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State of Rehabilitation Research in the Head and Neck Cancer Population: Functional Impact vs. Impairment-Focused Outcomes

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Abstract

Purpose of Review Management of head and neck cancer (HNC) typically involves a morbid combination of surgery, radiation, and systemic therapy. As the number of HNC survivors grows, there is growing interest in rehabilitation strategies to manage HNC-related comorbidity. In this review, we summarize the current state of HNC rehabilitation research.

Recent Findings We have organized our review using the World Health Organization's International Classification of Function (ICF) model of impairment, activity, and participation. Specifically, we describe the current research on rehabilitation strategies to prevent and treat impairments including dysphagia, xerostomia, dysgeusia, dysosmia, odynophagia, trismus, first bite syndrome, dysarthria, dysphonia, lymphedema, shoulder syndrome, cervicalgia, cervical dystonia and dropped head syndrome, deconditioning, and fatigue. We also discuss the broader impact of HNC-related impairment by exploring the state of rehabilitation literature on activity, participation, psychosocial distress, and suicidality in HNC survivors.

Summary We demonstrate that research in HNC rehabilitation continues to focus primarily on impairment-driven interventions. There remains a dearth of HNC rehabilitation studies directly examining the impact of rehabilitation interventions on outcomes related to activity and participation. More high-quality interventional studies and reviews are needed to guide prevention and treatment of functional loss in HNC survivors.

Keywords Head and neck neoplasms · Rehabilitation · Quality of life · Speech · Pain · Function

Introduction

The American Joint Committee on Cancer defines head and neck cancer (HNC) as a group of malignancies that involve the "mucosal surfaces of the upper aerodigestive tract, including the oral cavity, pharynx, larynx, and paranasal sinuses, as well as cancers of the major and minor salivary glands" [1]. HNC is consistently one of the top ten most prevalent cancer types [2], comprising more than 4% of new cases of cancer worldwide in 2020 [3].

In the USA, the death rate from all cancer types has fallen precipitously from its peak in 1991 due to multiple factors including improved treatment and successful public health campaigns designed to increase early detection and reduce smoking [4]. Mortality due to HNC has also declined with changing demographics of the disease itself [2]. Most notably, human papilloma virus (HPV)–associated HNCs, which mainly affect the oropharynx and oral cavity, have increased in incidence, whereas cancers of the floor of the mouth and hypopharynx, which are associated with tobacco and alcohol

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use, have decreased [2]. HPV-positive malignancies tend to be more sensitive to treatment [2], and patients with HPV-positive disease tend to be younger and have fewer comorbidities [2]. As such, the 5-year overall survival for HNC is now greater than 60% [5].

Management of HNC typically involves a morbid combination of surgery, radiation, and systemic therapy. Unfortunately, each treatment modality has the potential to compromise function and quality of life (Fig. 1).

Radiation therapy (RT) causes both acute toxicity and late effects that can progress to impact function, even years after exposure (Fig. 2) [6, 7]. RT causes a process known as radiation fibrosis (RF), a progressive sclerosis of tissues within the radiation field, including bone, nerve, muscle, connective tissue, and visceral structures (Fig. 3). Any neural structure within the radiation field can be affected including the spinal cord, cervical (and upper thoracic) nerve roots, plexuses (brachial and cervical), peripheral nerves (cranial), and muscles. Such damage is termed "myelo-radiculo-plexo-neuro-myopathy" [6–9]. Cranial mononeuropathies are also common with at least one affected nerve injury identified in as many as 85% of patients treated for nasopharyngeal cancer and 14% of combined HNC survivors [10, 11]. Time from treatment is a major factor in the presentation and progression of RF [8–12]. The clinical manifestations resulting from RF are termed radiation fibrosis syndrome (RFS). RFS contributes to many functional impairments including dysphagia, dysarthria, trismus, lymphedema, shoulder dysfunction, cervicalgia and dropped head syndrome, cancer-related fatigue, and deconditioning, among others [13].

The surgical approach and extent of dissection also relate directly to acute and chronic impairments observed in HNC survivors. Historically, radical neck dissections (RNDs) involved the gross total resection of regional lymph nodes, the sternocleidomastoid muscle, the jugular vein, and the spinal accessory nerve [14]. Fortunately, selective neck dissection (SND), a procedure that

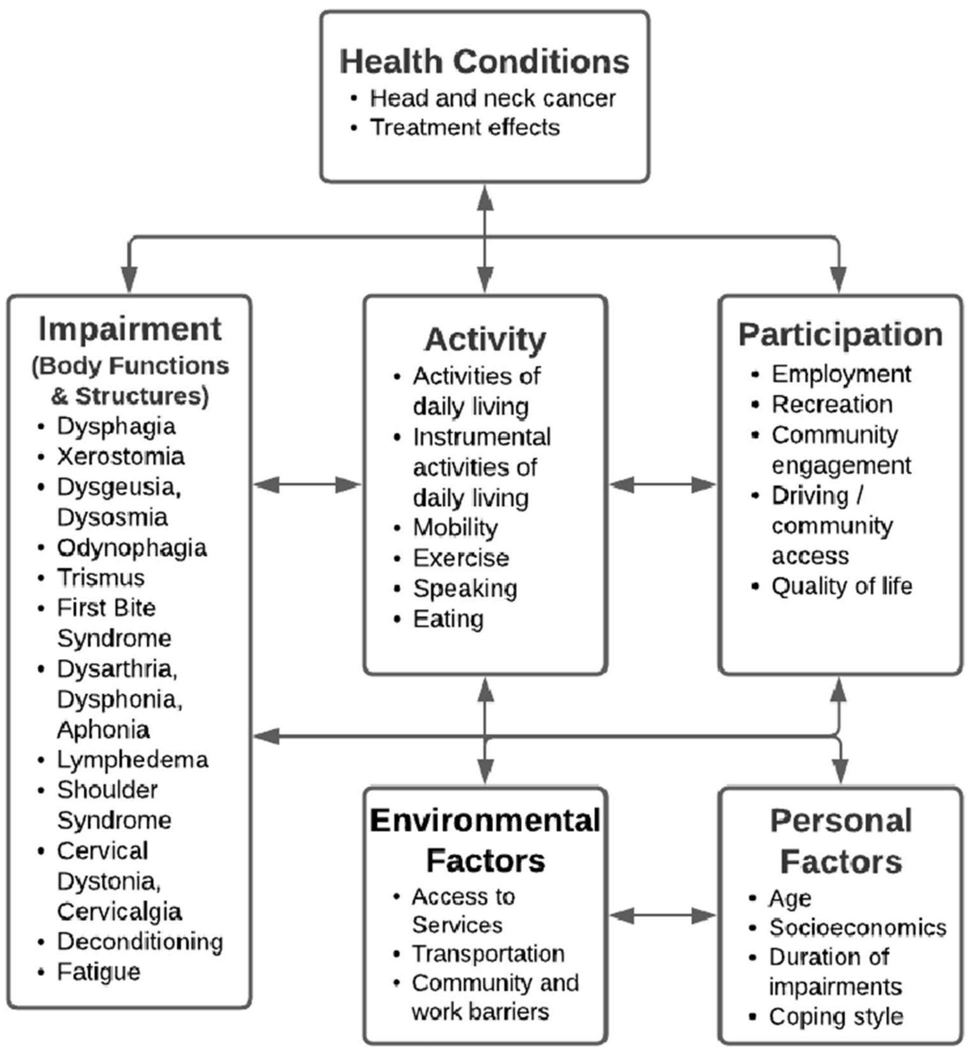

Fig. 1 Adaptation of the *International Classification of Functioning* framework for head and neck cancer survivors. The configuration has been altered from standard formatting to highlight the plethora of functional impairments in this population

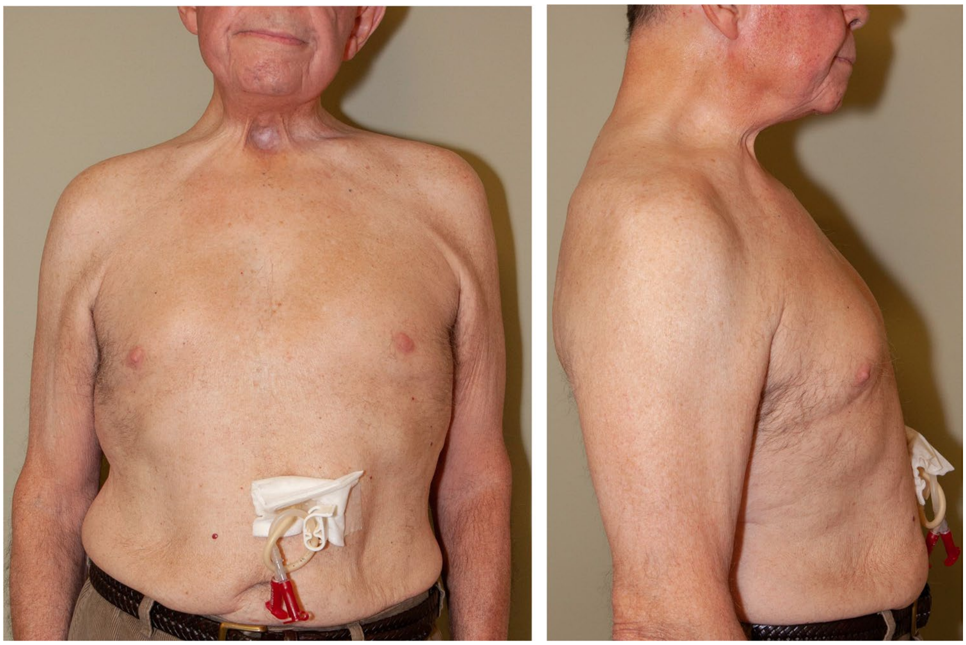

Fig. 2 A 76-year-old man with a history of squamous cell carcinoma of the base of the left tongue diagnosed 9 years previously. He was treated with cisplatin and intensity-modulated radiation therapy with 5400 cGy in 30 fractions to the tongue base and upper cervical lymphatics and 5000 cGy in 25 fractions to the low anterior neck. He has severe radiation fibrosis syndrome with myelo-radiculo-plexo-neuro-myopathy, cervical dystonia, trismus, face and neck lymphedema, dysphagia, and dysphonia. Note the marked cervical and thoracic atrophy, including the upper pectoral muscles indicating significant neuromuscular damage to the cervical nerve roots, brachial plexus, and peripheral nerves and muscles encompassed by the radiation field. The protraction and tilt of his head with circumferential atrophy and induration of the neck is what is expected in radiation-induced cervical dystonia. There is lymphedema of the face and neck anteriorly. He is unable to safely eat and has a peg for nutrition

preserves neurovascular and muscular structures when feasible, is now often the preferred surgical approach [15]. Surgical intervention can result in spinal accessory neuropathy (SAN), shoulder droop, cervical dystonia, neuropathies, lymphedema, and adhesive capsulitis [16–18].

As the number of HNC survivors grows, there has been a corresponding increase in associated functional loss. There has also been growing interest in rehabilitation strategies to improve functional outcomes in HNC survivors [19]. Our previously published scoping review identified 150 observational studies and 35 controlled studies on HNC rehabilitation between 1990 and 2017 [19]. The publication rate over the study timeframe increased by 390%, with more than half of the articles published after 2010. Since the publication of our scoping review, interventional studies on the topic of HNC rehabilitation have continued to increase [pending publication Cheng et al.].

Here we provide an update on rehabilitation research in the HNC population since the conclusion of our scoping review in 2017. We also highlight seminal works regarding rehabilitation interventions for the treatment of specific impairments. We have organized our review of HNC rehabilitation interventions using the World Health Organization's International Classification of Function (ICF) model of impairment, activity limitation, and participation restriction (Fig. 1) [20].

Impairments

Dysphagia

Dysphagia, or difficulty swallowing, is the most common symptom impacting eating in HNC survivors [21] with a 2-year prevalence of 45% [22]. Those at highest risk are oropharyngeal cancer survivors treated within the preceding 2 years with high-dose radiation to swallowing structures [23] and those with subsequent lymphedema [24].

Preventing dysphagia is an area of growing interest. The vast majority of exercise-based prevention programs for dysphagia in a recent review had positive outcomes; however, the optimal protocol is unclear [25]. Potential protocols range from general oral stretches to swallowing-specific exercises such as Mendelsohn's maneuver and effortful swallow, Shaker, and Masako maneuvers [25].

For rehabilitation of dysphagia, evidence for swallowing exercises was previously inconclusive [26, 27], but a recent meta-analysis of 19 randomized controlled trials

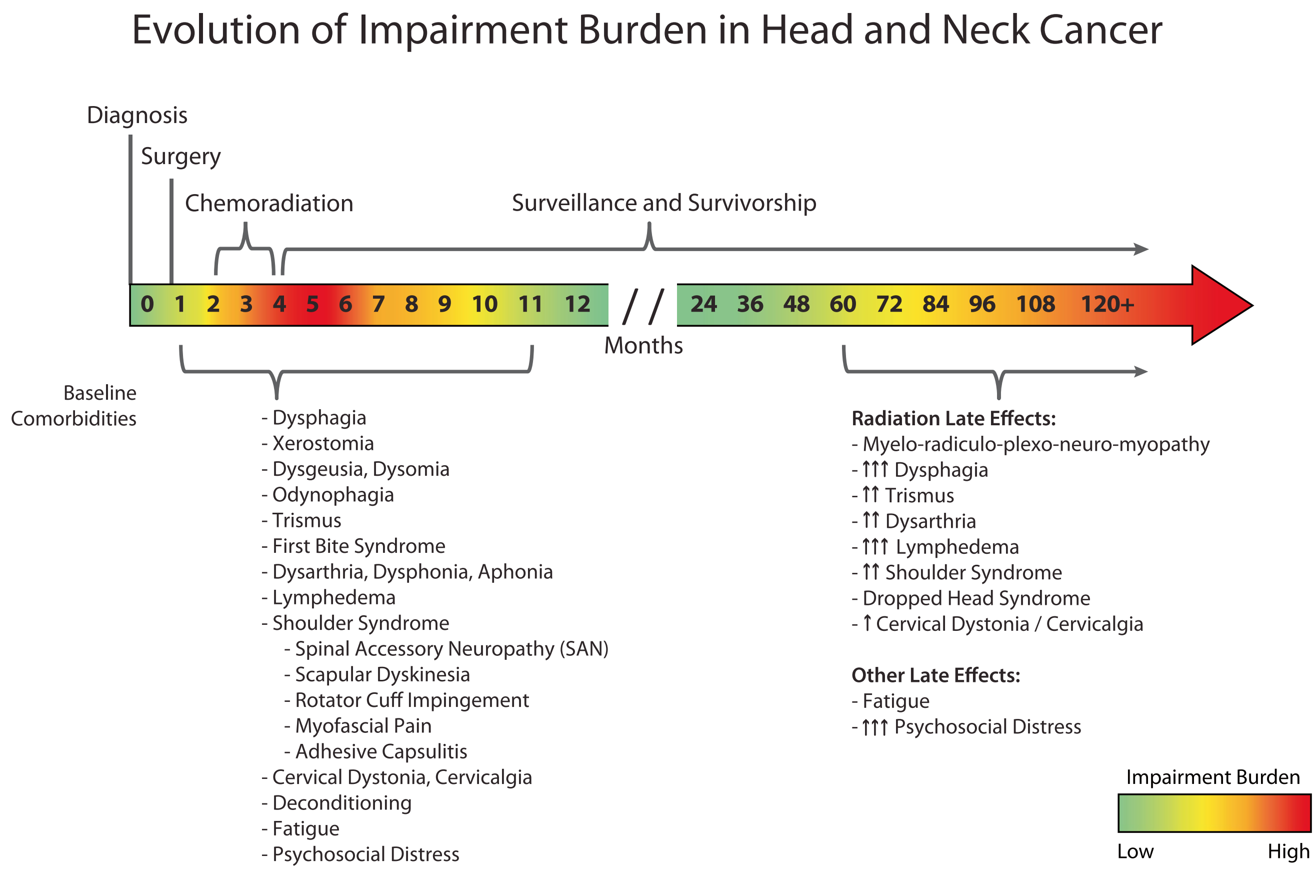

Fig. 3 Potential evolution of multiple impairments in head and neck cancers over time. Severity depends on the timing and type of treatment(s), baseline patient comorbidities, and other patient- and rehabilitation-related factors. In the treatment or early survivorship phases, many impairments result directly from acute treatment and tend to improve over time (e.g., post-surgical or post-radiation swelling and incomplete neurologic injuries). For other impairments, including those related to radiation fibrosis syndrome, a reoccurrence or worsening of symptoms from the immediate post-treatment phase is often observed and is combined with the emergence of delayed impairments (e.g., dropped head syndrome, progressive lymphedema, shoulder syndrome). This figure is not meant to represent an exhaustive list of impairments and acknowledges it is often the combination of impairments in the survivorship phase that leads to progressive disability and psychosocial distress

(RCTs) with 1100 HNC patients [28] has demonstrated swallowing-based exercises to be beneficial for treatment of dysphagia. Oral exercises also decreased aspiration in a small, high-quality RCT [29]. Incorporating behavioral change techniques such as practical social support, behavioral practice, self-monitoring of behavior, and presence of a credible source delivering the intervention may enhance intervention efficacy [30]. Adding biofeedback has not yet shown a clear benefit in a meta-analysis of 23 studies with extremely limited data and high variability [31]. Compensatory strategies such as changing posture [32], changing food and liquid consistencies [33, 34], and using intraoral prosthetics [35] are commonly employed to decrease aspiration risk [36] although with surprisingly limited evidence.

Xerostomia

Xerostomia, or dry mouth, can lead to sore throat, dental caries, altered taste, and worsening dysphagia in HNC survivors [37]. Although the advancement of the radiation technique has significantly decreased the incidence, up to 50% of patients treated with intensity-modulated radiation therapy (IMRT) still suffer from xerostomia [38, 39]. Preventatively, multiple interventions favor efficacy, but not clearly. For use of pilocarpine, a muscarinic receptor agonist, during radiation, a meta-analysis of 6 RCTs all published before 2010 showed a significant increase in unstimulated salivary flow rate in 3 of the studies, clinician-rated xerostomia, and patient-reported xerostomia, all around 3–6 months post-treatment, but no effects on stimulated salivary flow rate

[40]. In comparison, a larger older systematic review including many of the same studies concluded that no guideline recommendation for pilocarpine use during radiotherapy could be made due to mixed evidence from RCTs [41]. Likewise, amifostine, a free radical scavenger, has similar low-quality evidence supporting an efficacy similar to that of pilocarpine in a 2017 Cochrane review [42]. A more recent randomized double-blind trial that closed prematurely due to slow patient accrual did not support amifostine pretreatment before radiation to reduce xerostomia and showed more severe acute non-salivary radiation toxicity in the amifostine group [43]. Acupuncture is safe and feasible, although without firm evidence, supporting routine use in a recent systematic review of 5 studies with large heterogeneity [44]. Photobiomodulation increased both unstimulated and stimulated salivary flows in a meta-analysis of 5 small clinical trials limited by high heterogeneity [45].

Restorative strategies mainly involve stimulating salivary secretion or artificial lubrication [41]. To stimulate salivary secretion, muscarinic agonists are often used, of which pilocarpine is the most recommended [39, 41, 46, 47], although a Cochrane review disputes its efficacy [42]. Acupuncture has been used for pilocarpine-resistant xerostomia [38, 48] with the most recent meta-analysis showing continued low-quality evidence for some benefits [49, 50]. Transcutaneous electrical nerve stimulation (TENS) over salivary glands and acupuncture-like transcutaneous nerve stimulation is safe, feasible, and potentially superior to pilocarpine due to lack of medication side effects [51]; however the optimal TENS setting is unknown [51, 52]. The use of artificial lubrication is common practice and recommended although with little evidence. Gustatory and masticatory stimulation by acidic substances and chewing gum is supported by limited evidence [38, 41, 53]. Mucosal lubricants and saliva substitutes are recommended for short-term relief [41] although recent trials show unclear benefits [54, 55] and the superiority of oral moisturizing jelly is questionable [56, 57]. An immunologically active saliva substitute, however, recently showed significant effectiveness in a double-blind randomized placebo-controlled trial [58]. Patients may also choose to frequently moisten their mouth with water, eat moist foods, and use a room humidifier [38, 59]. Integrative treatments of photobiomodulation [60, 61], hyperbaric oxygen therapy [39, 62, 63], herbs [64–66], honey [67], and zinc [68] have been increasing, although there is inconclusive evidence due to limited high-quality RCTs with small sample sizes. Stem cell and gene therapy for xerostomia are under investigation although heretofore without published human trials [38].

Dysgeusia

Dysgeusia, or taste alteration, is another common impairment that impacts eating in HNC; its prevalence is about 25% [69]. Contributing factors include radiation [70], glossectomy [71], reduced saliva [72], and chorda tympani or taste bud damage [73]. Evidence for both prevention and management of dysgeusia is lacking. A recent scoping review proposed a dysgeusia management algorithm based on minimal mixed evidence for various supplements, anti-xerostomia agents, nutrition interventions, oral care, dietary counseling, and swallowing exercises [74]. Zinc supplementation has contradictory evidence [70, 74].

Dysosmia

Dysosmia, or disordered smell perception, is also common and impacts eating and appetite [72]. Although dysosmia is poorly studied in the rehabilitation literature, a recent small RCT of limited quality showed long-term improvements with olfactory rehabilitation using the nasal airflow-inducing maneuver, or “polite yawning” with the mouth closed [75].

Odynophagia

Many other cancer- and treatment-related effects contribute to difficulty eating in HNC including odynophagia from oral mucositis [23], which occurs in virtually all patients treated with radiation [76] and can also be chemotherapy induced. The prevalence and difficulty of adequate relief have made the study of its prevention and treatment of great interest. In addition to maintaining good oral hygiene, preventative interventions including keratinocyte growth factor [77], low-level laser therapy [78–80], honey [81, 82], curcumin [83], and glutamine [84] mostly decrease the incidence of severe oral mucositis although not necessarily the overall incidence in recent meta-analyses. The latter four agents also alleviate pain from oral mucositis [80–84].

Additional agents for controlling pain from oral mucositis includes topical morphine [85], benzydamine [80], sodium bicarbonate mouthwash [80], chlorhexidine [80], diphenhydramine-lidocaine-antacid mouthwash [86], and methadone [86], which have shown efficacy in recent reviews and meta-analyses. For intractable pain due to oral mucositis, methylene blue oral rinse shows promise with clinically dramatic efficacy in a recent large cohort study [87]. Among other confounders, the efficacy of these interventions can vary depending on whether the mucositis was radiation induced or induced by a specific chemotherapy agent [77, 80].

Trismus

Trismus, or inability to fully open the mouth, is a common complication of head and neck cancer and its treatment [13, 88]. It is commonly defined as maximal inter-incisal opening (MIO) of ≤ 35 mm [89]. HNC survivors with a large tumor near masticatory muscles are most likely to develop trismus [90]. A recent systematic review and meta-analysis including 2786 HNC survivors reports the prevalence of trismus to be 17.3% at baseline increasing to a peak of 44.1% at 6 months, decreasing to 32.1% at 12 months, and continuing at an average of 32.6% at 3–10 years.

Prevention of trismus and other radiation-induced late effects while maintaining or improving oncologic outcomes for HNC survivors is a key investigative focus. While jaw exercise is feasible and well-tolerated during radiotherapy treatment, multiple studies and systematic reviews have not demonstrated it to be effective in preventing trismus in this setting [91–94]. Surprisingly, the addition of the Dynasplint Trismus System® reduced compliance with therapeutic recommendations calling into question its potential as a modality to prevent trismus [95].

Although no rehabilitation strategies have been demonstrated to reliably prevent trismus, modifications to the HNC treatment strategy have impacted the prevalence of trismus. A recent systematic review and meta-analysis demonstrated that IMRT is significantly less likely to cause trismus than 2-dimensional radiotherapy [96]. Several recent systematic reviews and meta-analyses have suggested that intraoral stents may reduce oral complications, including trismus [97–100]. Higher mean radiation doses to the ipsilateral masticatory muscle group, lateral pterygoid, or masseter muscles are significantly associated with worsening mouth opening [101]. Limiting these structures to 40 Gy for tumors not invading the muscles of mastication may minimize risk of developing trismus. A randomized trial comparing transoral robotic surgery (TORS) with concurrent neck dissection to radiotherapy demonstrates more cases of trismus in the TORS plus neck dissection group (26%) compared to the radiotherapy group (3%) [102].

There is no clear consensus on optimal rehabilitation interventions to treat trismus in HNC survivors [103]. In patients with trismus, jaw exercise improves mouth opening [94]. The most effective timing of exercise intervention and the optimal protocol to improve trismus are not clear [92, 93]. Support of exercise interventions via telephone has positive effects on both adherence and outcomes [104]. While a variety of stretching devices are available to treat trismus in HNC survivors, there is no data supporting the efficacy of any device over another [103, 105, 106]. The TheraBite® jaw motion rehabilitation system (Atos Medical) did not demonstrate superiority to wooden spatulas in a randomized feasibility study [106, 107]. The intensity of the stretching protocol, pain during exercise, fitting issues, and medical deterioration present a challenge to compliance with jaw-stretching devices for many HNC survivors [106]. Botulinum toxin injections into the masseter may be beneficial as a component of multimodal management for trismus in HNC survivors [108].

First Bite Syndrome

First bite syndrome (FBS) results from loss of sympathetic innervation of the ipsilateral parotid gland, leaving it hypersensitive to parasympathetic stimulation [109]. This results in an intense and painful contraction of the parotid myoepithelial cells with initiation of mastication ("first bite") that improves with subsequent bites. Diagnosis of FBS is clinical. Direct injury to the cervical sympathetic trunk from parotid or parapharyngeal surgery is the most common cause of FBS in HNC [109, 110]. There are no recent interventional studies or reviews on rehabilitation strategies to prevent or treat FBS. Treatment evidence is limited to case reports/series and includes botulinum toxin injections and neuropathic pain medications [110, 111].

Dysarthria and Dysphonia

Difficulty speaking can be subdivided into dysarthria and dysphonia, impaired motor components of speech and impaired sound production at the larynx, respectively [112]. Dysarthria is more common in oral and oropharyngeal cancers followed by nasal and nasopharyngeal cancers [113]. No literature on prehabilitation was found. For rehabilitation, small observational studies found that articulation exercises improved objective nasality [113] and increased brain activation on fMRI [114].

Dysphonia, also referred to as voice impairment or hoarseness, frequently co-occurs with dysphagia [115–117]. The incidence is highly dependent on the involved anatomy, cancer treatment, and time post-treatment. Cancer treatment–related dysphonia is more common when radiation or surgery affects the base of the tongue, velopharynx, or recurrent laryngeal nerve [118, 119]. Voice impairment peaks at 10 weeks post-CRT [120]. Long-term voice problems can occur in about 70% of HNC patients [120–122], with high prevalence of severe impairment post-laryngectomy for laryngeal cancer [117]. In contrast, early laryngeal cancer treated non-surgically can result in minimal (0–6%) subsequent voice impairment [123, 124]. Non-laryngeal HNC patients can have lower prevalence of 17–39% at > 5 years post-CRT.

No specific interventional studies or reviews were identified on the prevention of dysphonia; however, a clinical practice guideline (CPG) for dysphonia prevention endorsed strategies such as adequate hydration, air humidification, use of amplification, and rest. The CPG also advised avoiding smoke, alcohol, caffeine, drying medications, and overuse including excessive throat clearing and coughing [119]. Voice rehabilitation is standard of care [125] for treatment of dysphonia, albeit with sparse and low-quality recent evidence showing trends towards improved voice function [126–129]. Adjunctively, biofeedback has been used for esophageal speech therapy after total laryngectomy although a small study did not find additional benefits [130]. The addition of a psychology intervention to speech therapy, however, did improve the acceptance and use of the new voice in laryngectomized patients [75]. A larger study determined that neuromuscular electrical stimulation (NMES) had short-term benefits in patients with nasopharyngeal cancer. Among the speech therapy options for patients with laryngectomy, tracheoesophageal speech is slightly favored over esophageal speech and electrolarynx according to a recent systematic review [131]. Overall, voice rehabilitation can be cost-saving from a societal perspective [132].

Lymphedema

Lymphedema is the accumulation of protein-rich lymphatic fluid within the soft tissues, which can progress to cause a chronic inflammatory, fibrosclerotic, and fibrofatty deposition process resulting in permanent deformity [133]. HNC-associated lymphedema is secondary to disruption of the lymphatic structures by tumor and/or HNC treatment, and often involves both internal and external structures. Internal lymphedema refers to swelling in the underlying mucosa and soft tissue of the upper aerodigestive tract [134]. External lymphedema refers to visible swelling in the soft tissues of the head and neck. Not only does head and neck lymphedema leads to swelling and skin changes, but it can also impact swallowing, phonation, cervical range of motion, body image, and quality of life [135, 136].

Recent studies have estimated the prevalence of HNC-associated lymphedema to be more than 90% [134]. However, HNC-associated lymphedema has historically been understudied, underdiagnosed, and undertreated [134, 137, 138]. This is in part because internal lymphedema is not readily apparent to an external examiner. Additionally, the lack of a contralateral "normal" structure for comparison enables even external head and neck lymphedema to be underdiagnosed [13]. HNC-associated lymphedema is also challenging to measure and stage. Although several diagnostic scales have been developed, there are no standardized diagnostic criteria [139]. A CT measurement tool was created with preliminary data demonstrating validity [140]. Patient-reported outcome measures have recently been revised and have preliminary validity, but further rigorous testing is pending [141, 142]. The revised Patterson Edema Scale has also demonstrated reliability [143].

Extrapolating data from breast cancer–related lymphedema suggests that prompt identification and treatment improves outcomes [134]. As such, despite challenges with diagnosis, the American Cancer Society Head and Neck Cancer Survivorship Care Guidelines now recommend evaluating for lymphedema and referring to rehabilitation specialists for treatment [13]. Nonetheless, at this time, there is also a relative dearth of high-level evidence to guide both prevention and treatment of HNC-associated lymphedema. A recent systematic review concluded that "Evidence for the efficacy of all types of lymphedema therapy is limited by paucity of large randomized controlled trials" [144].

Despite limited data, rehabilitation management of lymphedema is currently the standard of care and is centered around complete decongestive therapy (CDT). CDT includes manual lymphatic drainage (MLD); short stretch compression bandaging; compression garments; exercises for the face, neck, and oral cavity; and skin care. Formal lymphedema therapy is typically followed by ongoing lifelong home self-care incorporating MLD and compression [145].

Research on CDT predominantly consists of cohort studies. Importantly, nearly all demonstrate that HNC survivors respond favorably to CDT [145–150]. Since the publication of the systematic review by Tyker et al. [144] in 2019, two randomized control trials have also been published. First, a small RCT ($n = 21$) showed that lymphedema improved with CDT and home-based program compared to control; however, the CDT was more efficacious than the home-based program [151]. Second, in a randomized wait-list control trial ($n = 43$), advanced pneumatic compression devices (APCDs) were supported as being safe and preliminarily efficacious [142]. APCDs had also previously been shown to be an effective part of a home self-care maintenance program [152, 153].

With regard to internal lymphedema specifically, we were unable to identify any interventional studies that examined the impact of rehabilitation interventions on this outcome. A small observational pilot study of 7 patients, although unable to detect a significant change in internal lymphedema based on endoscopic exam, did note that 85% patients reported improvement in dysphagia and dysphonia with use of an APCD [154]. Overall, more high-level evidence is needed for the prevention, diagnosis, and treatment of HNC-associated lymphedema.

Shoulder Syndrome

Shoulder and neck dysfunction or "shoulder syndrome" represents a diverse group of musculoskeletal and neurologic impairments, which, either in isolation or through combined effect on shoulder biomechanics, result in pain or impaired mobility [155]. Although the largest contributor to shoulder disability and by the far most studied is spinal accessory neuropathy (SAN), shoulder syndrome also comprises shoulder droop, scapular dyskinesia, rotator cuff impairment, subacromial impingement, myofascial pain, and adhesive capsulitis [17, 155, 156]. Recent studies examining the prevalence of shoulder syndrome demonstrate wide variability (9–100%) based on the extent of surgical resection and degree of radiation exposure [155, 157–159].

Rehabilitation measures to prevent shoulder-related impairment in HNC have not been widely studied. However, there is a growing literature base on prevention of shoulder-related disability in breast cancer survivors demonstrating the potential for future interventional studies which may also apply to HNC [160, 161]. While not directly related to rehabilitation interventions, surgical planning remains the most important consideration when seeking to prevent future shoulder disability in HNC. SAN is vulnerable to surgical dissection when performed at levels 2b and 5 due to SAN traction or devascularization [159, 162]. In a recent interventional study, surgical omission of level 2b nodes resulted in significantly lower scores of impairment as measured by the Neck Dissection Impairment Index (NDII) [159]. Similar findings were observed in a systematic review comparing rates of shoulder impairment in those undergoing only SND (9–25%) compared to RND (10–100%) [155, 157].

Few interventional studies have examined intraoperative, early, or delayed post-surgical rehabilitation in those at risk of shoulder impairment [155, 157, 163]. In a randomized controlled trial of 54 participants, brief biphasic electrical stimulation of the SAN for 60 min immediately following neck dissection resulted in significantly improved Constant-Murley Shoulder Scores (CMSs) at 1 month compared to control [162]. The CMS is a composite score of pain, activities of daily living, shoulder mobility, and strength [164]. A 2020 systematic review also supported progressive resistance training (PRT) in HNC patients with shoulder disability as measured by the Shoulder Pain and Disability Index (SPADI) [157]. Pooled results from four of the included studies ($n = 214$) support PRT over conventional therapy for pain and patient-reported measures of disability; however, no significant differences in shoulder active range of motion (AROM) have been consistently observed [165–168]. More recently, Chen et al. (2020) have called some of these results into question, suggesting many of the included PRT studies were conducted months following surgical dissection or radiation, and may not fully apply to the early rehabilitation period [163]. In another recent RCT, early (i.e., immediate post-surgery but pre-radiation) motor control therapy was found to significantly improve shoulder pain and shoulder AROM in abduction and reduce compensatory muscle activation in oral HNC patients compared to progressive exercise alone [163]. Finally, there remains no clear consensus whether hospital- or home-based programs are superior in terms of outcomes [169, 170]; however, data and the 2016 American Cancer Society–published Head and Neck Cancer Survivorship Care Guidelines also clearly recommend surveillance and treatment of shoulder impairment post-HNC treatment [13].

Cervicalgia, Cervical Dystonia, and Dropped Head Syndrome

The neck is a highly nuanced part of human anatomy, which contains more than 20 muscles with associated connective tissue, vascular supply, nerves, and adjacent critical visceral organs. This complex anatomy is delicately balanced, and subject to damage by HNC and its treatment with subsequent pain and disability. Cervicalgia, cervical dystonia, and dropped head syndrome are common in HNC survivors [6, 7, 13, 171]. Neck pain was present in 33% of HNC survivors in a small study [172]. The incidence of cervical dystonia and dropped head syndrome has not been reported. Neck disability, including pain, has been reported to affect more than half of head and neck cancer survivors [173]. Cervicalgia is multifactorial but generally neuromusculoskeletal in etiology. Damage to purely sensory branches of the cervical plexus from neck dissection and/or RT can cause neuropathic pain in the distribution of the greater auricular, transverse cervical, lesser occipital, and/or supraclavicular nerves. Similarly, direct damage to motor nerves and muscles can result in painful spasms of the cervical musculature. These spasms are generally accompanied by fibrosis of the muscles, tendons, ligaments, and other cervical tissues leading to restricted range of motion and/or dystonic posturing of the neck known as cervical dystonia or torticollis. As the cervicothoracic paraspinal muscles become more dysfunctional, progressive dropped head syndrome (DHS) can result. Clinically, DHS can range in severity from mild weakness and fatigue that is worse at the end of the day to chin-on-chest deformity. We were unable to find any controlled interventional studies, reviews, or meta-analyses published since 2017 dedicated to the prevention or rehabilitation management of neck dysfunction in HNC survivors.

Clinical management of neck dysfunction in HNC survivors is generally multimodal and based on the specific impairment [6, 7, 171]. Treatment usually begins with physical therapy emphasizing key modalities such as myofascial release, postural retraining, core stabilization, and neuromuscular reeducation. Nerve-stabilizing agents such as pregabalin and gabapentin are useful for neuropathic pain and may reduce muscle spasm. Duloxetine may assist with neuropathic pain, and opioids may be needed in rare cases. For patients with cervical dystonia, botulinum injections into the sternocleidomastoid and scalene muscles may be helpful but caution is advised as injection into the posterior cervical musculature can precipitate dropped head syndrome [9].

Deconditioning and Fatigue

Fatigue often affects physical function in HNC survivors and is part of a cycle of deconditioning, inactivity, increased fatigue, and eventual sarcopenia and cachexia. Fatigue is prevalent in up to 86% of HNC survivors [174]. Although prehabilitation involving whole-body exercise is common practice, no literature specific to the HNC population was identified regarding preventing cancer-related fatigue (CRF). A Cochrane review concluding aerobic exercise improves CRF [175] in the general cancer population did not specifically address HNC survivors. Recent investigations specific to the HNC population do address the impact on fatigue of other exercise types and modes of delivery. Less fatigue was experienced with an autonomous individualized exercise plan delivered during post-surgical hospitalization in a RCT. Studies with alternative physical activity interventions (yoga, Tai Chi, and Qigong [176]) more frequently decreased fatigue than studies with traditional exercises in a systematic review. Pilot and feasibility studies show promising benefits for fatigue with home-based fitness graded exergames, which are video games that use a motion-based interface to engage individual in physical activity [177]; progressive resistance training in cachectic survivors; and eccentric strengthening followed by neuromuscular electrical stimulation which triggers a sequence of contractions via surface electrodes [178]. A recent meta-analysis of pharmacologic interventions for fatigue in the general cancer population found 15 RCTs with 1238 participants showing clinically insignificant benefits for psychostimulant and wakefulness agents (including armodafinil, methylphenidate, and dexmethylphenidate) and clinically significant benefits of 3 natural products in studies with uncertain to high risk of bias, including 1 study on Tualang honey for HNC-related fatigue [179, 180]. Fatigue in HNC patients was not improved with American ginseng [181] or guarana [182] in recent RCTs.

Deconditioning, as with fatigue, is usually addressed with exercise. The benefit of exercise on physical function is well-established for the general cancer population [183], and there is emerging literature specific to HNC patients. Preventative exercise programs during chemotherapy for HNC can improve physical and cardiopulmonary fitness [184, 185]. A recent systematic review [186] and meta-analysis [187] demonstrated that physical activity consisting of resistance and aerobic exercises benefit body composition and physical function, supporting recommendations in multiple HNC survivorship guidelines [13, 188, 189].

Nutrition and weight loss are also major concerns HNC patients with compromised swallowing function as they contribute to the interrelated symptoms of fatigue, deconditioning, sarcopenia, and cachexia. The impact is increased susceptibility to treatment-related toxicities and poor clinical outcomes [190]. Nutritional interventions typically involve oral nutrition supplementation including protein supplementation to meet caloric intake and protein goals. These have been studied in the prehabilitation phase to improve treatment tolerance [191–194] and to improve physical function [187]. However, prophylactic G-tube placement is controversial due to the risk for disuse atrophy of swallowing muscles after even brief intervals of disuse [195]. A large retrospective observational study showed that maintained oral intake and swallowing exercise adherence during chemoradiation can significantly reduce the duration of gastrostomy tube use [195]. Further nuances of nutritional management are beyond the scope of this paper.

Activity and Participation

Our prior scoping review revealed a lack of HNC rehabilitation studies directly examining the impact of rehabilitation interventions on outcomes related to activity and participation [19]. Unfortunately, there remains a dearth of high-quality research in these domains. Although many observational studies examine quality of life (QoL) in HNC [196–200], which may be considered a proxy for activity and participation, we did not identify any recent interventional studies that directly target specific activity and participation outcomes such as interventions to improve independence with activities of daily living (ADLs) and instrumental activities of daily living (IADLs), and participation including return to work, community, and family roles.

Although we did not identify any recent interventional studies that directly address activity and participation, several recent reviews have shed light on the broader impact of HNC-related functional loss. One review published in 2017 used qualitative synthesis of 12 relevant studies to gain a deeper understanding of the influence and experiences of HNC patients with dysphagia, dysgeusia, oral mucositis, and xerostomia as it relates to activities of daily living, social lives, and professional experiences [201]. A meta-synthesis published in 2018 examined 13 studies of HNC patients undergoing chemotherapy and/or radiation and explored the impact of treatment on patients' daily lives [202]. Both reviews emphasize that focal impairments do not occur in isolation but as a cluster, contributing to significant activity and participation limitations. Another 2018 review demonstrates that HNC survivors are at increased risk of body image dissatisfaction due to the visible disfigurement which occurs in the setting of tumor burden and treatment [203]. Another recent review details the nutrition-related burden and its impact on self-care in HNC [204]. Although not specific to HNC, a recent clinical practice guideline for dysphonia evaluates the significant loss in work productivity due to dysphonia particularly for people with vocally demanding work such as entertainers, legal professionals, teachers, telemarketers, coaches, and clergy [119].

Psychosocial Distress and Suicide

It is well-documented that HNC survivors are at significantly higher risk for psychosocial distress and suicide than age-matched controls and patients with other cancer types [205–210]. Although reasons for suicidal ideation in HNC survivors are not fully understood, there are documented demographic factors [208] and function-related factors [211] that increase a patient's risk for suicide. Based on current evidence, a combination of pharmacological and psychosocial interventions that enhance peer support and resilience appears to most effectively prevent suicide [211]. We also postulate that access to interventions that effectively address functional impairment, activity limitation, and participation restriction may also reduce HNC-related distress and risk of suicide. High-quality research in this domain is needed to reduce the risk of this preventable cause of mortality in HNC.

Conclusions

Rehabilitation research in HNC continues to focus primarily on impairment-driven interventions and outcomes related to speaking and swallowing. More high-quality interventional studies and reviews are needed to improve management of trismus, lymphedema, first bite syndrome, neck and shoulder dysfunction, HNC-related fatigue, and many other impairments that are important to the quality of life in HNC survivors. Specific interventions for HNC-related activity limitations and participation restrictions are also urgently needed to reduce both morbidity and mortality in this growing population of cancer survivors.

Declarations

Conflict of Interest Sara Parke declares that she has no conflict of interest. David Langelier declares that he has no conflict of interest. Jessica Tse Cheng declares that she has no conflict of interest. Cristina Kline-Quiroz declares that she has no conflict of interest. Michael Dean Stubblefield has received compensation for service as a consultant from Tactile Medical.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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