration of this goal focused on priming or optimizing the swallow environment prior to mobilizing intrinsic swallowing musculature represents a novel element of our proposed MT swallow therapy program, called MANTLE (*Man*ual *T*herapy for Fibrosis-Related *L*ate *E*ffect Dysphagia).

[INSERT FIGURE 1, **Cervical extension and aspiration improved in case example after manual therapy**]

Preliminary unpublished clinical data from the investigators detect an average 11-degree improvement in a fibrosis-related endpoint of cervical extension after a single session of MT ($p<0.001$), and notable qualitative remarks about functional gains after MT in clinical practice (e.g., "that's the first time I've felt myself swallow in years"). These early observations helped motivate the development of the MANTLE therapy program and this trial. Acknowledging the typically progressive and refractory nature of late

fibrotic effects, it is critical to understand the durability of improved CROM and whether this translates to better swallowing function.

Objectives:

Therefore, the pilot MANTLE trial proposes to study a novel, adjunctive MT program in patients with fibrosis-related late-RAD with the following objectives:

1) To determine the feasibility and safety of MANTLE as a program of treatment for fibrosis-related dysphagia in HNC survivors
2) To estimate effect size, dose-response (number of treatment sessions to normalized cervical range of motion), and durability of MANTLE for improving cervical range of motion in HNC survivors with fibrosis-related late dysphagia
3) To examine functional outcomes after MANTLE in HNC survivors with fibrosis-related late effects and their association with change in dysphagia grade, cervical extension, and other cofactors.

Methods

Study Design

MANTLE is a single-institution, prospective single-arm pilot trial of MT in patients with late dysphagia after head and neck RT. Clinical schedules in the Section of Speech Pathology and Audiology at the University of Texas MD Anderson Cancer Center (Houston, Texas, USA) are screened to identify eligible patients referred for post-radiation swallow assessment. The investigators will enroll consecutive patients who meet eligibility and give written informed consent. Target enrollment is 24 participants who start the MANTLE program, with up to 32 participants enrolled during screening. The first

participant enrolled August 6, 2018; trial completion is projected to occur in April 2021. MT is delivered according to a standard protocol for 6 weeks followed by a 6 week wash-out period. Feasibility and safety will be examined. Serial assessments also include CROM, imaging, and PROs. The trial schema is depicted in *Figure 2*.

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312). The principles of informed consent in the current edition of the Declaration of Helsinki will be implemented before any protocol-specific procedures or interactions are carried out. Informed consent will be obtained, in accordance with 21 CFR 50.25. The written consent document will embody the elements of informed consent, as described in the Declaration of Helsinki and will also comply with local regulations of the Institutional Review Board (IRB) of MDACC.

Protocol amendments impacting eligibility, outcome, and/or analysis will submitted for IRB approval, communicated through the institutional electronic protocol system to all relevant investigators, and updated in trial registration.

[INSERT FIGURE 2, **MANTLE trial schema.**]

Inclusion criteria:

1) Age ≥ 18 years

2) Late DIGEST grade ≥2 dysphagia on Modified Barium Swallow (MBS) ≥2 years after curative-intent radiotherapy for head and neck cancer

3) Grade ≥2 CTCAE v4.0 fibrosis

4) Willing and able to return for 10 sessions that taper in frequency over 6 weeks of therapy

Exclusion criteria:

1) Active recurrent or second primary head and neck, central nervous system, or thoracic cancer at time of enrollment

2) Active osteoradionecrosis or other non-healing wounds (e.g., fistula, ulcer, soft tissue necrosis) in MT regions of interest at time of enrollment

3) History of subtotal or total glossectomy or total laryngectomy

4) Functionally limiting cardiac, pulmonary, or neuromuscular disease

5) Current tracheostomy

Treatment

MT is commonly used in cancer survivors after RT and in the cervical region for pain and other indications.(27-29) The proposed MT program was developed by dysphagia-specialized speech pathologists (SLP) dually licensed in massage therapy (HM) and certified in lymphedema therapy (CLT) (HM, CPB, KS) and summarized using the TIDieR template(30).

The MANTLE program added hierarchical goals for cervical biomechanics to the goals of a published swallowing-focused MT program developed jointly by speech pathologists and a head and neck anatomist.(27) MANTLE conceptualizes and sequences the mobilization targets from superficial to deep as detailed in Table 1. First, targeting cervical extension to address the common "head-drop" post-RT fibrotic cervical posture to a more natural, upright swallowing-optimized state (conjectured by the authors to be favorable for swallowing safety in the setting of pharyngeal residue) as shown in *Figure 1*. Lateral flexion and cervical rotation are subsequently targeted to prime the tissues to access deeper

swallowing regions-of-interest (ROIs) including the tongue, pharynx, and larynx as summarized in *Table 1*. Building on Level I evidence from patients with non-cancer cervical pathology (i.e., benign neck pain), the proposed MANTLE program combines myofascial release (MFR) and massage with range of motion (ROM) exercise to iteratively mobilize swallowing-related ROIs with a HEP for stretch and to initiate strengthening where stimulable .(31-33)

Table 1.Manual therapy program for late effect dysphagia (MANTLE Program)

Table 1. Manual Therapy Program for Late Effect Dysphagia (MANTLE Program)

Functional Goal	**Region Of Interest (ROI)**	**MT Techniques**	**Home Exercise Program (HEP) (3x/day for 12 weeks)**	
			Exercises	
			Stretch	**Strengthening**
Improve cervical extension[a]	Upper/mid back and circumferential neck	1. Myofascial release (MFR): separating soft tissue layers, reduce tension between structures 2. Massage: increase vascularity and mobility by manipulation of muscular attachments and muscle bellies 3. Passive range of motion (PROM): clinician-directed joint and soft tissue mobilization without active muscle contraction (after tissue softening) 4. Active Assist Range of Motion (AAROM)/Active Range of Motion (AROM): clinician supported soft tissue and joint mobilization with patient assisted muscle contraction transitioning to patient-independent muscle contraction 5. Strengthen: cervical and laryngeal ROM against resistance 6. Post strengthening repeat PROM/AROM	3 exercises	2 exercises
Improve lateral flexion and cervical rotation[b]	Bilateral neck		6 exercises	2 exercises
Improve movement in muscles involved in deglutition	Anterior neck/oral cavity[3]: prioritized in order of severity of patient-specific deficits: oral cavity, oropharynx, larynx, pharynx			

[a]In addition to MT, HEP targets upper and lower cervical spine stretch and strengthening

[b]In addition to MT, HEP targets cervical retraction, scapular retraction, suboccipital stretch, and upper chest/pectoralis stretch

In the MANTLE trial, an SLP (HM) who is a licensed massage and certified lymphedema therapist (LMP and CLT) provided training to SLPs with CLT designations to perform the late-RAD MT program. Patients are seen for 10 sessions over 6 weeks with titrating intensity (Week 1: 3 sessions, Weeks 2-3: 2 sessions weekly, Weeks 4-6: 1 session weekly). The 10 sessions performed by the SLP in clinic include soft tissue mobilization and instruction on a cervical stretching/strengthening home exercise program (HEP). After the 10 sessions (over 6 weeks), the patient then transitions to exclusive home practice of the HEP using a standardized clinical handout but without clinician assistance for a 6 week wash-out period.

Subject registration

All adult men and women scheduled for routine clinical MBS at MDACC are considered for participation in this study without regard to race, gender, or socioeconomic status. Central registration is used for tracking study accrual and eligibility. Registration procedures include the following:

- Interested patients are given an explanation of the study to include potential risks and benefits by the principal investigator, co-investigator, or other designated medical personnel.
- Investigator or other trained, designated personnel obtain signed informed consent before any study-specific procedures are performed.
- The subject is seen and evaluated by the principal investigator, co-investigator, or designee prior to enrollment. Screening assessments are performed.
- The principal investigator, co-investigator or designee evaluate eligibility based on inclusion/exclusion criteria stated in this protocol.

Screening evaluations

Patients are evaluated by the speech pathologist and referring physician or advanced practice provider in the interdisciplinary head and neck cancer program. Medical history, oral motor examination, and oropharyngeal swallow function are recorded. The electronic medical record is reviewed for relevant history pertaining to eligibility criteria.

Study evaluations

Table 2: Summary of Treatment Evaluations

Table 2. Schedule of Evaluation Procedures for MANTLE Trial

Assessment	Method	Domain	Endpoints	Scale	Pre-MT	During-MT	Post-MT	Post-washout
CROM	Goniometer Assessment (clinic)	Cervical range of motion	Cervical extension, lateral flexion, rotation	Continuous	X	X[a]	X	X
MBS	Fluoroscopy	Dysphagia severity grade	DIGEST[26]	Ordinal: 0 (best), 4 (worst)	X		X	
		Swallow kinematics	CASM[27]	Continuous	X		X	
Lymphedema/fibrosis rating	Clinician grading (physical exam)	Severity of lymphedema/fibrosis	CTCAE fibrosis, HN-LEF	Ordinal	X	X[d]	X	X
MIO	Therabite ruler (clinic)	Mouth opening	mm interincisal opening	Continuous	X		X	X
LROM	Therabite ruler (clinic)	Lingual range of motion	Tongue protrusion,	Continuous	X		X	X

			lateralization, elevation					
MDADI[28]	PRO (20-item)	Swallowing-related QOL	Composite, Global, & subscale scores	Continuous: 20 (worst), 100 (best)	X		X	X
MDASI-HN[29]	PRO (31-item)[b]	Symptom burden	Symptom severity, symptom interference	Continuous: 0 (best), 10 (worst)	X	X[c]	X	X
LSIDS-H&N	PRO (64-item)	Lymphedema/fibrosis specific symptoms	Symptom severity associated with lymphedema and fibrosis		X		X	X
PSS-HN[31]	Interview (3-item)	Functional status	Diet, Eating, Speech subscales	Ordinal: 0 (worst), 100 (best)	X	X[d]	X	X
MRI	Imaging	Soft tissue kinetics	T1 signal intensity	Continuous	X		X	X
(Optional)EMG (tongue) EMG+NCS (trap)	Electromyography	Innervation	4-point denervation potentials grade	Ordinal	X		X	

Abbreviations: MBS, modified barium swallow, EMG, electromyography, DIGEST, Dynamic Imaging Grade of Swallowing Toxicity, CASM, Computational Analysis of Swallowing Mechanics, CROM, Cervical Range of Motion, MDADI, MD Anderson Dysphagia Inventory, MDASI, MD Anderson Symptom Inventory, PSS-HN, Performance Status Scale Head and Neck Cancer. [a]CROM collected at each MT visit. [b]28-item MDASI-HN with 3 special interest items. [c]MDASI collected bi-weekly during MT. [d]collected at mid-point of MT.

Outcomes are assessed according to the schedule outlined in Table 2. To facilitate retention, all patient-completed questionnaires may be completed by paper or electronic means (i.e., via REDCap), and data collection procedures are aligned with clinical visits (34, 35). Outcome data will be collected from all participants; regardless of deviations from the therapy protocol. Details of data collection procedures follow.

Cervical Range of Motion: Patients were in an upright, seated position to reflect their natural cervical swallowing posture as the start position when CROM was measured. Clinic chairs were placed in a reproducible, fully upright standard position for every measurement. A goniometer measures CROM (degrees) to assess active cervical spine ROM. Five core CROM measures include cervical extension, sagittal plane at rest, lateral flexion (left/right), coronal plane at rest, and lateral rotation (left/right). The primary CROM measure of interest is cervical extension. Cervical extension measures are highly reliable (ICC=.90). Average extension measures in healthy adults aged 60 to 69 range from 57 degrees in males (SD: 10.5) to 65 degrees in females (SD: 13.3). Cervical extension measures decrease by approximately 5 degrees for each decade of life.(36) Lingual and jaw range of motion are also measured per published methods(37, 38).

Lymphedema/Fibrosis Grading: Clinician-grading of lymphedema/fibrosis is conducted according to the published Head and Neck-Lymphedema Fibrosis (HN-LEF)(39, 40), Common Terminology Criteria for Adverse Events (CTCAE) (41), and MD Anderson adaptation of the Foeldi lymphedema rating(42), per physical examination of the patient. Clinical grading is a brief assessment that can be completed in <15 minutes using all 3 complementary sets of grading methods.

Modified Barium Swallow (MBS) Studies: Digital videos from clinical MBS will be scored by a trained speech pathologist blinded to the patient, study, and follow-up interval using methods including the *Dynamic Imaging Grade for Swallowing Toxicity (DIGEST)*(43) and *Computational Analysis of Swallowing Mechanics (CASM)* (44, 45).

MRI: Multiparametric, serial MRI are acquired with a 1.5 T to 3.0T GE Discovery 750 MRI scanner (GE Healthcare, Wisconsin, USA) using laterally placed 6-element flex coils centered on the base of tongue region. Feasibility and optimization of this MRI paradigm have been described by the investigative team(46), with particular emphasis on immobilization using dedicated H&N coils and a flat insert table with an indexed base plate. Multiparametric imaging will be performed longitudinally (pre-, post-MT, and post-washout). *Table 3* summarizes candidate acquisitions for this study. Our primary candidate imaging biomarker of MANTLE-related soft-tissue change is normalized $\Delta T1_{normalized}$ signal intensity, as we have previously published this parameter's relevance as a dose-dependent soft tissue anatomic imaging biomarker of fibrosis.(47) ROI delineation will be done using the investigators' published method and will include, among our published library of 72 normal structures, the following swallowing-relevant OARs: mylohyoid, geniohyoid, and constrictors.

Table 3. Candidate quantitative imaging parameters selected for MANTLE trial

Acquisition type	Imaging parameter/biomarkers	Tissue injury correlate
T1-pre/post contrast	T1 intensity, T1/R1, T1-rho	Radiation associated fibrosis
T2/T2* Map	T2 contrast, T2*	Radiation associated edema
DTI	Muscle fiber tractography and fractional anisotropy	Muscle/nerve fiber/tumor microstructure, directionality tracts
DCE	Perfusion parameters (K_{trans}, K_{ep})	Tissue perfusion/ Microvessel permeability

Optional Intramuscular electromyography (EMG) and nerve conduction study (NCS) assess insertional activity in the tongue (XII nerve) as a marker of denervation(48). EMG recordings are conducted by a neurologist trained in clinical neurophysiology and denervation potentials graded per:

0 None

1 Persistent, single trains of potentials in at least 2 areas

2 Moderate number of potentials in 3 or more areas

3 Many potentials in all areas

4 Full interference pattern of potentials

EMG and nerve conduction studies will also be taken in the trapezius muscle (XI nerve), as the region is easily accessible for non-invasive EMG with NCS and represents a muscle within the irradiated field with lower cranial nerve innervation. Both quantitative and qualitative EMG will be assessed. NCS will be assessed quantitatively, with waveforms generated from which we acquire amplitude, latency, and conduction velocity(49). Optional EMG will not be conducted if platelets <50,000.

M.D. Anderson Dysphagia Inventory (MDADI) is a written questionnaire to evaluate dysphagia-specific QOL in H&N cancer patients.(50) The 20-item MDADI questionnaire quantifies an individual's global, physical, emotional, and functional perceptions of his or her swallowing ability. In an internal validation in 100 patients with HNC, concurrent validity was found to be moderate by comparison with the Performance Status Scale for Head and Neck Cancer Patients (Spearman correlation, 0.47-0.61). Correlation with the physical functional subscale (Spearman correlation, 0.40) and emotional subscale of SF-36 (36-Item Short Form Survey) (Spearman correlation, 0.36) demonstrated convergent and divergent validity, respectively, of the MDADI. Test-retest reliability (physical, 0.86; emotional, 0.88; functional, 0.88) and internal consistency reliability (overall Cronbach's alpha, 0.96) were sound.

M.D. Anderson Symptom Inventory for Head and Neck Cancer (MDASI-HN) is a patient-reported outcome questionnaire designed to measure severity or burden of systemic and head and neck (HN) specific symptoms and their interference with or effect on patients' daily functioning. This 28-item multi-symptom inventory includes 13 core items ("systemic symptoms": pain, fatigue, sleep, *etc*.), nine HN-specific items ("local symptoms": dry mouth, mucus, shortness of breath, taste, *etc*.), and six interference items (activity, work, relations, *etc*.). The core MDASI items have been validated for use in cancer patient populations regardless of the specific diagnosis or type of therapy and thus can be used to compare overall burden of disease between different types of cancer(51). The HN-specific items were validated internally with regard to construct and concurrent validity in HN cancer patients.(52, 53) Internal consistency reliability is high in the core, HN-specific, and interference items (Cronbach's alphas of 0.72-0.92). Validated linguistic translations (Chinese, French, German, Greek, Italian, Spanish, and Turkish) of the MDASI-HN may be administered to non-English speaking participants.

Lymphedema Symptom Intensity and Distress Survey – Head and Neck (LSIDS-H&N) (54) is a 64-item instrument designed to assess lymphedema symptoms in head and neck cancer patients. Survey items were selected to address six domains (head and neck-specific functioning, systemic symptoms, psychosocial issues, altered sensation symptoms, neck-shoulder musculoskeletal/skin symptoms, and miscellaneous symptoms) identified by an expert panel. Preliminary testing of LSIDS-H&N demonstrated both feasibility and readability.

Performance Status Scale for Head and Neck Cancer Patients (PSS-HN) is a clinician-rated instrument rated by a semi-structured interview consisting of three questions: normalcy of diet, public eating, and understandability of speech.(55) The PSS-HN has been psychometrically validated and recommended by

the National Comprehensive Cancer Network for measurement of swallowing and speech performance in patients with HNC.

Adherence Logs: standard clinical adherence logs are given to track adherence to the HEP performed throughout the entire MANTLE trial. Patients are asked to complete paper logs with check boxes to count completion of each HEP component on a daily basis. Logs are returned and reviewed at live MT sessions in attempt to validate responses or clarify ambiguity.

Follow-up intervals

Post-MT and post-wash out evaluations (specified in *Table 2*) will be conducted immediately after the 6 week training period with an allowable window of 2 weeks.

Safety and Feasibility

Safety and Feasibility of MT: Feasibility of MANTLE will be assessed by estimating program completion rates, sources of attrition, and adherence (i.e., clinical attendance, and adherence to home exercise program). Process evaluation checklists will be completed after each session to examine fidelity to the MANTLE treatment program, and patients will be asked to log their home practice using a study-specific adherence form. AEs are also assessed and recorded. Cervical MT is a safe therapy in many populations. Risk of serious adverse events is estimated to be 6 in 10 million[42,43]. Serious AEs relate to cardiovascular risk and are more common when providing a thrust manipulation technique that is employed in this protocol. Mild AEs, while still rare (estimated 1% to 2% of patients), are more common and can include local discomfort, headache, lightheadedness, falls, and fatigue. SAEs were not encountered in our preliminary retrospective review of patients receiving MT.

Data Management

The data is maintained in an institutionally approved electronic data capture system with an integrated codebook. Data management adheres to institutional guidelines and policies for maintaining confidentiality to protect PHI from public viewing by safeguarding storage and disposal of documents containing PHI and computer workstations and databases that access PHI. Data validation will include missing data reports range checks for data values, and logic checks for plausible relationships. The PI, statistician, and data manager will have access to the final trial dataset.

Monitoring

The trial will be monitored by the Office of Protocol Research at the MD Anderson Cancer Center subject to independent audit by MD Anderson's Internal Audit Department in accordance with the Texas Internal Audit Act and the University of Texas System Board of Regents and the Internal Audity Activity Charter. Adverse events will be recorded by the study team. The IRB will be notified of any related grade three or greater adverse events and provided data to permit a safety review of the study treatment. The IRB may request additional meetings or safety reports as deemed necessary.

Patient and Public Involvement

The investigators did not formally engage a patient or public stakeholder team in trial development or recruitment strategies. Study data will be disseminated via peer-reviewed publication made publicly available through PubMed Central, and shared with participants through this medium.

Statistical Considerations

Statistical analysis and sample size justification

The primary objective of MANTLE is to determine feasibility based on the program completion rate. Investigators planned to enroll 24 patients and estimated an attrition rate of 20% to achieve a final sample size of 19 participants. Program completion rate is estimated from the participants who start the MANTLE program after screening procedures excluding screen failures and those who withdrawal before therapy starts. Note, the final protocol was amended to account for unanticipated prolonged treatment interruption or delay due to the institutional suspension of live clinical services and clinical research in response to the COVID-19 pandemic. For that reason, investigators increased maximum accrual to 32 participants and will cease enrollment after 24 participants start treatment without any COVID-19-related interruptions. The primary analysis will include the 24 participants who started MT and who did not experience the COVID-19-related interruption of study participation. Any study withdrawals or interruptions in study participation for reasons other than COVID interruptions will be part of this feasibility analysis. In addition, as a sensitivity analysis, all available data, including any data collected from the participants interrupted by the COVID-19 research suspension, will be analyzed in a stratified manner.

For analysis of the **primary objective** to determine the feasibility and safety of the MANTLE program, a completion rate of 75% will be considered the benchmark of feasibility. Completion rate will be defined by completion of the 6-week clinical MANTLE program without withdrawing and attending a minimum of 2 sessions plus the post-treatment assessment. Session attendance will be monitored separately to assess adherence and fidelity. We will summarize fidelity and adherence to the standard MANTLE protocol using quantitative and qualitative methods. Adverse events will be tabulated.

For analysis of the **secondary objective**, we chose cervical extension as the primary CROM measure of interest and as the direct treatment target due to our preliminary data suggesting significant

improvements after MT in patients with fibrosis-related late effects (1 session mean Δ: 11%; p<0.001) as well as our conjectured relevance of CROM to swallowing safety. Cervical extension CROM measures are also highly reproducible (ICC=.90) and are taken each standard MT session as part of routine clinical appointments to direct therapy. For this analysis, we will use simple descriptive statistics to first summarize baseline, post-MT1, and post-MT2 (after the six week wash-out period of exclusive home therapy) CROM measures for each anatomic plane. We will compare baseline to post-MT1 CROM measures using a one-sided paired *t*-test. With 24 patients and conservatively estimating an attrition rate of 20% based on our prior experience, the final sample size of 19 patients will provide 80% power to detect an effect size of d = 0.593, which corresponds to a $\Delta CROM_{baseline\text{-}post\text{-}MT}$ of 10.68 degrees (assuming the SD = 18 per our pilot data in HNC). To determine whether cervical extension normalizes within 10 sessions of clinician-administered MT, post-MT CROM raw scores will be converted to *z*-scores based on age- and sex-specific norms to estimate the proportion of participants with post-MT cervical extension scores that fall within 2 SDs of normative values. To examine the durability of response, we will normalize post-MT2 CROM measures to determine the percentage of participants who maintain or improve (*z*-score ≥ post-MT score – 2 SDs) post-wash-out. For the expected proportion of 80% who maintain or improve CROM, the 95% CI will extend 15% from the observed proportion. The number of MT sessions before normalization of CROM will be tabulated. In exploratory analysis, we will plot CROM measures across time and will consider using linear mixed models to account for repeated outcome measures with adjustment for clinicodemographic covariates.

For the analysis of our **tertiary objective** , we will conduct a stepwise multivariable analysis to explore covariant swallow morphometrics associated with change in dysphagia grade and cervical extension after MT using the published CASM method. Swallow coordinates from all frames of pre- and post-MT MBS studies and covariates (time, bolus type, $DIGEST_{pre}$, ΔDIGEST, age, sex, tumor site, surgery, ΔCROM,

$CROM_{post}$) will be specified in MorphoJ, an integrated morphometric software program, for stepwise analysis: 1) canonical variate analysis (CVA) to identify and rank covariates associated with swallow morphometric changes in patients improved/stable dysphagia (ΔDIGEST), 2) *post hoc* discriminant function analysis will be conducted next to visualize treatment-specific eigenvectors of swallowing muscle motion differences by covariates of interest from CVA (e.g., pre-post MT), and 3) morphometric regression to estimate post-RT eigenvectors associated with change in swallow severity per DIGEST and pre-post MT conditions. For CVA of k variables (12 coordinates motion) in G groups (DIGEST, MT), the total sample size must be larger than [(2k-4) + (G-1)],(56) requiring 21 patients.

Exploratory analyses

Secondary endpoints of MDADI, MDASI-HN, lingual and jaw ROM, lymphedema/fibrosis staging, lingual and jaw ROM, PSS-HN, and MRI parameters will be assessed according to their distributions (continuous: paired *t*-test or non-parametric Wilcoxon signed-rank test, ordinal: rank-invariant). Effect sizes, such as Cohen's *d*, with 95% confidence intervals will be calculated for each endpoint and interpreted. Exploratory analyses and correlative questions will be considered for hypothesis-generating purposes only.

Discussion

The highly focused long-term objective of the MANTLE trial is to improve swallowing function in some of the worst dysphagia presentations in HNC survivorship - that is, those with severe late-RAD we have shown to be often treatment refractory. The focus on late-RAD represents a departure from most therapy trials for RAD that suffer from population heterogeneity as a consequence of enrolling both early and late-RAD patients jointly, where the pathophysiology and trajectory of dysphagia almost certainly differs. By explicitly studying manual therapy (MT) effects solely in late (>2 years) post-radiated

survivors, this line of research offers specificity of target in examining the therapeutic potential of this commonly used, but rarely studied treatment modality. The endpoints are thoughtfully constructed to estimate effect sizes of various avenues of clinical benefit including mobility, functional change, QOL, and physical swallowing change. Any functional benefit for those with late-RAD could be meaningful as this represents a high burden, growing survivor population with disappointingly limited therapy options in current practice.

MANTLE was designed as a pilot study because we are trialing a novel therapy protocol intended for expansion to larger, confirmatory trials of efficacy or effectiveness in our program of research on radiation associated dysphagia. With the results of this pilot investigation, we expect to demonstrate that the novel MANTLE program is feasible and safe to examine in a larger program of research. Furthermore, we expect to estimate effect sizes achieved in secondary endpoints that will be necessary for power calculations in future trials of efficacy or effectiveness. The diverse outcomes panel was selected specifically to understand which data collection procedures (i.e., functional measures, questionnaires, imaging) may be sensitive to possible changes with MT and merit inclusion in future, larger studies.

Strengths and Limitations

The ideal dosing of MT for this indication is unknown. The dosing schedule is based on prior clinical experience as well as the MT evidence base. Published cervical MT programs vary in intensity from 4+ sessions over 2-7 weeks in populations with neck/shoulder dysfunction (31-33) to 12 sessions over 4 weeks in non-HNC populations with fibrosis-related late effects in other body regions(57). The MANTLE program is designed with 10 sessions over 6 weeks of clinician-directed MT simultaneous with the implementation of cervical HEP. Relative to other cervical MT programs in the literature, this represents

a fairly intense manual therapy schedule to match the known pathophysiology and duration of injury of the target population with late-RAD. The MANTLE therapy schedule is intentionally titrated using a scaffold approach in therapy schedule to offer more frequent upfront soft tissue manipulation while transitioning the patient to the independence of a HEP for maintenance. The investigators acknowledge that the therapy schedule developed for the MANTLE protocol may require further refinement as the results mature; however, 10 sessions over 6 weeks were judged by the investigators to represent a time interval during which therapy response should be detectable. Future directions of this trial might include adjusting the dosing of MT and HEP to achieve similar results.

The aims and outcome measures are thoughtfully constructed to provide pilot data regarding the feasibility/safety (Aim 1), dose and durability (Aim 2), and functional translation (Aim 3) of MANTLE as an adjunctive therapeutic modality for late-RAD. Upon completion of Aim 1, we expect to show a therapy completion rate of 75% as a marker of feasibility. For Aim 2, we expect to demonstrate that cervical range of motion can improve within 10 sessions of MANTLE in at least 80% of HNC survivors with late-RAD. Aim 3 will provide effect sizes estimates of swallowing function changes after MANTLE. In this pilot trial, we expect to observe attrition <25%, adherence >60%, no therapy-related grade ≥3 adverse events, and sufficient power to estimate Cohen's *d* effect size ≥0.50 for the primary secondary endpoint of interest CROM.

Cervical measurements are challenging to obtain in the Late-RAD population when severe cervical postural abnormalities are present. In order to achieve a more neutral or upright head position, cervical extension is required in the upper cervical, lower cervical, and upper thoracic spine. Due to the severity of head drop in the pilot data, we were unable to measure upper cervical movement in isolation to capture degree of head drop or forward head posture. Measurements were out of range and could not

be obtained with a traditional or Q-ROM computer-generated goniometer due to the degree of lower cervical flexion. Valid and reliable tools to measure forward head posture (FHP) in other populations such as craniovertebral angle measures merit exploration in future research in HNC survivors (58). The omission such postural measures and upper cervical extension/dorsal glide as an evaluation measurement is a limitation; it was recognized and accounted for by implementing dedicated stretching and strengthening exercises to target upper cervical spinal movements to improve FHP, if present.

Exploring functional endpoints of the therapeutic trial, we expect to also evaluate mechanism of functional change in swallowing (per DIGEST), muscle motion parameters (per CASM) associated with functional swallowing improvements (per DIGEST) using radiographic MBS studies. The post-MANTLE MBS is conducted immediately following 6 weeks of MT. Even healthy individuals may require 8 to 12 weeks to see functional improvement with stretching and strengthening (59, 60). As such, the post-MANTLE MBS after just 6 weeks of therapy may be earlier than maximal benefit is achieved. Nonetheless, at 6 weeks, any change detected on MBS could be more directly attributed to the MANTLE therapy prior to the wash-out period and may reflect stimulability in the tissue.

The final data collection is 12 weeks after starting MANTLE. While long-term follow-up of dysphagia progression after MANTLE is not feasible in the timeframe of this pilot trial, any positive changes in CROM, patient-reported outcomes, soft tissue (per MRI), or radiographic or perceived swallowing function is likely meaningful because late-RAD is currently considered a treatment refractory toxicity syndrome.

Future Directions

If proven safe and feasible, future studies will need to address/investigate efficacy, effectiveness, sustainability of therapeutic gains, ideal schedules, frequency and combination of MT techniques, and

best matching of mobility focused MT with direct functional therapies. For instance, might MANTLE prime the patient with late-RAD to achieve better functional gains during a bolus driven paradigm like the McNeil Dysphagia Therapy Program (61)? Future considerations should also include remote practice as it is rapidly expanding in the era of the COVID pandemic. With this in mind, it will become even more important to understand the outcome of the cervical HEP alone (without soft tissue manipulation as it is used in MANTLE) among patients with RAD who may not be able to access in-person clinical services for soft tissue manipulation. We believe that the proposed MANTLE trial could provide pilot data that might justify practice-changing clinical trials for the growing number of HNC survivors who have no proven options to manage late-RAD

Declarations

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Author contributions

All listed co-authors read and approved the manuscript, and performed the following:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of trial concept and data;

2. Drafting the work or revising it critically for important intellectual content;

3. Final approval of the version to be published;

4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Specific individual contributions in addition to all criteria above are listed as follows:

KH- Principal Investigator; Corresponding/primary author; conceived, coordinated, and directed all study activities, responsible for data collection, project integrity, manuscript content and editorial oversight and correspondence; direct oversight of study personnel.

HM- Manual therapy lead; developed MANTLE therapy program; trained MANTLE clinicians

SB – Operationalization and refinement of data collection procedure, primary trial manager.

KH, HM, CPB, KS, KW, SYL, CDF - Direct patient care provision, direct outcomes assessment and development and refinement of clinical data collection procedures.

CW- Developed statistical analysis plan.

CDF, JW - Responsible for programmatic and infrastructure oversight for MRI analysis and DICOM segmentation; direct and final oversight of MRI data collection; direct oversight of trainee personnel.

SYL - Direct and final oversight of surgical data collection.

KW – Direct and final oversight of EMG data collection.

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Ethics and Consent to Participate

The research protocol and informed consent document was approved by the Institutional Review Board at the University of Texas MD Anderson Cancer Center. The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312). The MANTLE research protocol was activated July 12, 2018 after IRB approval (2018-0052). The trial was prospectively registered with ClinicalTrials.gov on July 26, 2018 and first posted on ClinicalTrials.gov August 2, 2018 prior to enrollment of the first study participant on Aug 6, 2018 with projected study completion date in April, 2021.

Consent for publication: all authors provide consent for publication.

Competing interests: the authors declare no competing interests:

Availability of data and materials: not applicable

Figure Legends

Figure 1. Cervical extension and aspiration improved in case example after manual therapy.

Exemplar case before (top) and after (bottom) single session of MT 18 years post-treatment, surgery and radiotherapy for head and neck cancer. Note red arrows on modified barium swallow study depicting residual bolus in pharynx directed anteriorly toward airway with cervical posture in resting forward head drop (top), and directed posteriorly toward esophagus with cervical extension improved (bottom). While neither swallowing function or nor cervical biomechanics is normalized or ideal, functional gains were observed.

Figure 2. MANTLE trial schema.

Abbreviations: HNC, head and neck cancer; RT, radiotherapy; RAD, radiation associated dysphagia; MT, manual therapy; CROM, cervical range of motion; MBS, modified barium swallow; MRI, magnetic resonance imaging; PROs, patient reported outcomes

References (Vancouver)

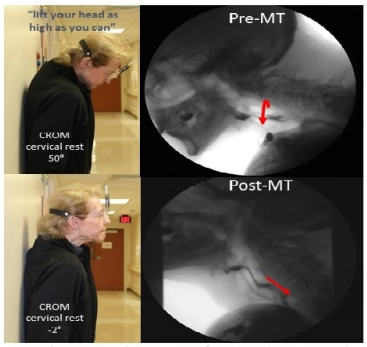
1. Hunter KU. Toxicities affecting quality of life after chemo-IMRT of oropharyngeal cancer: prospective study of patient-reported, observer-rated, and objective outcomes. Int J Radiat Oncol Biol Phys. 2013;85.
2. Eisbruch A, Kim HM, Feng FY, Lyden TH, Haxer MJ, Feng M, et al. Chemo-IMRT of oropharyngeal cancer aiming to reduce dysphagia: swallowing organs late complication probabilities and dosimetric correlates. Int J Radiat Oncol Biol Phys. 2011;81(3):e93-9.
3. Xu B, Boero IJ, Hwang L, Le QT, Moiseenko V, Sanghvi PR, et al. Aspiration pneumonia after concurrent chemoradiotherapy for head and neck cancer. Cancer. 2015;121(8):1303-11.
4. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol. 2011;29(32):4294-301.
5. Awan MJ. Late radiation-associated dysphagia (late-RAD) with lower cranial neuropathy after oropharyngeal radiotherapy: a preliminary dosimetric comparison. Oral Oncol. 2014;50.
6. M. D. Anderson Head Neck Cancer Symptom Working Group. Beyond mean pharyngeal constrictor dose for beam path toxicity in non-target swallowing muscles: Dose-volume correlates of chronic radiation-associated dysphagia (RAD) after oropharyngeal intensity modulated radiotherapy. Radiother Oncol. 2016;118(2):304-14.
7. Kamal M, Mohamed ASR, Volpe S, Zaveri J, Barrow MP, Gunn GB, et al. Radiotherapy dose-volume parameters predict videofluoroscopy-detected dysphagia per DIGEST after IMRT for oropharyngeal cancer: Results of a prospective registry. Radiother Oncol. 2018;128(3):442-51.
8. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tan PF, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. The New England journal of medicine. 2010;363(1):24-35.
9. Fakhry C, Westra WH, Li S, Cmelak A, Ridge JA, Pinto H, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst. 2008;100(4):261-9.
10. Weinberger PM, Yu Z, Haffty BG, Kowalski D, Harigopal M, Brandsma J, et al. Molecular classification identifies a subset of human papillomavirus--associated oropharyngeal cancers with favorable prognosis. J Clin Oncol. 2006;24(5):736-47.
11. Caudell JJ, Schaner PE, Meredith RF, Locher JL, Nabell LM, Carroll WR, et al. Factors associated with long-term dysphagia after definitive radiotherapy for locally advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2009;73(2):410-5.
12. Hutcheson KA, Lewin JS, Barringer DA, Lisec A, Gunn GB, Moore MW, et al. Late dysphagia after radiotherapy-based treatment of head and neck cancer. Cancer. 2012;118(23):5793-9.
13. Awan MJ, Mohamed AS, Lewin JS, Baron CA, Gunn GB, Rosenthal DI, et al. Late radiation-associated dysphagia (late-RAD) with lower cranial neuropathy after oropharyngeal radiotherapy: a preliminary dosimetric comparison. Oral Oncol. 2014;50(8):746-52.

14. Hutcheson KA. Late radiation-associated dysphagia (RAD) in head and neck cancer survivors. Perspectives on Swallowing and Swallowing Disorders (Dysphagia), 22 (2), 61–72. 2013.
15. Hutcheson KA, Yuk M, Hubbard R, Gunn GB, Fuller CD, Lai SY, et al. Delayed lower cranial neuropathy after oropharyngeal intensity-modulated radiotherapy: A cohort analysis and literature review. Head Neck. 2017.
16. Aggarwal P, Zaveri JS, Goepfert RP, Shi Q, Du XL, Swartz M, et al. Swallowing-related outcomes associated with late lower cranial neuropathy in long-term oropharyngeal cancer survivors: cross-sectional survey analysis. Head & neck. 2019;41(11):3880-94.
17. Hutcheson KA. Late Radiation-Associated Dysphagia (RAD) in Head and Neck Cancer Survivors. Perspectives on Swallowing and Swallowing Disorders (Dysphagia). 2013;22(2):11.
18. Rubin EB, Buehler AE, Halpern SD. States worse than death among hospitalized patients with serious illnesses. JAMA internal medicine. 2016;176(10):1557-9.
19. Langmore SE, McCulloch TM, Krisciunas GP, Lazarus CL, Van Daele DJ, Pauloski BR, 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:E1221-31.
20. Hutcheson KA, Kelly S, Weber RS, Lewin JS. Offering more for persistent dysphagia after head and neck cancer: The evolution of boot camp swallowing therapy. Combined Otolaryngology Spring Meeting; Boston, MA2015.
21. Van Daele DJ, Langmore SE, Krisciunas GP, Lazarus CL, Pauloski BR, McCulloch TM, et al. The impact of time after radiation treatment on dysphagia in patients with head and neck cancer enrolled in a swallowing therapy program. Head & neck. 2019;41(3):606-14.
22. Hutcheson KA, Yuk MM, Holsinger FC, Gunn GB, Lewin JS. Late radiation-associated dysphagia (late-RAD) with lower cranial neuropathy in long-term oropharyngeal cancer survivors: Video case reports. Head Neck. 2014.
23. Ghiam MK, Mannion K, Dietrich MS, Stevens KL, Gilbert J, Murphy BA. Assessment of musculoskeletal impairment in head and neck cancer patients. Support Care Cancer. 2017.
24. Stubblefield MD. Radiation fibrosis syndrome: neuromuscular and musculoskeletal complications in cancer survivors. PM & R : the journal of injury, function, and rehabilitation. 2011;3(11):1041-54.
25. Silbergleit AK, Schultz L, Krisciunas G, Langmore S. Association of Neck Range of Motion and Skin Caliper Measures on Dysphagia Outcomes in Head and Neck Cancer and Effects of Neck Stretches and Swallowing Exercises. Dysphagia. 2020;35(2):360-8.
26. Rowin J, Cheng G, Lewis SL, Meriggioli MN. Late appearance of dropped head syndrome after radiotherapy for Hodgkin's disease. Muscle & nerve. 2006;34(5):666-9.
27. 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):425-31.
28. Gross AR, Hoving JL, Haines TA, Goldsmith CH, Kay T, Aker P, et al. A Cochrane review of manipulation and mobilization for mechanical neck disorders. Spine (Phila Pa 1976). 2004;29(14):1541-8.
29. Gross AR, Kay T, Hondras M, Goldsmith C, Haines T, Peloso P, et al. Manual therapy for mechanical neck disorders: a systematic review. Manual therapy. 2002;7(3):131-49.

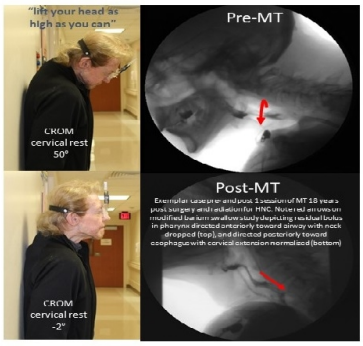
30. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ. 2014;348:g1687.
31. Page MJ, Green S, Kramer S, Johnston RV, McBain B, Chau M, et al. Manual therapy and exercise for adhesive capsulitis (frozen shoulder). Cochrane Database Syst Rev. 2014(8):Cd011275.
32. Camargo PR, Alburquerque-Sendin F, Avila MA, Haik MN, Vieira A, Salvini TF. Effects of Stretching and Strengthening Exercises, With and Without Manual Therapy, on Scapular Kinematics, Function, and Pain in Individuals With Shoulder Impingement: A Randomized Controlled Trial. J Orthop Sports Phys Ther. 2015;45(12):984-97.
33. Trott CA, Ruiz Aguila ME, Leaver AM. The clinical significance of immediate symptom responses to manual therapy treatment for neck pain: observational secondary data analysis of a randomized trial. Manual therapy. 2014;19(6):549-54.
34. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. Journal of Biomedical Informatics. 2009;42(2):377-81.
35. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. Journal of Biomedical Informatics. 2019;95:103208.
36. Youdas JW, Garrett TR, Suman VJ, Bogard CL, Hallman HO, Carey JR. Normal range of motion of the cervical spine: an initial goniometric study. Phys Ther. 1992;72:770-.
37. Dijkstra PU, Huisman PM, Roodenburg JL. Criteria for trismus in head and neck oncology. Int J Oral Maxillofac Surg. 2006;35(4):337-42.
38. Lazarus CL, Husaini H, Jacobson AS, Mojica JK, Buchbinder D, Okay D, et al. Development of a new lingual range-of-motion assessment scale: normative data in surgically treated oral cancer patients. Dysphagia. 2014;29(4):489-99.
39. Deng J, Ridner SH, Wells N, Dietrich MS, Murphy BA. Development and preliminary testing of head and neck cancer related external lymphedema and fibrosis assessment criteria. European journal of oncology nursing : the official journal of European Oncology Nursing Society. 2015;19(1):75-80.
40. Deng J, Dietrich MS, Ridner SH, Fleischer AC, Wells N, Murphy BA. Preliminary evaluation of reliability and validity of head and neck external lymphedema and fibrosis assessment criteria. European journal of oncology nursing : the official journal of European Oncology Nursing Society. 2016;22:63-70.
41. Common Terminology Criteria for Adverse Events (CTCAE). v4.03 ed. Bethesda, MD: National Institutes of Health, National Cancer Institute, Department of Health and Human Services; 2010.
42. Lewin JS, Hutcheson KA, Barringer DA, Smith BG. Preliminary experience with head and neck lymphedema and swallowing function in patients treated for head and neck cancer. Perspectives on Swallowing and Swallowing Disorders Dysphagia. 2010;19:45-52.
43. Rosenbek JC, Robbins JA, Roecker EB, Coyle JL, Wood JL. A penetration-aspiration scale. Dysphagia. 1996;11(2):93-8.
44. Schwertner RW, Garand KL, Pearson WG, Jr. A Novel Imaging Analysis Method for Capturing Pharyngeal Constriction During Swallowing. Journal of imaging science. 2016;1(1).

45. Pearson WG, Jr., Taylor BK, Blair J, Martin-Harris B. Computational analysis of swallowing mechanics underlying impaired epiglottic inversion. Laryngoscope. 2016;126(8):1854-8.
46. Ding Y, Mohamed AS, Yang J, Colen RR, Frank SJ, Wang J, et al. Prospective observer and software-based assessment of magnetic resonance imaging quality in head and neck cancer: Should standard positioning and immobilization be required for radiation therapy applications? Pract Radiat Oncol. 2015;5(4):e299-308.
47. Messer JA, Mohamed AS, Hutcheson KA, Ding Y, Lewin JS, Wang J, et al. Magnetic resonance imaging of swallowing-related structures in nasopharyngeal carcinoma patients receiving IMRT: Longitudinal dose-response characterization of quantitative signal kinetics. Radiother Oncol. 2016;118(2):315-22.
48. Perlman AL, Palmer PM, McCulloch TM, Vandaele DJ. Electromyographic activity from human laryngeal, pharyngeal, and submental muscles during swallowing. Journal of applied physiology (Bethesda, Md : 1985). 1999;86(5):1663-9.
49. Preston DC, Barbara E. Shapiro. Electromyography and Neuromuscular Disorders: Clinical-Electrophysiologic Correlations. 3rd ed: Saunders; 2013 2013.
50. Chen AY, Frankowski R, Bishop-Leone J, Hebert T, Leyk S, Lewin J, et al. The development and validation of a dysphagia-specific quality-of-life questionnaire for patients with head and neck cancer: the M. D. Anderson dysphagia inventory. Arch Otolaryngol Head Neck Surg. 2001;127(7):870-6.
51. Cleeland CS, Mendoza TR, Wang XS, Chou C, Harle MT, Morrissey M, et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. Cancer. 2000;89(7):1634-46.
52. Rosenthal DI, Mendoza TR, Chambers MS, Asper JA, Gning I, Kies MS, et al. Measuring head and neck cancer symptom burden: the development and validation of the M. D. Anderson symptom inventory, head and neck module. Head Neck. 2007;29(10):923-31.
53. Rosenthal DI, Mendoza TR, Fuller CD, Hutcheson KA, Wang XS, Hanna EY, et al. Patterns of symptom burden during radiotherapy or concurrent chemoradiotherapy for head and neck cancer: a prospective analysis using the University of Texas MD Anderson Cancer Center Symptom Inventory-Head and Neck Module. Cancer. 2014;120(13):1975-84.
54. Deng J, Ridner SH, Murphy BA, Dietrich MS. Preliminary development of a lymphedema symptom assessment scale for patients with head and neck cancer. Support Care Cancer. 2012;20(8):1911-8.
55. List MA, Ritter-Sterr C, Lansky SB. A performance status scale for head and neck cancer patients. Cancer. 1990;66(3):564-9.
56. Webster MA, Sheets HD. A practical introduction to landmark-based geometric morphometrics. Quantitative Method Paleobio. 2010;16:168-88.
57. Cho Y, Do J, Jung S, Kwon O, Jeon JY. Effects of a physical therapy program combined with manual lymphatic drainage on shoulder function, quality of life, lymphedema incidence, and pain in breast cancer patients with axillary web syndrome following axillary dissection. Support Care Cancer. 2016;24(5):2047-57.
58. Shaghayegh Fard B, Ahmadi A, Maroufi N, Sarrafzadeh J. Evaluation of forward head posture in sitting and standing positions. Eur Spine J. 2016;25(11):3577-82.
59. Jones DA, Rutherford OM. Human muscle strength training: the effects of three different regimens and the nature of the resultant changes. J Physiol. 1987;391:1-11.

60. Seo MW, Jung HC, Song JK, Kim HB. Effect of 8 weeks of pre-season training on body composition, physical fitness, anaerobic capacity, and isokinetic muscle strength in male and female collegiate taekwondo athletes. J Exerc Rehabil. 2015;11(2):101-7.
61. Carnaby-Mann GD, Crary MA. McNeill dysphagia therapy program: a case-control study. Archives of physical medicine and rehabilitation. 2010;91(5):743-9.

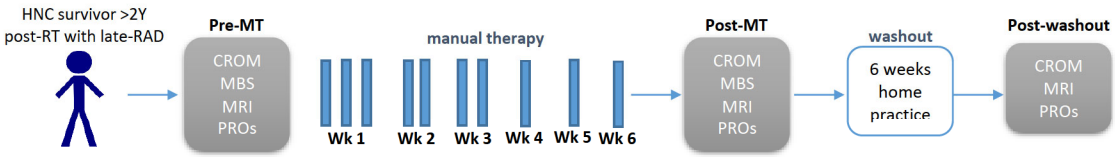


Exemplar case pre- and post 1 session of MT 18 years post surgery and radiation for HNC. Note red arrows on modified barium swallow study depicting residual bolus in pharynx directed anteriorly toward airway with neck dropped (top), and directed posteriorly toward esophagus with cervical extension normalized (bottom)



Cervical extension and asperation improved after manual therapy

108x72mm (300 x 300 DPI)



CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	Title, 1, 2, 7, 20
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	7
	2b	Specific objectives or research questions for pilot trial	7
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	8
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	17
Participants	4a	Eligibility criteria for participants	9
	4b	Settings and locations where the data were collected	8-9
	4c	How participants were identified and consented	8,11
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9, Table 1
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	11-16
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	N/A
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	N/A
Sample size	7a	Rationale for numbers in the pilot trial	19
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	N/A
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	N/A
Allocation concealment	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	N/A

mechanism			
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	N/A
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	N/A
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	17-20
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	N/A
	13b	For each group, losses and exclusions after randomisation, together with reasons	N/A
Recruitment	14a	Dates defining the periods of recruitment and follow-up	N/A
	14b	Why the pilot trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	N/A
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	N/A
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	N/A
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
	19a	If relevant, other important unintended consequences	N/A
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	21-23
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	20-21.23
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	N/A
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	23
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	1
Protocol	24	Where the pilot trial protocol can be accessed, if available	25
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	25
	26	Ethical approval or approval by research review committee, confirmed with reference number	26

Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.
*We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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*Man*ual *T*herapy for Fibrosis-Related *L*ate *E*ffect Dysphagia in Head and Neck Cancer Survivors: The Pilot MANTLE trial

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*Man*ual *T*herapy for Fibrosis-Related *L*ate *E*ffect Dysphagia in Head and Neck Cancer Survivors: The Pilot MANTLE trial

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Abstract

Introduction: Late dysphagia that develops or persists years after head and neck cancer (HNC) is a disabling survivorship issue. Fibrosis is thought to stiffen connective tissues and compress peripheral nerve tracts, thereby contributing to diminished strength, flexibility, and in some cases denervation of swallowing muscles. Manual therapy (MT) is used in cancer survivors for pain and other indications, but it is unknown if increasing blood flow, flexibility, and cervical range of motion (CROM) in the head and neck may improve late dysphagia.

Methods and Analysis: MANTLE is an NCI-funded prospective single-arm pilot trial evaluating the feasibility, safety, and therapeutic potential of MT in patients with late dysphagia after radiation therapy (RT) for HNC. Disease-free survivors ≥2 years after curative-intent RT for HNC with at least moderate dysphagia and ≥2 CTCAE v4.0 fibrosis are eligible. The target sample size is 24 participants who begin the MANTLE program. MANTLE is delivered in 10 MT sessions over 6 weeks with an accompanying home exercise program (HEP). Patients then transition to a 6-week post-washout period during which they complete the HEP and then return for a final post-washout evaluation. Feasibility (primary endpoint) and safety will be examined. Serial assessments include cervical range of motion, modified barium swallow (MBS) studies, quantitative magnetic resonance imaging (MRI), electromyography (optional), and patient-reported outcomes (PROs) as secondary, tertiary, and exploratory endpoints.

Ethics and dissemination: The research protocol and informed consent document was approved by the Institutional Review Board at the University of Texas MD Anderson Cancer Center. Findings will be disseminated through peer-reviewed publication that will be made publicly available on PubMed Central upon acceptance for publication, in compliance with NIH public access policy.

Trial registration: NCT03612531 US National Library of Medicine ClinicalTrials.gov, Registered 26 July 2018; https://clinicaltrials.gov/ct2/show/NCT03612531

Keywords: Head and neck cancer, speech pathology, radiation oncology

Article Summary (including strengths and limitations of study)

- MANTLE is a pilot, single arm feasibility trial of manual therapy for late radiation-associated dysphagia with strengths including a diverse panel of secondary endpoints examine functional, physical, and patient-reported outcomes.
- Strengths and limitations of this study: strengths include examination of a novel therapy for an often refractory condition with comprehensive outcome measures.
- Strengths and limitations of this study: limitations include pilot nature of the trial without a control group or lead-in and lack of cervical posture measures.

Introduction

Dysphagia is a priority issue for head and neck cancer (HNC) survivors. While noteworthy as a driver of quality of life (QOL) (1), chronic, persistent, or late dysphagia is also a serious health problem in long-term survivorship. Even in modern practice, chronic aspiration (airway entry of liquids or food) is a life-threatening manifestation of dysphagia afflicting up to 30% of survivors treated with definitive radiotherapy (RT) or chemoradiotherapy (CRT) (2). HNC survivors treated with CRT are 2.7 times more likely to develop aspiration pneumonia than non-cancer controls, and aspiration pneumonia confers a 42% increased risk of mortality among survivors(3).

There is a rapidly growing pool of HNC survivors at risk for late dysphagia. Almost half of HNCs are now human papillomavirus (HPV)-driven oropharyngeal cancers, the incidence of which is expected to increase through at least 2030(4). The vast majority of this fast-growing, large subgroup of HNC survivors has been treated with curative RT at doses of 60 Gray (Gy) or more to the pharyngeal axis sufficient to induce chronic or late radiation-associated dysphagia (RAD)(5-7). Distinct from tobacco-related HNC, HPV-associated HNC is diagnosed younger (median: 54 years)(8) with excellent two- and five-year survival probability of 95%(9) and 79%(10), respectively. For these reasons, modern HNC survivors with HPV-attributable oropharyngeal cancer have the potential to live many active years (even decades) with toxicities of RT.

While many survivors initially recover functional swallowing after acute effects of radiation resolve, an important subset develops debilitating persistent or late RAD. It is estimated 30 to 40% treated with current treatment regimens that prescribe 66-72 Gy radiotherapy develop chronic RAD, and a highly burdened subset progress significantly over subsequent years(7, 11).

Late-radiation associated dysphagia (late-RAD)(12-14) is a particularly challenging, typically progressive form of refractory dysphagia that manifests years into survivorship (median latency: 8 years, cumulative incidence 8% at

7-years survival) after a period of reasonable functional recovery(15). As the era of HPV-associated oropharyngeal cancer survivorship matures, the number of late-RAD cases grows. Late-RAD is among the most difficult late-effect conditions to manage in HNC survivors, associated with a cascade of functional decline. Late lower cranial neuropathies (LCNP) are highly prevalent in survivors with late-RAD, 48 to 83% in the investigators' prior work, and increase the likelihood of lifelong feeding tube dependence due to refractory aspiration(5, 12, 16). Despite standard therapies such as swallowing exercises with or without cervical esophageal dilation, 66% of late-RAD cases in the investigators' published case series became chronically feeding tube dependent in late survivorship at a median age of 64 years (9 years after cancer cure)(14, 17). The QOL and health implications of becoming feeding tube dependent for life at this active age are staggering(14). Recent work highlights the gravity of this among cancer patients who ranked feeding tube dependence as one of the top six outcomes of their cancer that they perceive to be worse than death(18).

Therapy success in survivors with RAD is time dependent. Work from our group and others suggest particularly disappointing responses in survivors who begin swallowing therapy more than 2 years after completing curative RT (19, 20). For instance, in the investigators' published case series of late-RAD, oral diet scores were observed to significantly deteriorate over a median follow-up of 10 months in the late post-RT period, despite standard swallowing exercise therapies with or without esophageal dilation. Likewise, in secondary analysis an NCI-funded multi-site swallowing therapy trial among 117 survivors with chronic and late RAD, response to swallowing therapy was time dependent. QOL and diet scores improved most among those who started therapy <1 year after RT, with little improvement evident among those who started therapy more than 2 years post RT(21).

Clinical experience supports that survivors with late-RAD almost universally present with palpable, high-grade fibrosis. Fibrosis is thought to compress peripheral nerve tracts, thereby contributing to denervation of critical swallowing muscles(22). Largely considered irreversible and potentially progressive, these normal tissue changes

disrupt the intricate sensorimotor processes required to simultaneously close the airway, open the esophagus, and push a bolus through the pharynx for successful swallowing. With mature fibrosis, late-RAD coexists with other problems including impaired cervical range of motion (CROM) and abnormal cervical posture(23). Broad manifestations of radiation injury have been referred to as radiation fibrosis syndrome (RFS) with progressive myelo-radiculo-plexo-neuro-myopathic changes resulting in a host of functional challenges including cervicalgia and head drop syndrome(24). A recent cross-sectional analysis of musculoskeletal impairment in 29 long-term HNC survivors reported 89% had abnormal cervical posture with significant deviation in cervical extension relative to normative ranges (z-score: 0.63, $p<0.001$). Postural and CROM impairments significantly correlated with patient-reported outcome (PRO) measures of shoulder and jaw function, but swallowing associations were not reported.(23) There are, however, emerging data to support a correlation between cervical biomechanics and swallowing. Better CROM and skin pliability (as a clinical marker of cervical fibrosis) associated significantly with swallowing safety per penetration-aspiration scale (PAS) scores from videofluoroscopic swallowing evaluations in survivors with chronic RAD, however, in this secondary analysis of clinical trial data, change in cervical ROM or pliability did not associate with change in swallowing function after swallowing therapy(25).

In long-term HNC survivors with late-RAD, circumferential cervical muscles can demonstrate reduced capacity for contraction and appropriate ROM due to RFS, which can result in a head drop position. Anterior and lateral cervical muscles are typically shortened and firm to touch due to progressive fibrotic tissue sclerosis. As a result of fibrotic cervical flexors, cervical extensors are overstretched and can become weak and atrophied over time (24, 26).

Cervical posture is empirically a critical background factor facilitating safe swallowing. That is, when swallowing in a head drop position, the path of least resistance for any residual bolus in the pharynx is down into the airway. This might contribute to gravity-assisted aspiration (GASP), whereby post-swallow residue enters the

airway more easily when the resting head posture is dropped. Indeed, GASP is a regular clinical observation in the investigators' practice. In contrast, with more normal upright cervical posture, residual bolus may dwell posteriorly in the pharynx waiting to be safely cleared into the esophagus on a subsequent swallow as shown as proof of concept in exemplar case in Figure 1.

Adjusting the swallow environment by improving cervical posture, as shown in *Figure 1*, is often overlooked as a therapeutic target for late-RAD. For these reasons and clinically recognizing the high prevalence of forward head drop co-occurring with late-RAD, neutralizing cervical posture by improving upper and lower cervical extension is the initial goal in the proposed MT program in this trial. Integration of this goal focused on priming or optimizing the swallow environment prior to mobilizing intrinsic swallowing musculature represents a novel element of our proposed MT swallow therapy program, called MANTLE (*Man*ual *T*herapy for Fibrosis-Related *L*ate *E*ffect Dysphagia).

[INSERT FIGURE 1, **Cervical extension and aspiration improved in case example after manual therapy**]

Preliminary unpublished clinical data from the investigators detect an average 11-degree improvement in a fibrosis-related endpoint of cervical extension after a single session of MT ($p<0.001$), and notable qualitative remarks about functional gains after MT in clinical practice (e.g., "that's the first time I've felt myself swallow in years"). These early observations helped motivate the development of the MANTLE therapy program and this trial. Acknowledging the typically progressive and refractory nature of late fibrotic effects, it is critical to understand the durability of improved CROM and whether this translates to better swallowing function.

Objectives:

Therefore, the pilot MANTLE trial proposes to study a novel, adjunctive MT program in patients with fibrosis-related late-RAD with the following objectives:

1) To determine the feasibility and safety of MANTLE as a program of treatment for fibrosis-related dysphagia in HNC survivors
2) To estimate effect size, dose-response (number of treatment sessions to normalized cervical range of motion), and durability of MANTLE for improving cervical range of motion in HNC survivors with fibrosis-related late dysphagia
3) To examine functional outcomes after MANTLE in HNC survivors with fibrosis-related late effects and their association with change in dysphagia grade, cervical extension, and other cofactors.

Methods

Study Design

MANTLE is a single-institution, prospective single-arm unblinded pilot trial of MT in patients with late dysphagia after head and neck RT. Clinical schedules in the Section of Speech Pathology and Audiology at the University of Texas MD Anderson Cancer Center (Houston, Texas, USA) are screened to identify eligible patients referred for post-radiation swallow assessment. The investigators will enroll consecutive patients who meet eligibility and give written informed consent. Target enrollment is 24 participants who start the MANTLE program, with up to 32 participants enrolled during screening. The first participant enrolled August 6, 2018; trial completion is projected to occur in April 2021. MT is delivered according to a standard protocol for 6 weeks followed by a 6 week wash-out period. Feasibility and safety will be examined. Serial assessments also include CROM, imaging, and PROs. The trial schema is depicted in *Figure 2*.

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312). The principles of informed consent in the current edition of the Declaration of Helsinki will be implemented before any

protocol-specific procedures or interactions are carried out. Informed consent will be obtained, in accordance with 21 CFR 50.25. The written consent document will embody the elements of informed consent, as described in the Declaration of Helsinki and will also comply with local regulations of the Institutional Review Board (IRB) of MDACC.

Protocol amendments impacting eligibility, outcome, and/or analysis are submitted for IRB approval, communicated through the institutional electronic protocol system to all relevant investigators, and updated in trial registration.

[INSERT FIGURE 2, **MANTLE trial schema.**]

Inclusion criteria:

1) Age ≥ 18 years
2) Late DIGEST grade ≥2 dysphagia on Modified Barium Swallow (MBS) ≥2 years after curative-intent radiotherapy for head and neck cancer
3) Grade ≥2 CTCAE v4.0 fibrosis
4) Willing and able to return for 10 sessions that taper in frequency over 6 weeks of therapy

Exclusion criteria:

1) Active recurrent or second primary head and neck, central nervous system, or thoracic cancer at time of enrollment
2) Active osteoradionecrosis or other non-healing wounds (e.g., fistula, ulcer, soft tissue necrosis) in MT regions of interest at time of enrollment
3) History of subtotal or total glossectomy or total laryngectomy

4) Functionally limiting cardiac, pulmonary, or neuromuscular disease

5) Current tracheostomy

Treatment

MT is commonly used in cancer survivors after RT and in the cervical region for pain and other indications.(27-29) The proposed MT program was developed by dysphagia-specialized speech pathologists (SLP) dually licensed in massage therapy (HM) and certified in lymphedema therapy (CLT) (HM, CPB, KS) and summarized using the TIDieR template(30).

The MANTLE program added hierarchical goals for cervical biomechanics to the goals of a published swallowing-focused MT program developed jointly by speech pathologists and a head and neck anatomist.(27) MANTLE conceptualizes and sequences manual therapy and mobilization targets from superficial to deep as detailed in Table 1. First, targeting cervical extension to address the common "head-drop" post-RT fibrotic cervical posture to a more natural, upright swallowing-optimized state (conjectured by the authors to be favorable for swallowing safety in the setting of pharyngeal residue) as shown in *Figure 1*. Lateral flexion and cervical rotation are subsequently targeted to prime the tissues to access deeper swallowing regions-of-interest (ROIs) including the tongue, pharynx, and larynx as summarized in *Table 1*. Building on Level I evidence from patients with non-cancer cervical pathology (i.e., benign neck pain), the proposed MANTLE program combines myofascial release (MFR) and massage with range of motion (ROM) exercise to iteratively mobilize swallowing-related ROIs with a HEP for stretch and to initiate strengthening where stimulable .(31-33) Table 1 displays the regions of interest where soft tissue mobilization is hierarchically applied by the clinician during MT in addition to the functional goals and specific MT techniques. The list of exercises, duration, and frequency in the HEP are also detailed in Table 1.

Table 1. Manual therapy program for late effect dysphagia (MANTLE Program)

Table 1. Manual Therapy Program for Late Effect Dysphagia (MANTLE Program)				
Functional Goal	**Regions Of Interest (ROI)**	**MT Techniques**	**Home Exercise Program (HEP)** Frequency (3x/day for 12 weeks)	
		Manual therapy techniques will include at least 1 or all of: myofascial release (MFR), massage, passive range of motion (PROM), Active Assist Range of Motion (AAROM). Following clinician directed MT, patients may complete Active Range of Motion (AROM) stretching and strengthening exercises during the session. MT hierarchically sequences through each row and may be applied in any and/or all ROIs.	**Exercises**	
			Stretch Duration: 5 slow, deep breaths	**Strengthening** Duration: 3 sets, 10 reps. Hold each isometric exercise for 3-5 seconds.
Improve cervical extension	Upper/mid back and circumferential neck	MFR, massage, PROM, AROM, AAROM, AROM applied to upper/mid back and circumferential neck	**3 stretches targeting** • AROM Posterior glide of lower cervical spine; PROM anterior glide upper cervical spine • AROM jaw protrusion in AROM cervical frontal plane • AROM cervical in sagittal plane	**2 exercises** • Cervical retraction glide + extension (isometric + resistance- upper and lower cervical spine) • Cervical retraction glide + flexion (isometric + resistance- upper and lower cervical spine)
Improve lateral flexion and cervical rotation	Circumferential neck, upper back and chest	MFR, massage, PROM, AROM, AAROM, AROM applied to circumferential neck, upper back and chest	**6 stretches targeting** • PROM cervical in frontal + sagittal planes • PROM cervical in transverse + sagittal planes • AROM cervical frontal + sagittal • AROM cervical transverse + sagittal (oblique) + frontal • AROM cervical transverse + PROM upper chest/lateral cervical • AROM cervical transverse with AROM upper extremity adduction	**2 exercises** • Cervical sagittal+ scapular retraction (isometric + resistance) • Cervical transverse + scapular retraction (isometric = resistance)
Improve movement in muscles involved in deglutition	Anterior neck/oral cavity: prioritized in order of severity of patient-specific deficits: oral cavity, oropharynx, larynx, pharynx	MFR, massage, PROM, AROM, AAROM, AROM applied to anterior neck and/or oral cavity		

In the MANTLE trial, an SLP (HM) who is a licensed massage and certified lymphedema therapist (LMP and CLT) provided training to SLPs with CLT designations to perform the late-RAD MT program. Patients are seen for 10 sessions over 6 weeks with titrating intensity (Week 1: 3 sessions, Weeks 2-3: 2 sessions weekly, Weeks 4-6: 1 session weekly). The 10 sessions performed by the SLP in clinic include soft tissue mobilization and instruction on a cervical stretching/strengthening home exercise program (HEP); regions and sequence of targets for soft tissue mobilization are detailed in Table 1. After the 10 sessions (over 6 weeks), the patient then transitions to a home practice of the HEP using a standardized clinical handout targeting cervical extension, bilateral cervical lateral flexion, and bilateral cervical rotation without clinician assistance for a 6-week wash-out period as detailed in *Table 1*.

Subject registration

All adult men and women scheduled for routine clinical MBS at MDACC are considered for participation in this study without regard to race, gender, or socioeconomic status. Central registration is used for tracking study accrual and eligibility. Registration procedures include the following:

- Interested patients are given an explanation of the study to include potential risks and benefits by the principal investigator, co-investigator, or other designated medical personnel.
- Investigator or other trained, designated personnel obtain signed informed consent before any study-specific procedures are performed.
- The subject is seen and evaluated by the principal investigator, co-investigator, or designee prior to enrollment. Screening assessments are performed.
- The principal investigator, co-investigator or designee evaluate eligibility based on inclusion/exclusion criteria stated in this protocol.

Screening evaluations

Table 2. Schedule of Evaluation Procedures for MANTLE Trial

Assessment	Method	Domain	Endpoints	Scale	Pre-MT	During-MT	Post-MT	Post-washout
CROM	Goniometer Assessment (clinic)	Cervical range of motion	Cervical extension, lateral flexion, rotation	Continuous	X	X[a]	X	X
MBS	Fluoroscopy	Dysphagia severity grade	DIGEST[26]	Ordinal: 0 (best), 4 (worst)	X		X	
		Swallow kinematics	CASM[27]	Continuous	X		X	
Lymphedema/fibrosis rating	Clinician grading (physical exam)	Severity of lymphedema/fibrosis	CTCAE fibrosis, HN-LEF	Ordinal	X	X[d]	X	X
MIO	Therabite ruler (clinic)	Mouth opening	mm interincisal opening	Continuous	X		X	X
LROM	Therabite ruler (clinic)	Lingual range of motion	Tongue protrusion, lateralization, elevation	Continuous	X		X	X
MDADI[28]	PRO (20-item)	Swallowing-related QOL	Composite, Global, & subscale scores	Continuous: 20 (worst), 100 (best)	X		X	X
MDASI-HN[29]	PRO (31-item)[b]	Symptom burden	Symptom severity, symptom interference	Continuous: 0 (best), 10 (worst)	X	X[c]	X	X
LSIDS-H&N	PRO (64-item)	Lymphedema/fibrosis specific symptoms	Symptom severity associated with lymphedema		X		X	X

			and fibrosis					
PSS-HN[31]	Interview (3-item)	Functional status	Diet, Eating, Speech subscales	Ordinal: 0 (worst), 100 (best)	X	X[d]	X	X
MRI	Imaging	Soft tissue kinetics	T1 signal intensity	Continuous	X		X	X
(Optional)EMG (tongue) EMG+NCS (trap)	Electromyography	Innervation	4-point denervation potentials grade	Ordinal	X		X	

Abbreviations: MBS, modified barium swallow, EMG, electromyography, DIGEST, Dynamic Imaging Grade of Swallowing Toxicity, CASM, Computational Analysis of Swallowing Mechanics, CROM, Cervical Range of Motion, MDADI, MD Anderson Dysphagia Inventory, MDASI, MD Anderson Symptom Inventory, PSS-HN, Performance Status Scale Head and Neck Cancer. [a]CROM collected at each MT visit. [b]28-item MDASI-HN with 3 special interest items. [c]MDASI collected bi-weekly during MT. [d]collected at mid-point of MT.

Patients are evaluated by the speech pathologist and referring physician or advanced practice provider in the interdisciplinary head and neck cancer program. Medical history, oral motor examination, and oropharyngeal swallow function are recorded. The electronic medical record is reviewed for relevant history pertaining to eligibility criteria.

Study evaluations

Table 2: Summary of Treatment Evaluations

Outcomes are assessed according to the schedule outlined in Table 2. To facilitate retention, all patient-completed questionnaires may be completed by paper or electronic means (i.e., via REDCap), and data collection procedures are aligned with clinical visits (34, 35). Outcome data will be collected from all participants; regardless of deviations from the therapy protocol. Details of data collection procedures follow.

Cervical Range of Motion: Patients were in an upright, seated position to reflect their natural cervical swallowing posture as the start position when CROM was measured. Clinic chairs were placed in a reproducible, fully upright standard position for every measurement. A goniometer measures CROM (degrees) to assess active cervical spine ROM. Five core CROM measures include cervical extension, sagittal plane at rest, lateral flexion (left/right), coronal plane at rest, and lateral rotation (left/right). The primary CROM measure of interest is cervical extension. Cervical extension measures are highly reliable (ICC=.90). Average extension measures in healthy adults aged 60 to 69 range from 57 degrees in males (SD: 10.5) to 65 degrees in females (SD: 13.3). Cervical extension measures decrease by approximately 5 degrees for each decade of life.(36) Lingual and jaw range of motion are also measured per published methods(37, 38).

Lymphedema/Fibrosis Grading: Clinician-grading of lymphedema/fibrosis is conducted according to the published Head and Neck-Lymphedema Fibrosis (HN-LEF)(39, 40), Common Terminology Criteria for Adverse Events (CTCAE) (41), and MD Anderson adaptation of the Foeldi lymphedema rating(42), per physical examination of the patient. Clinical grading is a brief assessment that can be completed in <15 minutes using all 3 complementary sets of grading methods.

Modified Barium Swallow (MBS) Studies: Digital videos from clinical MBS will be scored by a trained speech pathologist blinded to the patient, study, and follow-up interval using methods including the *Dynamic Imaging Grade for Swallowing Toxicity (DIGEST)*(43) and *Computational Analysis of Swallowing Mechanics (CASM)* (44, 45).

MRI: Multiparametric, serial MRI are acquired with a 1.5 T to 3.0T GE Discovery 750 MRI scanner (GE Healthcare, Wisconsin, USA) using laterally placed 6-element flex coils centered on the base of tongue region. Feasibility and

optimization of this MRI paradigm have been described by the investigative team(46), with particular emphasis on immobilization using dedicated H&N coils and a flat insert table with an indexed base plate. Multiparametric imaging will be performed longitudinally (pre-, post-MT, and post-washout). *Table 3* summarizes candidate acquisitions for this study. Our primary candidate imaging biomarker of MANTLE-related soft-tissue change is normalized $\Delta T1_{normalized}$ signal intensity, as we have previously published this parameter's relevance as a dose-dependent soft tissue anatomic imaging biomarker of fibrosis.(47) ROI delineation will be done using the investigators' published method and will include, among our published library of 72 normal structures, the following swallowing-relevant OARs: mylohyoid, geniohyoid, and constrictors.

Table 3. Candidate quantitative imaging parameters selected for MANTLE trial

Acquisition type	Imaging parameter/biomarkers	Tissue injury correlate
T1-pre/post contrast	T1 intensity, T1/R1, T1-rho	Radiation associated fibrosis
T2/T2* Map	T2 contrast, T2*	Radiation associated edema
DTI	Muscle fiber tractography and fractional anisotropy	Muscle/nerve fiber/tumor microstructure, directionality tracts
DCE	Perfusion parameters (K_{trans}, K_{ep})	Tissue perfusion/ Microvessel permeability

Optional Intramuscular electromyography (EMG) and nerve conduction study (NCS) assess insertional activity in the tongue (XII nerve) as a marker of denervation(48). EMG recordings are conducted by a neurologist trained in clinical neurophysiology and denervation potentials graded per:

0 None

1 Persistent, single trains of potentials in at least 2 areas

2 Moderate number of potentials in 3 or more areas

3 Many potentials in all areas

4 Full interference pattern of potentials

EMG and nerve conduction studies will also be taken in the trapezius muscle (XI nerve), as the region is easily accessible for non-invasive EMG with NCS and represents a muscle within the irradiated field with lower cranial nerve innervation. Both quantitative and qualitative EMG will be assessed. NCS will be assessed quantitatively, with waveforms generated from which we acquire amplitude, latency, and conduction velocity(49). Optional EMG will not be conducted if platelets <50,000. Optional EMG and nerve conduction studies were added as a secondary procedure after trial activation.

M.D. Anderson Dysphagia Inventory (MDADI) is a written questionnaire to evaluate dysphagia-specific QOL in H&N cancer patients.(50) The 20-item MDADI questionnaire quantifies an individual's global, physical, emotional, and functional perceptions of his or her swallowing ability. In an internal validation in 100 patients with HNC, concurrent validity was found to be moderate by comparison with the Performance Status Scale for Head and Neck Cancer Patients (Spearman correlation, 0.47-0.61). Correlation with the physical functional subscale (Spearman correlation, 0.40) and emotional subscale of SF-36 (36-Item Short Form Survey) (Spearman correlation, 0.36) demonstrated convergent and divergent validity, respectively, of the MDADI. Test-retest reliability (physical, 0.86; emotional, 0.88; functional, 0.88) and internal consistency reliability (overall Cronbach's alpha, 0.96) were sound.

M.D. Anderson Symptom Inventory for Head and Neck Cancer (MDASI-HN) is a patient-reported outcome questionnaire designed to measure severity or burden of systemic and head and neck (HN) specific symptoms and their interference with or effect on patients' daily functioning. This 28-item multi-symptom inventory includes 13 core items ("systemic symptoms": pain, fatigue, sleep, *etc*.), nine HN-specific items ("local symptoms": dry mouth, mucus, shortness of breath, taste, *etc*.), and six interference items (activity, work, relations, *etc*.). The core MDASI items have been validated for use in cancer patient populations regardless of the specific diagnosis or type of therapy and thus can be used to compare overall burden of disease between

different types of cancer(51). The HN-specific items were validated internally with regard to construct and concurrent validity in HN cancer patients.(52, 53) Internal consistency reliability is high in the core, HN-specific, and interference items (Cronbach's alphas of 0.72-0.92). Validated linguistic translations (Chinese, French, German, Greek, Italian, Spanish, and Turkish) of the MDASI-HN may be administered to non-English speaking participants.

Lymphedema Symptom Intensity and Distress Survey – Head and Neck (LSIDS-H&N) (54) is a 64-item instrument designed to assess lymphedema symptoms in head and neck cancer patients. Survey items were selected to address six domains (head and neck-specific functioning, systemic symptoms, psychosocial issues, altered sensation symptoms, neck-shoulder musculoskeletal/skin symptoms, and miscellaneous symptoms) identified by an expert panel. Preliminary testing of LSIDS-H&N demonstrated both feasibility and readability.

Performance Status Scale for Head and Neck Cancer Patients (PSS-HN) is a clinician-rated instrument rated by a semi-structured interview consisting of three questions: normalcy of diet, public eating, and understandability of speech.(55) The PSS-HN has been psychometrically validated and recommended by the National Comprehensive Cancer Network for measurement of swallowing and speech performance in patients with HNC.

Adherence Logs: standard clinical adherence logs are given to track adherence to the HEP performed throughout the entire MANTLE trial. Patients are asked to complete paper logs with check boxes to count completion of each HEP component on a daily basis. Logs are returned and reviewed at live MT sessions in attempt to validate responses or clarify ambiguity.

Follow-up intervals

Post-MT and post-wash out evaluations (specified in *Table 2*) will be conducted immediately after the 6 week training period with an allowable window of 2 weeks.

Safety and Feasibility

Safety and Feasibility of MT: Feasibility of MANTLE will be assessed by estimating program completion rates, sources of attrition, and adherence (i.e., clinical attendance, and adherence to home exercise program). Process evaluation checklists will be completed after each session to examine fidelity to the MANTLE treatment program, and patients will be asked to log their home practice using a study-specific adherence form. AEs are also assessed and recorded. Cervical MT is a safe therapy in many populations. Risk of serious adverse events is estimated to be 6 in 10 million[42,43]. Serious AEs relate to cardiovascular risk and are more common when providing a thrust manipulation technique that is employed in this protocol. Mild AEs, while still rare (estimated 1% to 2% of patients), are more common and can include local discomfort, headache, lightheadedness, falls, and fatigue. SAEs were not encountered in our preliminary retrospective review of patients receiving MT.

Data Management

The data is maintained in an institutionally approved electronic data capture system with an integrated codebook. Data management adheres to institutional guidelines and policies for maintaining confidentiality to protect PHI from public viewing by safeguarding storage and disposal of documents containing PHI and computer workstations and databases that access PHI. Data validation will include missing data reports range checks for data values, and logic checks for plausible relationships. The PI, statistician, and data manager will have access to the final trial dataset.

Monitoring

The trial will be monitored by the Office of Protocol Research at the MD Anderson Cancer Center subject to

independent audit by MD Anderson's Internal Audit Department in accordance with the Texas Internal Audit Act and the University of Texas System Board of Regents and the Internal Audity Activity Charter. Adverse events will be recorded by the study team. The IRB will be notified of any related grade three or greater adverse events and provided data to permit a safety review of the study treatment. The IRB may request additional meetings or safety reports as deemed necessary.

Patient and Public Involvement

The investigators did not formally engage a patient or public stakeholder team in trial development or recruitment strategies. Study data will be disseminated via peer-reviewed publication made publicly available through PubMed Central, and shared with participants through this medium.

Ethics and dissemination: The research protocol and informed consent document was approved by the Institutional Review Board at the University of Texas MD Anderson Cancer Center. Findings will be disseminated through peer-reviewed publication that will be made publicly available on PubMed Central upon acceptance for publication, in compliance with NIH public access policy.

Statistical Considerations

Statistical analysis and sample size justification

The primary objective of MANTLE is to determine feasibility based on the program completion rate. Investigators planned to enroll 24 patients and estimated an attrition rate of 20% to achieve a final sample size of 19 participants. Program completion rate is estimated from the participants who start the MANTLE program after screening procedures excluding screen failures and those who withdrawal before therapy starts. Note, the final protocol was amended to account for unanticipated prolonged treatment interruption or delay due to the institutional suspension of live clinical services and clinical research in response to the COVID-19 pandemic. For

that reason, investigators increased maximum accrual to 32 participants and will cease enrollment after 24 participants start treatment without any COVID-19-related interruptions. The primary analysis will include the 24 participants who started MT and who did not experience the COVID-19-related interruption of study participation. Any study withdrawals or interruptions in study participation for reasons other than COVID interruptions will be part of this feasibility analysis. In addition, as a sensitivity analysis, all available data, including any data collected from the participants interrupted by the COVID-19 research suspension, will be analyzed in a stratified manner. Stratification by COVID-19 treatment interruptions was added to the protocol after activation in response to the unanticipated study impact of the pandemic.

For analysis of the **primary objective** to determine the feasibility and safety of the MANTLE program, a completion rate of 75% will be considered the benchmark of feasibility. Completion rate will be defined by completion of the 6-week clinical MANTLE program without withdrawing and attending a minimum of 2 sessions plus the post-treatment assessment. Session attendance will be monitored separately to assess adherence and fidelity. We will summarize fidelity and adherence to the standard MANTLE protocol using quantitative and qualitative methods. Adverse events will be tabulated.

For analysis of the **secondary objective**, we chose cervical extension as the primary CROM measure of interest and as the direct treatment target due to our preliminary data suggesting significant improvements after MT in patients with fibrosis-related late effects (1 session mean Δ: 11%; $p<0.001$) as well as our conjectured relevance of CROM to swallowing safety. Cervical extension CROM measures are also highly reproducible (ICC=.90) and are taken each standard MT session as part of routine clinical appointments to direct therapy. For this analysis, we will use simple descriptive statistics to first summarize baseline, post-MT1, and post-MT2 (after the six week wash-out period of exclusive home therapy) CROM measures for each anatomic plane. We will compare baseline to post-MT1 CROM measures using a one-sided paired *t*-test. With 24 patients and conservatively

estimating an attrition rate of 20% based on our prior experience, the final sample size of 19 patients will provide 80% power to detect an effect size of d = 0.593, which corresponds to a $\Delta CROM_{baseline\text{-}post\text{-}MT}$ of 10.68 degrees (assuming the SD = 18 per our pilot data in HNC). To determine whether cervical extension normalizes within 10 sessions of clinician-administered MT, post-MT CROM raw scores will be converted to *z*-scores based on age- and sex-specific norms to estimate the proportion of participants with post-MT cervical extension scores that fall within 2 SDs of normative values. To examine the durability of response, we will normalize post-MT2 CROM measures to determine the percentage of participants who maintain or improve (*z*-score ≥ post-MT score – 2 SDs) post-wash-out. For the expected proportion of 80% who maintain or improve CROM, the 95% CI will extend 15% from the observed proportion. The number of MT sessions before normalization of CROM will be tabulated. In exploratory analysis, we will plot CROM measures across time and will consider using linear mixed models to account for repeated outcome measures with adjustment for clinicodemographic covariates.

For the analysis of our **tertiary objective** , we will conduct a stepwise multivariable analysis to explore covariant swallow morphometrics associated with change in dysphagia grade and cervical extension after MT using the published CASM method. Swallow coordinates from all frames of pre- and post-MT MBS studies and covariates (time, bolus type, $DIGEST_{pre}$, ΔDIGEST, age, sex, tumor site, surgery, ΔCROM, $CROM_{post}$) will be specified in MorphoJ, an integrated morphometric software program, for stepwise analysis: 1) canonical variate analysis (CVA) to identify and rank covariates associated with swallow morphometric changes in patients improved/stable dysphagia (ΔDIGEST), 2) *post hoc* discriminant function analysis will be conducted next to visualize treatment-specific eigenvectors of swallowing muscle motion differences by covariates of interest from CVA (e.g., pre-post MT), and 3) morphometric regression to estimate post-RT eigenvectors associated with change in swallow severity per DIGEST and pre-post MT conditions. For CVA of k variables (12 coordinates motion) in G groups (DIGEST, MT), the total sample size must be larger than [(2k-4) + (G-1)],(56) requiring 21 patients.

Exploratory analyses

Secondary endpoints of MDADI, MDASI-HN, lingual and jaw ROM, lymphedema/fibrosis staging, lingual and jaw ROM, PSS-HN, and MRI parameters will be assessed according to their distributions (continuous: paired *t*-test or non-parametric Wilcoxon signed-rank test, ordinal: rank-invariant). Effect sizes, such as Cohen's *d*, with 95% confidence intervals will be calculated for each endpoint and interpreted. Exploratory analyses and correlative questions will be considered for hypothesis-generating purposes only.

Discussion

The highly focused long-term objective of the MANTLE trial is to improve swallowing function in some of the worst dysphagia presentations in HNC survivorship - that is, those with severe late-RAD we have shown to be often treatment refractory. The focus on late-RAD represents a departure from most therapy trials for RAD that suffer from population heterogeneity as a consequence of enrolling both early and late-RAD patients jointly, where the pathophysiology and trajectory of dysphagia almost certainly differs. By explicitly studying manual therapy (MT) effects solely in late (>2 years) post-radiated survivors, this line of research offers specificity of target in examining the therapeutic potential of this commonly used, but rarely studied treatment modality. The endpoints are thoughtfully constructed to estimate effect sizes of various avenues of clinical benefit including mobility, functional change, QOL, and physical swallowing change. Any functional benefit for those with late-RAD could be meaningful as this represents a high burden, growing survivor population with disappointingly limited therapy options in current practice.

MANTLE was designed as a pilot study because we are trialing a novel therapy protocol intended for expansion to larger, confirmatory trials of efficacy or effectiveness in our program of research on radiation associated dysphagia. With the results of this pilot investigation, we expect to demonstrate that the novel MANTLE program is feasible and safe to examine in a larger program of research. Furthermore, we expect to estimate

effect sizes achieved in secondary endpoints that will be necessary for power calculations in future trials of efficacy or effectiveness. The diverse outcomes panel was selected specifically to understand which data collection procedures (i.e., functional measures, questionnaires, imaging) may be sensitive to possible changes with MT and merit inclusion in future, larger studies.

Strengths and Limitations

The ideal dosing of MT for this indication is unknown. The dosing schedule is based on prior clinical experience as well as the MT evidence base. Published cervical MT programs vary in intensity from 4+ sessions over 2-7 weeks in populations with neck/shoulder dysfunction (31-33) to 12 sessions over 4 weeks in non-HNC populations with fibrosis-related late effects in other body regions(57). The MANTLE program is designed with 10 sessions over 6 weeks of clinician-directed MT simultaneous with the implementation of cervical HEP. Relative to other cervical MT programs in the literature, this represents a fairly intense manual therapy schedule to match the known pathophysiology and duration of injury of the target population with late-RAD. The MANTLE therapy schedule is intentionally titrated using a scaffold approach in therapy schedule to offer more frequent upfront soft tissue manipulation while transitioning the patient to the independence of a HEP for maintenance. The investigators acknowledge that the therapy schedule developed for the MANTLE protocol may require further refinement as the results mature; however, 10 sessions over 6 weeks were judged by the investigators to represent a time interval during which therapy response should be detectable. Future directions of this trial might include adjusting the dosing of MT and HEP to achieve similar results.

The aims and outcome measures are thoughtfully constructed to provide pilot data regarding the feasibility/safety (Aim 1), dose and durability (Aim 2), and functional translation (Aim 3) of MANTLE as an adjunctive therapeutic modality for late-RAD. Upon completion of Aim 1, we expect to show a therapy completion rate of 75% as a marker of feasibility. For Aim 2, we expect to demonstrate that cervical range of

motion can improve within 10 sessions of MANTLE in at least 80% of HNC survivors with late-RAD. Aim 3 will provide effect sizes estimates of swallowing function changes after MANTLE. In this pilot trial, we expect to observe attrition <25%, adherence >60%, no therapy-related grade ≥3 adverse events, and sufficient power to estimate Cohen's *d* effect size ≥0.50 for the primary secondary endpoint of interest CROM.

Cervical measurements are challenging to obtain in the Late-RAD population when severe cervical postural abnormalities are present. In order to achieve a more neutral or upright head position, cervical extension is required in the upper cervical, lower cervical, and upper thoracic spine. Due to the severity of head drop in the pilot data, we were unable to measure upper cervical movement in isolation to capture degree of head drop or forward head posture. Measurements were out of range and could not be obtained with a traditional or Q-ROM computer-generated goniometer due to the degree of lower cervical flexion. Valid and reliable tools to measure forward head posture (FHP) in other populations such as craniovertebral angle measures merit exploration in future research in HNC survivors (58). The omission such postural measures and upper cervical extension/dorsal glide as an evaluation measurement is a limitation; it was recognized and accounted for by implementing dedicated stretching and strengthening exercises to target upper cervical spinal movements to improve FHP, if present.

Exploring functional endpoints of the therapeutic trial, we expect to also evaluate mechanism of functional change in swallowing (per DIGEST), muscle motion parameters (per CASM) associated with functional swallowing improvements (per DIGEST) using radiographic MBS studies. The post-MANTLE MBS is conducted immediately following 6 weeks of MT. Even healthy individuals may require 8 to 12 weeks to see functional improvement with stretching and strengthening (59, 60). As such, the post-MANTLE MBS after just 6 weeks of therapy may be earlier than maximal benefit is achieved. Nonetheless, at 6 weeks, any change detected on MBS could be more directly attributed to the MANTLE therapy prior to the wash-out period and may reflect

stimulability in the tissue.

The final data collection is 12 weeks after starting MANTLE. While long-term follow-up of dysphagia progression after MANTLE is not feasible in the timeframe of this pilot trial, any positive changes in CROM, patient-reported outcomes, soft tissue (per MRI), or radiographic or perceived swallowing function is likely meaningful because late-RAD is currently considered a treatment refractory toxicity syndrome.

Future Directions

If proven safe and feasible, future studies will need to address/investigate efficacy, effectiveness, sustainability of therapeutic gains, ideal schedules, frequency and combination of MT techniques, and best matching of mobility focused MT with direct functional therapies. For instance, might MANTLE prime the patient with late-RAD to achieve better functional gains during a bolus driven paradigm like the McNeil Dysphagia Therapy Program (61)? Future considerations should also include remote practice as it is rapidly expanding in the era of the COVID pandemic. With this in mind, it will become even more important to understand the outcome of the cervical HEP alone (without soft tissue manipulation as it is used in MANTLE) among patients with RAD who may not be able to access in-person clinical services for soft tissue manipulation. We believe that the proposed MANTLE trial could provide pilot data that might justify practice-changing clinical trials for the growing number of HNC survivors who have no proven options to manage late-RAD

Declarations

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Author contributions

All listed co-authors read and approved the manuscript, and performed the following:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of trial concept and data;

2. Drafting the work or revising it critically for important intellectual content;

3. Final approval of the version to be published;

4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Specific individual contributions in addition to all criteria above are listed as follows:

KH- Principal Investigator; Corresponding/primary author; conceived, coordinated, and directed all study activities, responsible for data collection, project integrity, manuscript content and editorial oversight and correspondence; direct oversight of study personnel.

HM- Manual therapy lead; developed MANTLE therapy program; trained MANTLE clinicians

SB – Operationalization and refinement of data collection procedure, primary trial manager.

KH, HM, CPB, KS, KW, SYL, CDF - Direct patient care provision, direct outcomes assessment and development and refinement of clinical data collection procedures.

CW- Developed statistical analysis plan.

CDF, JW - Responsible for programmatic and infrastructure oversight for MRI analysis and DICOM segmentation; direct and final oversight of MRI data collection; direct oversight of trainee personnel.

SYL - Direct and final oversight of surgical data collection.

KW – Direct and final oversight of EMG data collection.

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Ethics and Consent to Participate

The research protocol and informed consent document was approved by the Institutional Review Board at the University of Texas MD Anderson Cancer Center. The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312). The MANTLE research protocol was activated July 12, 2018 after IRB approval (2018-0052). The trial was prospectively registered with ClinicalTrials.gov on July 26, 2018 and first posted on ClinicalTrials.gov August 2, 2018 prior to enrollment of the first study participant on Aug 6, 2018 with projected study completion date in April, 2021.

Consent for publication: all authors provide consent for publication.

Competing interests: the authors declare no competing interests:

Availability of data and materials: not applicable

Figure Legends

Figure 1. Cervical extension and aspiration improved in case example after manual therapy.

Exemplar case before (top) and after (bottom) single session of MT 18 years post-treatment, surgery and radiotherapy for head and neck cancer. Note red arrows on modified barium swallow study depicting residual bolus in pharynx directed anteriorly toward airway with cervical posture in resting forward head drop (top), and directed posteriorly toward esophagus with cervical extension improved (bottom). While neither swallowing function or nor cervical biomechanics is normalized or ideal, functional gains were observed.

Figure 2. MANTLE trial schema.

Abbreviations: HNC, head and neck cancer; RT, radiotherapy; RAD, radiation associated dysphagia; MT, manual therapy; CROM, cervical range of motion; MBS, modified barium swallow; MRI, magnetic resonance imaging; PROs, patient reported outcomes

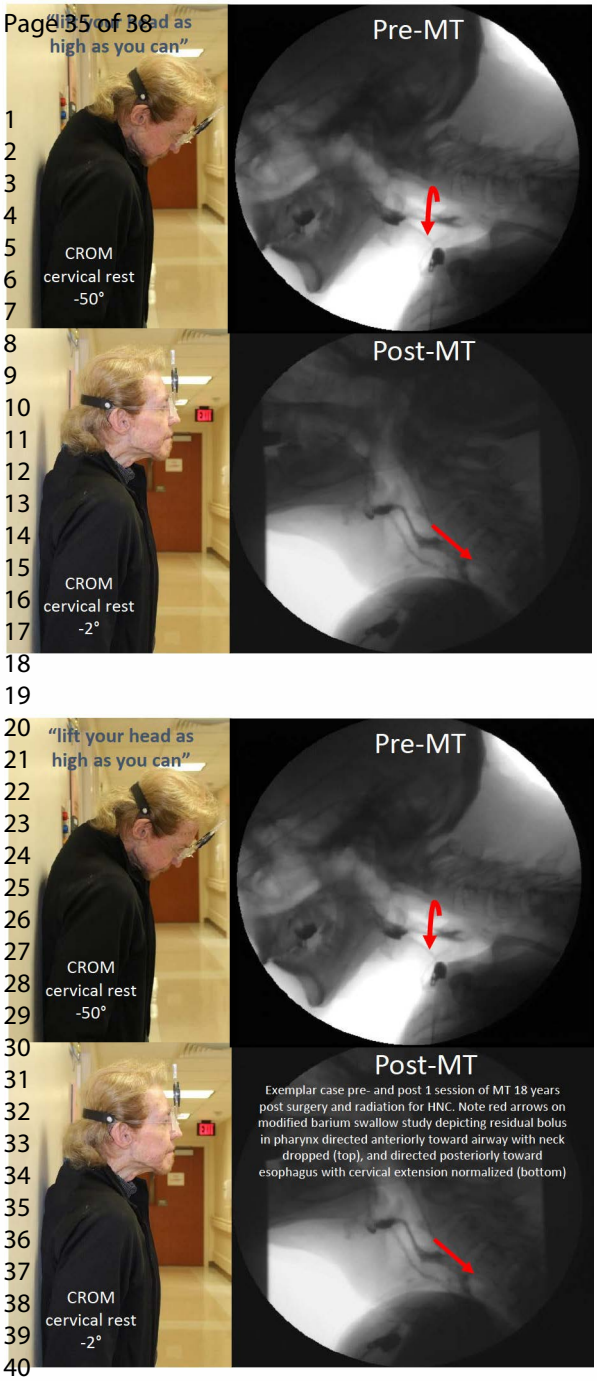
References (Vancouver)

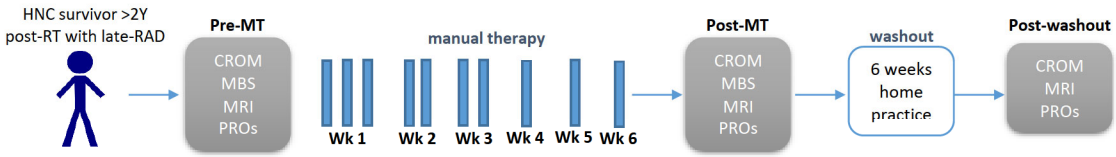
1. Hunter KU. Toxicities affecting quality of life after chemo-IMRT of oropharyngeal cancer: prospective study of patient-reported, observer-rated, and objective outcomes. Int J Radiat Oncol Biol Phys. 2013;85.
2. Eisbruch A, Kim HM, Feng FY, Lyden TH, Haxer MJ, Feng M, et al. Chemo-IMRT of oropharyngeal cancer aiming to reduce dysphagia: swallowing organs late complication probabilities and dosimetric correlates. Int J Radiat Oncol Biol Phys. 2011;81(3):e93-9.
3. Xu B, Boero IJ, Hwang L, Le QT, Moiseenko V, Sanghvi PR, et al. Aspiration pneumonia after concurrent chemoradiotherapy for head and neck cancer. Cancer. 2015;121(8):1303-11.
4. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol. 2011;29(32):4294-301.
5. Awan MJ. Late radiation-associated dysphagia (late-RAD) with lower cranial neuropathy after oropharyngeal radiotherapy: a preliminary dosimetric comparison. Oral Oncol. 2014;50.
6. M. D. Anderson Head Neck Cancer Symptom Working Group. Beyond mean pharyngeal constrictor dose for beam path toxicity in non-target swallowing muscles: Dose-volume correlates of chronic radiation-associated dysphagia (RAD) after oropharyngeal intensity modulated radiotherapy. Radiother Oncol. 2016;118(2):304-14.
7. Kamal M, Mohamed ASR, Volpe S, Zaveri J, Barrow MP, Gunn GB, et al. Radiotherapy dose-volume parameters predict videofluoroscopy-detected dysphagia per DIGEST after IMRT for oropharyngeal cancer: Results of a prospective registry. Radiother Oncol. 2018;128(3):442-51.
8. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tan PF, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. The New England journal of medicine. 2010;363(1):24-35.
9. Fakhry C, Westra WH, Li S, Cmelak A, Ridge JA, Pinto H, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst. 2008;100(4):261-9.
10. Weinberger PM, Yu Z, Haffty BG, Kowalski D, Harigopal M, Brandsma J, et al. Molecular classification identifies a subset of human papillomavirus--associated oropharyngeal cancers with favorable prognosis. J Clin Oncol. 2006;24(5):736-47.
11. Caudell JJ, Schaner PE, Meredith RF, Locher JL, Nabell LM, Carroll WR, et al. Factors associated with long-term dysphagia after definitive radiotherapy for locally advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2009;73(2):410-5.
12. Hutcheson KA, Lewin JS, Barringer DA, Lisec A, Gunn GB, Moore MW, et al. Late dysphagia after radiotherapy-based treatment of head and neck cancer. Cancer. 2012;118(23):5793-9.
13. Awan MJ, Mohamed AS, Lewin JS, Baron CA, Gunn GB, Rosenthal DI, et al. Late radiation-associated dysphagia (late-RAD) with lower cranial neuropathy after oropharyngeal radiotherapy: a preliminary dosimetric comparison. Oral Oncol. 2014;50(8):746-52.
14. Hutcheson KA. Late radiation-associated dysphagia (RAD) in head and neck cancer survivors. Perspectives on Swallowing and Swallowing Disorders (Dysphagia), 22 (2), 61–72. 2013.
15. Hutcheson KA, Yuk M, Hubbard R, Gunn GB, Fuller CD, Lai SY, et al. Delayed lower cranial neuropathy after oropharyngeal intensity-modulated radiotherapy: A cohort analysis and literature review. Head Neck. 2017.

16. Aggarwal P, Zaveri JS, Goepfert RP, Shi Q, Du XL, Swartz M, et al. Swallowing-related outcomes associated with late lower cranial neuropathy in long-term oropharyngeal cancer survivors: cross-sectional survey analysis. Head & neck. 2019;41(11):3880-94.
17. Hutcheson KA. Late Radiation-Associated Dysphagia (RAD) in Head and Neck Cancer Survivors. Perspectives on Swallowing and Swallowing Disorders (Dysphagia). 2013;22(2):11.
18. Rubin EB, Buehler AE, Halpern SD. States worse than death among hospitalized patients with serious illnesses. JAMA internal medicine. 2016;176(10):1557-9.
19. Langmore SE, McCulloch TM, Krisciunas GP, Lazarus CL, Van Daele DJ, Pauloski BR, 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:E1221-31.
20. Hutcheson KA, Kelly S, Weber RS, Lewin JS. Offering more for persistent dysphagia after head and neck cancer: The evolution of boot camp swallowing therapy. Combined Otolaryngology Spring Meeting; Boston, MA2015.
21. Van Daele DJ, Langmore SE, Krisciunas GP, Lazarus CL, Pauloski BR, McCulloch TM, et al. The impact of time after radiation treatment on dysphagia in patients with head and neck cancer enrolled in a swallowing therapy program. Head & neck. 2019;41(3):606-14.
22. Hutcheson KA, Yuk MM, Holsinger FC, Gunn GB, Lewin JS. Late radiation-associated dysphagia (late-RAD) with lower cranial neuropathy in long-term oropharyngeal cancer survivors: Video case reports. Head Neck. 2014.
23. Ghiam MK, Mannion K, Dietrich MS, Stevens KL, Gilbert J, Murphy BA. Assessment of musculoskeletal impairment in head and neck cancer patients. Support Care Cancer. 2017.
24. Stubblefield MD. Radiation fibrosis syndrome: neuromuscular and musculoskeletal complications in cancer survivors. PM & R : the journal of injury, function, and rehabilitation. 2011;3(11):1041-54.
25. Silbergleit AK, Schultz L, Krisciunas G, Langmore S. Association of Neck Range of Motion and Skin Caliper Measures on Dysphagia Outcomes in Head and Neck Cancer and Effects of Neck Stretches and Swallowing Exercises. Dysphagia. 2020;35(2):360-8.
26. Rowin J, Cheng G, Lewis SL, Meriggioli MN. Late appearance of dropped head syndrome after radiotherapy for Hodgkin's disease. Muscle & nerve. 2006;34(5):666-9.
27. 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):425-31.
28. Gross AR, Hoving JL, Haines TA, Goldsmith CH, Kay T, Aker P, et al. A Cochrane review of manipulation and mobilization for mechanical neck disorders. Spine (Phila Pa 1976). 2004;29(14):1541-8.
29. Gross AR, Kay T, Hondras M, Goldsmith C, Haines T, Peloso P, et al. Manual therapy for mechanical neck disorders: a systematic review. Manual therapy. 2002;7(3):131-49.
30. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ. 2014;348:g1687.
31. Page MJ, Green S, Kramer S, Johnston RV, McBain B, Chau M, et al. Manual therapy and exercise for adhesive capsulitis (frozen shoulder). Cochrane Database Syst Rev. 2014(8):Cd011275.
32. Camargo PR, Alburquerque-Sendin F, Avila MA, Haik MN, Vieira A, Salvini TF. Effects of Stretching and Strengthening Exercises, With and Without Manual Therapy, on Scapular

Kinematics, Function, and Pain in Individuals With Shoulder Impingement: A Randomized Controlled Trial. J Orthop Sports Phys Ther. 2015;45(12):984-97.
33. Trott CA, Ruiz Aguila ME, Leaver AM. The clinical significance of immediate symptom responses to manual therapy treatment for neck pain: observational secondary data analysis of a randomized trial. Manual therapy. 2014;19(6):549-54.
34. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. Journal of Biomedical Informatics. 2009;42(2):377-81.
35. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. Journal of Biomedical Informatics. 2019;95:103208.
36. Youdas JW, Garrett TR, Suman VJ, Bogard CL, Hallman HO, Carey JR. Normal range of motion of the cervical spine: an initial goniometric study. Phys Ther. 1992;72:770-.
37. Dijkstra PU, Huisman PM, Roodenburg JL. Criteria for trismus in head and neck oncology. Int J Oral Maxillofac Surg. 2006;35(4):337-42.
38. Lazarus CL, Husaini H, Jacobson AS, Mojica JK, Buchbinder D, Okay D, et al. Development of a new lingual range-of-motion assessment scale: normative data in surgically treated oral cancer patients. Dysphagia. 2014;29(4):489-99.
39. Deng J, Ridner SH, Wells N, Dietrich MS, Murphy BA. Development and preliminary testing of head and neck cancer related external lymphedema and fibrosis assessment criteria. European journal of oncology nursing : the official journal of European Oncology Nursing Society. 2015;19(1):75-80.
40. Deng J, Dietrich MS, Ridner SH, Fleischer AC, Wells N, Murphy BA. Preliminary evaluation of reliability and validity of head and neck external lymphedema and fibrosis assessment criteria. European journal of oncology nursing : the official journal of European Oncology Nursing Society. 2016;22:63-70.
41. Common Terminology Criteria for Adverse Events (CTCAE). v4.03 ed. Bethesda, MD: National Institutes of Health, National Cancer Institute, Department of Health and Human Services; 2010.
42. Lewin JS, Hutcheson KA, Barringer DA, Smith BG. Preliminary experience with head and neck lymphedema and swallowing function in patients treated for head and neck cancer. Perspectives on Swallowing and Swallowing Disorders Dysphagia. 2010;19:45-52.
43. Rosenbek JC, Robbins JA, Roecker EB, Coyle JL, Wood JL. A penetration-aspiration scale. Dysphagia. 1996;11(2):93-8.
44. Schwertner RW, Garand KL, Pearson WG, Jr. A Novel Imaging Analysis Method for Capturing Pharyngeal Constriction During Swallowing. Journal of imaging science. 2016;1(1).
45. Pearson WG, Jr., Taylor BK, Blair J, Martin-Harris B. Computational analysis of swallowing mechanics underlying impaired epiglottic inversion. Laryngoscope. 2016;126(8):1854-8.
46. Ding Y, Mohamed AS, Yang J, Colen RR, Frank SJ, Wang J, et al. Prospective observer and software-based assessment of magnetic resonance imaging quality in head and neck cancer: Should standard positioning and immobilization be required for radiation therapy applications? Pract Radiat Oncol. 2015;5(4):e299-308.
47. Messer JA, Mohamed AS, Hutcheson KA, Ding Y, Lewin JS, Wang J, et al. Magnetic resonance imaging of swallowing-related structures in nasopharyngeal carcinoma patients receiving IMRT: Longitudinal dose-response characterization of quantitative signal kinetics. Radiother Oncol. 2016;118(2):315-22.

48. Perlman AL, Palmer PM, McCulloch TM, Vandaele DJ. Electromyographic activity from human laryngeal, pharyngeal, and submental muscles during swallowing. Journal of applied physiology (Bethesda, Md : 1985). 1999;86(5):1663-9.
49. Preston DC, Barbara E. Shapiro. Electromyography and Neuromuscular Disorders: Clinical-Electrophysiologic Correlations. 3rd ed: Saunders; 2013 2013.
50. Chen AY, Frankowski R, Bishop-Leone J, Hebert T, Leyk S, Lewin J, et al. The development and validation of a dysphagia-specific quality-of-life questionnaire for patients with head and neck cancer: the M. D. Anderson dysphagia inventory. Arch Otolaryngol Head Neck Surg. 2001;127(7):870-6.
51. Cleeland CS, Mendoza TR, Wang XS, Chou C, Harle MT, Morrissey M, et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. Cancer. 2000;89(7):1634-46.
52. Rosenthal DI, Mendoza TR, Chambers MS, Asper JA, Gning I, Kies MS, et al. Measuring head and neck cancer symptom burden: the development and validation of the M. D. Anderson symptom inventory, head and neck module. Head Neck. 2007;29(10):923-31.
53. Rosenthal DI, Mendoza TR, Fuller CD, Hutcheson KA, Wang XS, Hanna EY, et al. Patterns of symptom burden during radiotherapy or concurrent chemoradiotherapy for head and neck cancer: a prospective analysis using the University of Texas MD Anderson Cancer Center Symptom Inventory-Head and Neck Module. Cancer. 2014;120(13):1975-84.
54. Deng J, Ridner SH, Murphy BA, Dietrich MS. Preliminary development of a lymphedema symptom assessment scale for patients with head and neck cancer. Support Care Cancer. 2012;20(8):1911-8.
55. List MA, Ritter-Sterr C, Lansky SB. A performance status scale for head and neck cancer patients. Cancer. 1990;66(3):564-9.
56. Webster MA, Sheets HD. A practical introduction to landmark-based geometric morphometrics. Quantitative Method Paleobio. 2010;16:168-88.
57. Cho Y, Do J, Jung S, Kwon O, Jeon JY. Effects of a physical therapy program combined with manual lymphatic drainage on shoulder function, quality of life, lymphedema incidence, and pain in breast cancer patients with axillary web syndrome following axillary dissection. Support Care Cancer. 2016;24(5):2047-57.
58. Shaghayegh Fard B, Ahmadi A, Maroufi N, Sarrafzadeh J. Evaluation of forward head posture in sitting and standing positions. Eur Spine J. 2016;25(11):3577-82.
59. Jones DA, Rutherford OM. Human muscle strength training: the effects of three different regimens and the nature of the resultant changes. J Physiol. 1987;391:1-11.
60. Seo MW, Jung HC, Song JK, Kim HB. Effect of 8 weeks of pre-season training on body composition, physical fitness, anaerobic capacity, and isokinetic muscle strength in male and female collegiate taekwondo athletes. J Exerc Rehabil. 2015;11(2):101-7.
61. Carnaby-Mann GD, Crary MA. McNeill dysphagia therapy program: a case-control study. Archives of physical medicine and rehabilitation. 2010;91(5):743-9.





CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	Title, 1, 2, 7, 20
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	7
	2b	Specific objectives or research questions for pilot trial	7
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	8
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	13, 17
Participants	4a	Eligibility criteria for participants	8-9
	4b	Settings and locations where the data were collected	8-9
	4c	How participants were identified and consented	8,11
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9-10, Table 1
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	11-16
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	N/A
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	N/A
Sample size	7a	Rationale for numbers in the pilot trial	19
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	N/A
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	N/A
Allocation concealment	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	N/A

mechanism			
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	N/A
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	N/A
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	17-20
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	N/A
	13b	For each group, losses and exclusions after randomisation, together with reasons	N/A
Recruitment	14a	Dates defining the periods of recruitment and follow-up	N/A
	14b	Why the pilot trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	N/A
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	N/A
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	N/A
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
	19a	If relevant, other important unintended consequences	N/A
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	21-23
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	20-21.23
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	N/A
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	23
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	1
Protocol	24	Where the pilot trial protocol can be accessed, if available	16, 25
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	25
	26	Ethical approval or approval by research review committee, confirmed with reference number	26

Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.
*We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.