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CHARACTERIZING RISK & BURDEN OF LOWER CRANIAL NEUROPATHY (LCNP) AS LATE EFFECT AMONG OROPHARYNGEAL CANCER SURVIVORS

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DEDICATION

To my dad late Dr. Vijay Prakash, mom Dr. Aruna Prakash, Rohit, Sameer, and my brother Dr. Prashant Prakash.

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PREFACE

"I don't have a choice as to my "new" normal, so I do what I can to continue to find enjoyment and fulfillment in life." –Ed Steger, head and neck cancer survivor

My dad, late Dr Vijay Prakash (Professor, Internal Medicine & Cardiology) and my mother Dr. Aruna Prakash (Gynecology & Obstetrics) devoted their entire life to the service of their patients and their immense dedication has inspired me the most in my journey as an epidemiologist with training in dentistry to pursue head and neck cancer research. Working as a dentist in India with oral cancer patients, losing beloved family members and friends to cancer and having witnessed the immense suffering that cancer brings to the patient and their families has further fueled my passion to pursue to pursue head and neck cancer research.

Lower cranial neuropathy (LCNP) is a clinical condition of great concern, often accompanied with late radiation-associated dysphagia, which may enhance risk of aspiration pneumonia and contribute to debilitating functional morbidity with increased feeding tube dependence, hospitalization, weight loss, and life-threatening complications. During data abstraction, I have often observed LCNP patients describe their anguish with problems eating, swallowing, and embarrassment in eating in social settings contributing to feelings of social isolation which can be exacerbated sometimes by speech and hearing problems. It is my hope that this dissertation research will improve our understanding of late LCNP, to inform ongoing surveillance recommendations, targeted prevention, supportive care, and treatment interventions for patients with late LCNP to prevent functional decline and improve quality of life in these patients.

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parents, for setting an example through their life-long pursuit of providing treatment to their patients and teaching me the value of compassion and empathy to patients who suffer. Lastly, I am thankful to my loving husband Rohit who has supported me every step of the way. To my biggest cheerleader my son Sameer – this journey would not be possible without your encouragement and support. Thank You!

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ABSTRACT

Background: Lower cranial neuropathy (LCNP) is a rare but potentially disabling late effect of radiotherapy (RT) and other head and neck cancer therapies. Survivors who develop late LCNP may experience profound functional impairment with deficits in swallowing, speech, and voice. The aims of this research were: 1) to quantify the cumulative incidence of late LCNP and identify clinical predictors of late LCNP; 2) to investigate the impact of late LCNP on severity of cancer treatment-related symptoms, general functional impairment (GFI), and single item scores of the most severe symptoms; and 3) to quantify the association of late LCNP with swallowing-related quality of life (QoL) and functional status among long-term oropharyngeal cancer (OPC) survivors.

Methods: For the first aim of this dissertation the study population included 2,021 OPC survivors (median survival: 6.8 years) who received primary treatment at MD Anderson Cancer Center from 2000 to 2013. A retrospective cohort study was conducted and late LCNP events for all three studies were defined by neuropathy of the glossopharyngeal (IX),

vagus (X), and/or hypoglossal (XII) nerves ≥3-months after cancer therapy and abstracted from medical records along with other study variables. For the second and third study, a cross-sectional survey analysis among 889 OPC survivors nested within a retrospective cohort of OPC survivors treated during January 2000 -December 2013 at MD Anderson Cancer Center was conducted (56% response rate). The survey included MD Anderson Symptom Inventory Head and Neck Cancer Module (MDASI-HN) and MD Anderson Dysphagia Inventory (MDADI) among other items. For the first study, cumulative incidence of LCNP was estimated using the Kaplan Meir method with adjustment for competing risks using time to event as the underlying metric. Log-rank test was used to assess differences between groups by LCNP status, and multivariable Cox proportional hazard models were fit. For the second study, the primary outcome variable was the mean of the top 5 most severely scored symptoms from MD Anderson Symptom Inventory Head and Neck Cancer Module (MDASI-HN) out of all 22 core and HNC-specific symptoms. Secondary outcomes included mean MDASI-HN interference scores and single item scores of the most severe symptoms. Multivariate models regressed MDASI-HN scores on late LCNP status adjusting for clinical covariates. Finally, for the third study, multivariate models regressed MDADI scores on late LCNP status adjusting for clinical covariates.

Results: For the first study; 4.4% (n=88) OPC survivors were diagnosed with late LCNP with median time to LCNP onset after treatment of 5.4 (range, 0.3-14.1; IQR: 1.6-8.5) years post-treatment. Cumulative incidence of LCNP among all OPC survivors was 0.02 (95% CI: 0.02-0.03), 0.06 (95% CI: 0.05-0.08), and 0.10 (95% CI: 0.08-0.13) at 5 years, 10 years, and 18 years of follow-up, respectively. Multivariable Cox regression identified T4 stage vs T1

stage (HR: 3.82; 95%CI: 1.85-7.86, p=0.000) and accelerated RT fractionation vs standard RT fractionation (HR 2.15, 95%CI 1.34-3.45, p=0.002) independently associated with late LCNP status, adjusting for age, subsite, T-stage, smoking and therapeutic modality.

In the second and third, cross-sectional survey analysis study overall, 4% (n=36) of 889 OPC survivors (median survival time: 7 years) developed late LCNP with median time to onset of 5.25 years post-treatment. Late LCNP was significantly associated with worse mean top 5 MDASI-HN symptom scores (coefficient, 1.54; 95%CI, 0.8, 2.2) adjusting for age, survival time, sex, therapeutic modality, T-stage, subsite, type of radiotherapy, smoking, and normal diet prior to treatment. Late LCNP was also associated with single item scores for difficulty swallowing/chewing (coefficient, 2.25; 95%CI, 1.3, 3.1), mucus (coefficient, 1.97; 95%CI, 1.0, 2.9), fatigue (coefficient, 1.35; 95%CI, 0.4, 2.2), choking (coefficient, 1.53; 95%CI, 0.6, 2.4), and voice/ speech symptoms (coefficient, 2.3; 95%CI, 1.6, 3.0) in multivariable models. However late LCNP was not significantly associated with mean interference scores after correction for multiple comparisons. LCNP cases reported significantly worse mean composite MDADI (LCNP: 68.0 vs. no LCNP: 80.2, p<0.001). Late LCNP independently associated with worse mean composite MDADI (β= -6.7, p=0.015, 95%CI: -12.0, -1.3) as well as all MDADI domains after multivariate adjustment. Finally, LCNP cases were more likely to have a feeding tube at time of survey (OR= 20.5; 95%CI, 8.6 to 48.9), history of aspiration pneumonia (OR= 23.5; 95%CI, 9.6 to 57.6), and tracheostomy (OR= 26.9; 95%CI, 6.0 to 121.7).

Conclusion: Risk of late LCNP progressed over time to exceed 10% cumulative risk over survivors' lifetime even though it is considered a rare late effect. Our prediction model enabled identification of OPC survivors who had T4 tumors and those who received accelerated fractionation RT treatment as having higher risk of late LCNP. In the large survey study, OPC survivors with late LCNP reported significantly worse cancer treatment-related symptoms, significantly poorer swallowing-related QOL and had significantly higher likelihood of poor functional status demonstrating the impact of late LCNP on both symptom severity and functional burden. Further, efforts are necessary to investigate the risk and predictors for this disabling late effect of cancer treatment, address severity of treatment-related symptoms and optimize swallowing outcomes to improve QoL among growing numbers of relatively younger OPC survivors, who are expected to survive decades after treatment.

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BACKGROUND

Oropharyngeal Cancer (OPC)

The incidence of OPC is increasing by 5% each year and it is projected that by 2030 about half of head and neck cancers (HNC) will be OPC.[1] This phenomenon is attributable to the epidemic of HPV-associated OPC which is usually diagnosed in patients, who are middle aged, male, white, non-smokers and non-drinkers and have a higher socioeconomic status relative to individuals diagnosed with tobacco-related head and neck cancers.[1-4] They also tend to have a history of higher number of sexual partners and are often diagnosed at a more advanced stage.[1-4] As a consequence of modern regimens of organ preserving radiotherapy, favorable biology, and improved prognosis due to better response to treatment among HPV associated OPC patients, these patients have good survival rates and are often expected to live for decades despite advanced stage disease.[2-4] HPV associated HNC patients have a 3-year overall survival rates of 82%, in comparison to 57% among HPV negative HNC patients (with tobacco related cancer).[2] HPV positive HNC also have better 5-year overall survival (RR=0.4; 95%CI 0.2-1.08) than non-HPV related tumors.[3] Further HPV associated HNC are more likely to occur in the oropharynx, especially base of tongue or tonsil and HPV positive tonsillar tumors at time of diagnosis. Primary tumors are more likely to be smaller with regional lymph node metastasis making most stage IV at presentation.[4]

As the lifespan of OPC survivors increase, they are more likely to experience severe side-effects over time due to delayed or late adverse effects of tumor and cancer treatment. OPC survivors experience excess morbidity and disability compared to other cancer survivors, as these side-effects lead to problems in swallowing, eating, breathing, and

speaking. According to a survey study in 2004, 52% of HNC patients of mixed sites experience disability due to cancer treatment and are unable to work due to these problems.[5]

Cranial Nerves

Cranial Nerves (CN) comprise of 12 pairs of nerves that emerge from the brainstem. They regulate smell, sight, speech taste, movement of eyes, eye muscles, facial muscles, shoulder and neck muscles, and many other physiologic processes in the body.[6-8]These nerves are numbered using roman numerals, in the order they emerge from the brainstem and their names convey their function.[6-8]

CN carry sensory or afferent fibers that conduct neural information from sensory receptors in the head and neck region to the brain and terminate in sensory cranial nerve nuclei. These nuclei are generally located laterally in the brainstem.[8, 9]The sensory component of CN includes general sensory, visceral sensory, and special sensory fibers which conduct smell, sight, taste, balance, and hearing signals to the brain.[8, 9]CN also carry motor or efferent fibers, which conduct regulatory neural input back from brain to target receptors (muscles) and other parts of the body. The neuronal cell bodies of these fibers are present in the motor cranial nerve nuclei, located more medially in the brainstem.[8, 9] Further CN also transmit somatic motor, branchial motor, and parasympathetic motor fibers which supply voluntary muscles (skeletal muscles), involuntary muscles, and provide parasympathetic innervation to the viscera respectively.[8,9] Most cranial CN are mixed,

carrying both sensory and motor nerve fibers but some only carry sensory or only motor fibers.[8,9]

Lower cranial nerves (LCN)

Lower cranial nerves (LCN) include glossopharyngeal (IX), vagus (X), accessory (XI) and hypoglossal (XII) nerves which provide innervation to the pharynx, larynx, and shoulder, neck and tongue muscles respectively.[10]

Glossopharyngeal Nerve (IX)

Glossopharyngeal Nerve (IX) is a mixed sensory and motor nerve, which innervates the tongue and the pharynx.[8, 9] General sensory fibers of CN IX provide general sensory input from the soft palate, pharynx, oropharynx, tympanic membrane, Eustachian tube, and the posterior third of the tongue (also supplied by special sensory fibers of CN IX which provide taste sensation).[8,9]These fibers descend in the spinal trigeminal tract and the sensory fibers from tongue, tonsils, soft palate, and pharynx terminate in the spinal trigeminal nucleus.[8,9] The sensory fibers from the tympanic nerve carry pain signals and also terminate in the spinal trigeminal nucleus.[8,9] Visceral sensory fibers from CN IX conduct neural information from carotid body and sinus, to monitor blood pressure and arterial oxygen in the internal carotid artery.[8,9] They pass through the jugular foramen, enter the medulla, descend in the tractus solitarius and terminate in the nucleus solitarius.[8,9] Special sensory fibers from CN IX carry taste signals from the taste buds in posterior one-third of the tongue, pass

through the jugular foramen, enter the medulla, ascend in the tractus solitarius and terminate in the rostral gustatory part of nucleus solitarius.[8,9]

Parasympathetic preganglionic motor CN IX fibers are located in the inferior salivatory nucleus and the nucleus ambiguus in the medulla.[8, 9] Nerve axons from inferior salivatory nucleus exit the cranial cavity via foramen ovale, synapse on the otic ganglion to supply the parotid gland and regulate its secretory function.[8]Axons from the nucleus ambiguus innervate the carotid body and sinus and regulate the vasodilation of blood vessels.[8]

Branchial motor fibers of CN IX emerge from the nucleus ambiguus, where the synapse between upper motor neurons passing through the corticobulbular tract and lower motor neurons occurs.[8] These lower motor neuron axons exit the cranial cavity through the jugular foramen.[8] They innervate the stylopharyngeus muscle, which plays a role in pharyngeal elevation to mediate swallowing and speech.[8] This muscle facilitates swallowing, by elevating pharynx and larynx, to allow bolus of food to pass. [6, 7]

CN IX Injury: CN IX exits the medulla of the brain stem along with CN X and XI, via the jugular foramen. Thereby tumor-related and treatment-related toxicity can affect all three nerves together and lead to nerve impairment.[8, 9] CN IX injury can lead to swallowing impairment, from the loss of function of the stylopharyngeus and also contribute to ipsilateral loss of taste sensation over the posterior third of tongue.[8, 9]

Vagus Nerve (X)

Vagus Nerve is a mixed sensory and motor nerve. It innervates major areas of the body from the brainstem to the splenic flexure in the transverse colon.[8, 9] General sensory fibers of CN X conduct somatosensory information including touch, temperature, and pain from the larynx, laryngopharynx, concha, external auditory canal, tympanic membrane, and the posterior meninges.[8, 9] These fibers pass through the jugular foramen, enter the medulla, ascend in the spinal trigeminal tract and synapse in the spinal trigeminal nucleus.[8, 9] From this nucleus, second-order axons carry neural information to the thalamus and the sensory cortex.[8] Visceral sensory fibers of CN X, conduct visceral neural input from the aortic arch baroreceptors, aortic body chemoreceptors, the larynx above the vocal cords (via internal laryngeal nerve),the larynx below the vocal cords (via recurrent laryngeal nerve), epiglottis, and base of tongue.[8] These afferent fibers pass through the jugular foramen, enter the medulla, descend in tractus solitarius and synapse in the nucleus solitarius.[8] Neural signals from the nucleus are relayed to the reticular formation and the hypothalamus, and help to regulate numerous cardiac, respiratory and gastrointestinal functions.[8] Branchial motor fibers of CN X emerge from nucleus ambiguus, where the bilateral corticobulbular fibers carrying upper motor neuron axons synapse.[8]These fibers exit the cranial cavity through the jugular foramen and branch out into the pharyngeal, superior laryngeal, and recurrent laryngeal nerves.[8]

Pharyngeal Branch of CN X: The pharyngeal branch via the pharyngeal plexus, provides innervation to all the muscles of pharynx, soft palate (excluding stylopharyngeus, supplied by

CN IX and tensor veli palitini by CN V), and the palatoglossus muscle in the base of tongue.[8] The Palatoglossus; contracts to either lower the soft palate or raise the posterior part of the tongue.[11,12] The levator veli palatine; elevates and retracts the soft palate, the palatopharyngeus; narrows the oropharynx, elevates the pharynx and guides the food bolus down to lower pharynx and also produces some laryngeal elevation.[11,12] The muscularis uvulae; shortens and elevates the uvula.[11,12]

Superior laryngeal Nerve (Branch of CN X): This nerve supplies the cricothyroid muscles and inferior pharyngeal constrictor.[8, 9]The cricothyroid muscles help to elongate and tighten the vocal cords and thereby contribute to phonation.[13]The inferior pharyngeal constrictor comprises of thryopharyngeus and cricopharyngeus, and the latter relaxes during swallowing to enable food bolus to pass downwards towards the esophagus.[6, 7]

Recurrent laryngeal nerve (Branch of CN X): This nerve supplies the other intrinsic muscles of the larynx, which contribute to phonation by altering the shape of the glottis and altering the length and tension of the vocal cords.[8, 9, 11-13]

The parasympathetic motor fibers of CN X, emerge from the cell bodies in the dorsal motor nucleus of CN X and medial part of nucleus ambiguus.[8] These efferent fibers exit the cranial cavity through the jugular foramen and innervate the pharynx, larynx, viscera of the thorax and abdomen, cardiac muscle and the aortic bodies.[8] They help to regulate numerous cardiac, respiratory and gastrointestinal physiological functions.[8, 9] Overall CN X plays a

critical role in swallowing, as it regulates the posterior elevation of tongue, soft palate movement, velar elevation, closure of glottis and pharyngeal constriction allowing bolus transport into the esophagus. It contributes to phonation by regulating intrinsic movements of larynx.[11, 12]

CN X Injury: CN X is very similar to CN IX in structure, function and they arise from the same cranial nerve nuclei in the brain stem and exit the skull base together through the jugular foramen accompanied by CN XI.[8, 9] Therefore, these nerves are likely to be injured concurrently.[8, 9]

Damage to CN X, can lead to paralysis of the pharyngeal muscles, larynx and vocal cords, and thereby contribute to dysphagia and speech impairment.[8-10] Unilateral vagal injury can lead to reduced pharyngeal muscle movement, which can cause loss of adequate soft palate elevation, dysphagia, palatal droop on the affected side. Palatal drooping can result in passage of food into the nasal cavity during swallowing and thereby cause aspiration[8, 9]It can also cause reduced vocal cord vibration, leading to hoarseness and reduced pitch of voice.[8, 9] Thereby bilateral CN X injury, can cause bilateral pharyngeal paresis, severe dysphagia, bilateral paralysis of vocal cords and severe speech impairment.[8, 9]

Hypoglossal (XII) nerve

Hypoglossal (XII) nerve is a motor nerve and only carries somatic efferent fibers.[13]These fibers emerge from the hypoglossal nucleus in the tegmentum of the medulla,

from which neural information is relayed by the corticobulbular tract to the cortex.[8] Efferent fibers of CN XII exit the cranial cavity, through the hypoglossal foramen and pass medially to CN IX, X and XI.[8] They innervate the extrinsic tongue muscles (except palatoglossus) which regulate tongue movement.[8,11,12] The genioglossus mediates tongue protrusion, tongue retraction, and draws the tongue downward, thereby helping in food bolus transport.[11,12] The hyoglossus retracts and depresses the tongue and elevates the hyoid bone, whereas styloglossus is responsible for upward and backward movement of the tongue.[11,12] These efferent fibers also provide nerve supply to all the intrinsic tongue muscles which alter the shape of the tongue.[8,11,12] These muscles include the superior longitudinal; which shortens the tongue and turns its tip upward, the inferior longitudinal; which shortens the tongue and turns its tip downward, the transverse; which narrows and elongates tongue, and the vertical; which flattens tongue.[11,12]

CN XII Injury: The hypoglossal nuclei are in close proximity to each other, therefore tumor-related and treatment-related toxicity contributing to nuclear injury, is likely to affect both nuclei leading bilateral nerve impairment of the tongue.[8, 9]

Lesions of hypoglossal nuclei in the brainstem and unilateral lesions of CN XII can cause ipsilateral tongue paralysis, atrophy of tongue muscles, wrinkled tongue appearance, tongue fasciculations, and mild speech impairment.[8,9] In cases with ipsilateral paralysis of CN XII, when the tongue is protruded it deviates towards the affected side, due to the genioglossus action on the unaffected side, which can over time lead to tongue fasciculations and atrophy.[8,9] Bilateral CN XII injury leads to bilateral tongue paresis, inability in tongue

protrusion, atrophy, fibrillations, severe dysphagia, and speech impairment. Reduced lingual motion may contribute to swallowing apraxia, oral residue, bolus formation problems, and reduced bolus movement, thereby leading to extensive swallowing toxicity.[8-13]

In summary injury to lower cranial nerves can lead to profound functional impairment in terms of dysphagia, vocal cord paresis with or without accompanying lingual weakness [14,15] often with co-existing problems in speech and voice and shoulder impairment .[10,14,16,17] Therefore lower cranial nerve injury can have an adverse impact on swallowing-related QoL among OPC patients.[16,18]

Lower Cranial Neuropathy (LCNP)

Lower cranial neuropathies (LCNP) are a rare, but severe late effect induced by damage due to radiotherapy or surgery.[14,15,19] LCNP can occur both unilaterally and bilaterally and can affect glossopharyngeal (IX), vagus (X), accessory (XI), and hypoglossal (XII) nerves.[14,15,18,19]These nerves are critical to the oropharyngeal phase of swallowing mechanism and speech production and shoulder movement. [14-16, 18, 19]

According to a recent report, the incidence of late LCNP among 59 OPC survivors was 5% at 5.7years (Hutcheson, et al).[15] Nerve palsies have delayed occurrence.[14, 15,19]According to a previous study among NPC patients, late LCNP was reported 12 months to 240 months after radiation treatment.[19] Therefore, there is need for long-term surveillance of late LCNP among HNC and OPC patients.[14, 15, 19]

Previous studies have suggested that, malignant tumor invasion may cause upper cranial nerve neuropathy, whereas radiation associated injury is more likely to cause lower cranial nerves neuropathy (LCNP).[20] Therefore, competing causes of nerve palsy, like second primary, recurrent, and metastatic tumors need to be assessed, and such patients need to be excluded, in order to identify patients with treatment-associated late LCNP.

Mechanism of Nerve Injury

Radiation injury to cranial nerves can be acute; days after exposure to radiation or late; which occurs months and years after exposure to radiation.[21] Acute radiation injury is rare with standard fractionation RT treatment among HNC patients, and late radiation toxicity is more commonly reported. According to previous literature, different theories postulate that, late LCNP can be caused by peripheral nerve and brainstem injury.[15, 21-23]

Peripheral Nerve Injury Theory

Peripheral nerves including cranial nerves and spinal nerves are considered to be relatively resistant to radiation injury.[15, 21-23] Literature suggests however, that radiotherapy may contribute to peripheral nerve injury by axonal degeneration, suppression of Schwann cell proliferation, and fibrosis of connective tissues. [15, 21-24]

Axonal Degeneration

Radiotherapy (RT) can cause cranial nerve injury directly by axonal degeneration.[24]This axonal injury may contribute to local demyelination, membrane instability or vascular endothelial injury which may lead to ischemia, fibrosis, secondary neural injury, and eventually myokymia.[21, 25]

Myokymia is clinically observable continuous rippling or undulating involuntary muscular movement, which can be mistaken for fasciculations and has been documented among neuropathies with nerve compression or entrapment.[25, 26] Myokymia can occur in some muscles innervated by cranial nerves and is often a clinical symptom of radiation associated LCNP.[15]

Vascular Injury

Radiotherapy(RT) may contribute to cranial nerve injury indirectly by causing vascular endothelial injury.[21] Endothelial cells in capillaries are extremely radiation sensitive and RT injury can cause thrombosis, obstruction, and capillary destruction.[21] It has been suggested that at standard fractionation schedule, RT dose of 50-60 Gy can cause arterial damage.[27] However capillary injury can occur at RT doses > 40 Gy.[27] This vascular injury can lead to ischemia and fibrosis of surrounding connective and soft tissues adjacent to nerves.[21,27] Thereby damage to blood vessels can contribute to axonal degeneration and cranial nerve injury.[15,21]

Fibrosis

It is postulated that connective tissue and soft tissue fibrosis may lead to nerve compression injury or loss of vascular supply to the nerve sheath. [21,26,28] Tissue pressure due to fibrosis, can cause blood supply interference or direct neural vascular damage, extensive vascular sclerosis, and microvascular damage contributing to axonal degeneration leading to fibrosis induced nerve infiltration, compression, and thereby nerve injury.[15,17,24,27-29] According to a previous study among NPC patients, 12/19 (63%) patients with radiation-related cranial nerve palsy reported fibrosis of neck muscles and other studies have supported this association.[17] The authors postulated, neck fibrosis may cause compression of cranial nerves passing through the neck, leading to cranial nerve palsy.[17] This idea was supported by the fact, that CN XII, CN X, and recurrent laryngeal nerve (branch of CN X) were most frequently damaged in this study and these nerves pass through the anterior portion of the neck, which receives substantial amounts of RT.[17] Other studies have shown similar results.[30-32] Another study reported 6/7 NPC patients, treated with parapharyngeal radiation boost developed CN XII palsy on the boosted side.[33] Other studies have speculated that neurovascular fibrosis in the parapharyngeal region and fibrosis of the retroparotid space may contribute to neuropathy of CN IX, X, XI, XII though exact mechanism was not described. [15,16,32]

Schwann cell Depletion

Schwann cells play a prominent role in the peripheral nervous system. They provide support to neurons, produce the myelin sheath around axons, and help in axon regeneration and neuronal survival.[34] RT toxicity of cells, can cause increased expression of vascular endothelial growth factor (VEGF), which can contribute to enhanced permeability of blood vessels.[34] Consequently interstitial edema may occur, leading to fibroblast cell growth causing axonal compression, which in combination with hypoxia may contribute to axonal degeneration and subsequent Schwann cell proliferation.[34] This Schwann cell accumulation, may lead to increased cellular expression of RT injury and contribute to their cell death (leading to depletion of Schwann cell), which in turn may trigger myelin loss and additional axonal degeneration.[34] Thereby Schwann cell depletion, may contribute to loss of nerve fibers, nerve cell injury and eventually impairment of peripheral nerves.[34]

Wallerian Degeneration

RT-induced peripheral nerve injury can also lead to Wallerian Degeneration, which involves axonal skeleton breakdown distal to injury site. [21,34,35] Schwann cells reject the myelin component of their plasma membrane leading to disintegration of the myelin sheath.[35] This degenerated myelin contains myelin-associated glycoprotein, which further suppresses regeneration of damaged axons.[35] Wallerian Degeneration may also lead to initiation of inflammatory mechanisms and it has been suggested that the release of pro-inflammatory cytokines and growth factors, may mediate biological processes including inflammation and

fibrosis, which can cause late radiation nerve damage.[21,34,35]Thereby this degenerative process, has been reported after RT in some studies and may contribute to nerve impairment in both the peripheral and the central nervous system.[11]

It has also been suggested that if surgery or tumor invasion damages the vascular supply of cranial nerves, they may become more susceptible to radiation injury. [21]

In summary, RT may contribute to extensive injury and ischemia of nerves, causing functional nerve impairment, and late LCNP.[15, 17]

Brainstem Injury Theory

A complementary theory suggests, that high RT dose to malignant lesions or RT targets near the base of the skull or the bulbar region can lead to brain stem injury, which in turn can cause lower cranial nerve dysfunction.[21, 36] This theory is supported by documentation of LCNP among NPC, which is close to the skull base and brain stem.[23] It is postulated that base of skull irradiation, can lead to a different combination of CN X, XI, and XII palsies.[23] This is especially relevant with IMRT, which may lead to unintended higher RT dose to non-target regions, like the brainstem relative to older RT planning methods. Radiation field overlap may contribute to formation of "hot-spots" and could cause development of radiation associated late LCNP.[23, 37]

Brainstem

The brainstem is located in the posterior cranial fossa and is an extremely important sensitive region of the brain containing sensory and motor neural pathways, that connect the brain with rest of the body.[9, 21] It comprises of the midbrain, the pons, and the medulla oblongata.[21] It also contains the corticospinal tract, posterior column medial lemniscus pathway, and the spinothalamic tract and numerous cranial nerve nuclei.[21]

All the cranial nerves except CN III (oculomotor) and CN IV (trochlear), emerge from their nuclei located within the tegmentum of the brainstem.[9, 21]The nuclei of CN IX, X, XI, and XII are located in close proximity to each other in the medulla, whereas the nuclei of CN V, VI, VII, and VIII are located in the pons.[21] Thereby, it is postulated that high radiation dose to brainstem, may cause injury to the cranial nerve roots and the nuclei.[21] This theory may be supported by Bulbar palsy, which includes CN IX, X, XI, and XII dysfunction which is suggested to be caused by brainstem lesions in cranial nerve nuclei or lower cranial nerve injury outside of brainstem.[38]

It has also been suggested that, brainstem damage may depend on volume of brainstem tissue being irradiated, during fractionated radiation treatment rather than maximum radiation dose received.[21] A previous study reported that, RT dose of 60, 53 and 50 Gy when 1/3, 2/3 and 3/3 of the brainstem is irradiated at a fractionation of 2Gy/fraction had a 5% brainstem injury risk after 5 years of RT exposure.[39] Another study reported that, total volume brainstem irradiation with a RT dose ≥ 65 Gy resulted in a 50% increased risk of treatment related toxicity after 5 years post-RT.[21] A multivariate analysis also revealed that brainstem volume irradiated with > 60 Cobalt-Grey equivalent (CGE), was significantly

associated with brainstem damage. In fact, if greater than 0.9cc of the brainstem was irradiated with > 60 CGE, there was a significant increase in risk of brainstem injury.[21]

It has also been suggested that, radiation associated risk of brainstem toxicity may increase if targeted tumor is large, is in close proximity to the brainstem and radiation dose is high.[21] Further as cranial nerves are considered to be radiation resistant, it has been suggested that RT dose of radiation to the brainstem may be a more influential factor leading to cranial nerve injury.[21]Therefore, brainstem injury due to cancer treatment, may be a potential risk factor for late LCNP and needs to be investigated in future prospective studies.[15, 21]

Neuromuscular Junction and Muscle Contraction

Neural transmission of signals from the nerve to the muscle occurs at the neuromuscular junction, which is initiated by the conduction of action potential to the axon terminal.[21, 40]This leads to its depolarization, which enables the opening of voltage-dependent calcium channels, to allow influx of Calcium ions into the axon terminal. These ions trigger the release of neurotransmitter Acetylcholine (ACh) into the synaptic cleft. ACh in turn binds to Nicotinic Acetycholine receptors located in post-synaptic membrane, leading to opening of ion channels to enable sodium ion influx into muscle cell. This produces a muscle action potential, which is transmitted by a chain of processes including, depolarization of sarcolemma, excitation-contraction coupling and leads to myofibril contraction and eventually target muscle contraction.[21, 40] Muscle contraction and relaxation, is thereby regulated by neural input from the cranial nerves.[21,40] Therefore, RT can also potentially

cause damage to the neuromuscular junction and lead to treatment related toxicities like late LCNP.

Potential Risk Factors of LCNP

According to previous literature, potential factors which may predispose patients to treatment associated late LCNP include radiation dose, radiation field, radiation fractionation, surgery, systemic therapy, and individual sensitivity to treatment.[15, 18]

Radiation Dose

Radiation dose is most commonly suggested in literature as the chief predisposing factor for late LCNP, but the contributing threshold dose is not known.[15] According to a study among NPC patients cranial neuropathy is rare, but has, typically been reported among patients treated with daily RT dose of 180-200 centigrays per day, which is the current standard fractionated dose for OPC.[17] Cumulative radiation dose to nasopharynx >70Gy was identified as a significant predictor for cranial neuropathy (RR = 1.961, p =0.009) and lower cranial neuropathy (RR= 3.088, p < 0.001), as it could potentially lead to muscle fibrosis and subsequent nerve toxicity.[20] Similarly, a previous study of late LCNP reported a total radiation dose of about 70 Gy and higher among 3 among OPC survivors with LCNP.[15,14]

Regional Dose along Nerve Tracts: It has been suggested that the dose to regions-of interest (ROI) in the RT field, containing nerve tracts may play a more pivotal role in late treatment-related toxicity than total RT dose.[41] The superior pharyngeal constrictor (SPC) region, comprises of minor nerve tracts and the constrictor and longitudinal pharyngeal muscles, which are important for pharyngeal shortening during swallowing for bolus propulsion into the esophagus.[41] A small retrospective case-control study of 38 OPC patients, reported that mean SPC dose was significantly associated with cranial neuropathy and late radiation associated dysphagia, controlling for T-stage and total RT dose.[41] Majority (8/10) of LCNP cases in the study, received a mean SPC dose of ≥ 70 Gy.[41] The authors reported that a mean threshold dose of 62 Gy to the SPC region can differentiate between OPC survivors with LCNP versus those without LCNP. [41]Mean SPC dose was also associated in numerous other small clinical studies, with radiation associated dysphagia, use of feeding tubes during RT, and oropharyngeal swallowing efficiency after chemoradiation.[42-44] Thereby it has been suggested that high mean SPC dose may have a detrimental impact on swallowing and functional outcomes years after treatment, and can contribute to late toxic effects including late LCNP among OPC survivors.[41]

Radiation Fields

HNC and OPC patients, may include irradiation fields comprised of healthy tissues, lower cranial nerves, and pharyngeal mucosa, and ionizing RT treatment can cause nerve injury, swallowing toxicity and speech impairment.[39,45] Thereby RT field may be a predisposing factor for late LCNP.[15,39,45] Among NPC patients, incorporation of facial-

cervical RT fields was suggested to be associated with lower radiation associated cranial neuropathy incidence and longer latency in comparison to use of facial-cervical split fields.[16,46] Further overlap of radiation fields during IMRT treatment may lead to development of "hot spots" as described earlier, and may contribute to late LCNP.[15, 23] Some studies have documented a higher risk of LCNP among patients, who receive irradiation involving the carotid sheath, the parapharyngeal space and large subdigastric and retropharyngeal lymph nodes.[15] It has also been suggested that CN XII injury only and CN X injury only, may be due to RT toxicity to submandibular space and carotid sheath respectively. [23]

Path of Lower Cranial Nerves and Nerve Injury: Path of lower cranial nerves in the head and neck region, may make them more susceptible to injury. NPC and OPC tumors may cause compression of lower cranial nerves in the suprahyoid neck.[42] NPC tumors can also affect the carotid space and compress CN XII as it exits the Hypoglossal canal, and thereby affect CN IX to CN XI as they pass through the jugular foramen.[42] RT dose of ≥ 70Gy to the carotid sheath, may result in lower cranial nerve injury, as CN XII passes through this region to innervate the hyoglossus muscle and the tongue.[18, 28] It is postulated that, proximity of CN XII to the base of the tongue, which receives high RT dose, as well pressure from laryngeal airway masks can lead to fibrosis, loss of vascularity, nerve entrapment, and damage.[16, 43] Therefore LCNP among NPC patients can occur due to malignant tumor invasion, and at lower doses of radiation treatment to the brain stem and oral cavity.[28]

Chemotherapy

Chemotherapy drugs are cytotoxic as they can destroy cancer cells, and modify radio sensitivity of cells either by, altering their cell-cycle phase or by interfering with repair of radiation initiated double-strand DNA breaks.[21] An earlier study among NPC patients, reported that chemotherapy was significantly associated with development of cranial neuropathy (RR=1.42, p=0.021).[20] A clinical trial among stage III and stage IVB NPC patients, revealed that late cranial neuropathy was significantly increased among patients treated with RT and concurrent adjuvant chemotherapy (p=0.042) than those treated with RT only.[44] Similarly, in another study 6.3% of HNC patients, who received intra-arterial Cisplatin therapy developed cranial neuropathy shortly after treatment.[42] This is not a standard procedure for cisplatin administration, and other studies have not reported similar associations.[42] Chemoradiotherapy, is standard multi-modality treatment for stage III-IV HNC and OPC, but combined effects of RT and chemotherapy may contribute to increased treatment-related toxicity. Therefor future studies need to assess chemotherapy, as a predictor of late LCNP among HNC and OPC survivors.

Fractionation Schedule

Radiation dose fraction may also influence late LCNP. It has been suggested that among NPC patients, if fractionation dose is increased from 180cGy to 420 cGy there may be an increased risk of cranial nerve toxicity.[17] A previous study among NPC patients, reported that RT fractionation schedule was a significant predictor of upper cranial nerve neuropathy

and not significantly associated lower cranial nerve neuropathy.[20] The authors suggested that the lack of significant association between lower cranial nerve neuropathy and RT fractionation schedule, maybe due to lower cranial nerves being more affected by fibrosis.[20] An earlier randomized trial among NPC patients, reported that accelerated hyper-fractionation radiation treatment, was associated with higher late LCNP incidence than conventional fractionation (13.0% vs 8.7%) over a median follow-up of 59.2 months.[33,47]Therefore, fractionation schedule of RT needs to be assessed in future studies, as a predisposing factor for LCNP among OPC survivors.

Surgical Treatment

Surgical treatment along the course of cranial nerves may cause nerve damage and contribute to late LCNP. It has been suggested that, if surgery causes damage to vascular supply of cranial nerves, they may become more susceptible to radiation injury.[21] Also depending on the operating field, isolated cranial nerve palsy or multiple cranial nerve injury may occur.[42] Further, if surgery involves the sublingual region, hypoglossal nerve injury may occur.[35] Neck Dissection has also been documented to lead to paralysis of CN VII, CN X, CN XI, and CN XII.[33] Reports suggest CN XI paralysis is most common treatment related toxicity related to radical neck dissection with an incidence of about 62%.[34, 35]

Genetic Susceptibility

A previous study postulated that individual sensitivity possibly due to genetic susceptibility, may contribute to CN XII palsy among NPC patients treated with standard RT dose of 66 Gy.[28]The authors supported their idea by reporting that 4/14 patients in the study, with radiation-related neuropathy did not receive high dose of radiation.[28] In another retrospective study among 130 OPC patients, ERCC4 T2505C polymorphism was suggested to be associated with enhanced recovery from toxicity due to radiation treatment.[49] ERCC4 is a gene which plays a role in repairing cell damage, due to ionizing effects of radiation.[48] This gene, is involved in recognition of site of injury, recombination repair, and mismatch repair.[48] ERCC4 T2505C polymorphism is reported with a allele frequency of about 36% and was associated with lower risk of long term feeding tube placement (OR=0.2; 95% confidence interval, 0.06-0.67) controlling for age, chemotherapy, T and N stage.[48] Other reports have suggested a positive association between genetic markers and risk of radiation related tissue toxicity, and future genetic studies are needed to explore this association. [20, 49]

In summary, earlier studies have suggested that radiation dose, radiation field, radiation fractionation, surgery, systemic therapy, and individual sensitivity to treatment may influence risk of late LCNP among NPC patients.[7] Thereby these variables were assessed in our study and investigated as potential predictors of late LCNP among OPC survivors.

Latency Period for Cranial Neuropathy

A previous study among 59 OPC survivors by Hutcheson et al., reported a latency period from time of RT treatment to presentation of late LCNP with a median of 5.7 years and range of 4.6-7.6 years.[15] An inverse relationship between the length of latency period between radiation treatment and presentation of late LCNP symptoms and dose of treatment has been suggested.[16,20] This association has also been reported in clinical studies of injury of brachial plexus and experimental animal studies.[23] It has been suggested that more precise information about nerve palsy onset, may lead to a stronger association between latency period and dose.[23] Case reports have also suggested that, though there may be a substantial delay in appearance late LCNP symptoms, but once nerve palsy occurs consequential decline in functional status is progressive and rapid over subsequent months.[15,25]

Progression of late LCNP

Late LCNP is a progressive disease. An earlier prospective study among 3 OPC survivors with LCNP, suggested that these patients could experience severe decline in function overtime, as per patient reported MDADI scores.[15] Long-term deterioration of swallowing function was also noted using clinician rated modified barium swallow (MBS) scores as per validated Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) criteria, as well as diet score rated on the Performance Status Scale of Head and Neck Cancer (PSS-HN).[15] An earlier study among NPC patients had reported a late LCNP cumulative incidence of 5.7%, 17.4%, 27.1%, and 37.3% over a 5, 10, 15, and 20-year follow up respectively.[20]

Therefore, the risk of cranial nerve damage increases overtime and as a late treatment-associated toxicity, LCNP has long term implications on the functional status of survivors. Further, as survival probabilities improve for OPC late-effects like neuropathy are more likely to occur, and patients should be followed for extended periods of time to assess and treat these late complications.

Late LCNP and Late Radiation-Associated Dysphagia (late RAD)

Late Radiation Associated Dysphagia (late RAD) is a severe form of dysphagia, which occurs among HNC patients many years after RT. It may contribute to severe problems in swallowing, eating, and extreme functional impairment in pharyngeal phase of swallowing, which may cause swallowing inefficiency, pharyngeal residue, and silent aspiration.[19] Overtime about 85% of OPC survivors with late-RAD, develop pneumonia and more than 60% of them required long-term gastronomy tube placement.[19, 41]

OPC patients in recent times tend to be middle-aged and are expected to survive decades after treatment, thereby it is more likely that these patients may develop late toxicities like late RAD.[1, 19]This idea is supported by findings from a recent study, which reported that that 86% patients with late-RAD were OPC survivors.[19]

The prevalence of Late RAD is low with an estimated rate of 12%.[19, 22] However as majority of OPC patients survive and eventually transition from oncologic management to care of primary care physicians, they may be lost to follow-up. Therefore, lack of adequate

surveillance may contribute to lower prevalence estimates of late toxicities like late RAD and even late LCNP.

Patients with late RAD also often present with lower cranial neuropathies.[19] It is postulated that LCNP potentially leads to the accelerated functional decline among patients with late RAD.[19] Late RAD patients often have unilateral paralysis, muscle wasting leading up to atrophy of lingual and pharyngeal musculature implicating a prominent role of nerve injury in the functional decline experienced by these patients.[47] In an earlier case series 48% of patients with late RAD had clinically-detectable cranial neuropathies, and cranial nerve XII and X palsies were most commonly reported.[48] Further, another study reported that 90% of patients with late RAD displayed evidence of some evidence of loss of innervation to suprahyoid muscles in the pharynx when tested by EMG.[50]

Bulbar Palsy along with neuromuscular fibrosis, is suggested to contribute to functional impairment among late RAD patients.[19] A recent case report indicated that treatment-related LCNP may play a major role in late RAD, and precipitate delayed but extreme chronic oropharyngeal impairment and increased pharyngeal impairment, as recorded by modified barium swallow (MBS) studies.[14] It was reported that Late LCNP patients with late-RAD, experienced deterioration of diet and speech scores, as reflected by Performance Status Scale for Head and Neck cancer (PSS-HN) scores.[14] They reported low scores with MD Anderson Dysphagia Inventory (MDADI), which reflected overall impairment of swallowing related quality of life.[14] Further, the functional status of cases emulated the trajectory of neuropathy experienced by patient i.e. if the late LCNP remained stable, physiologic impairment experienced by patient remained steady and if the late LCNP

was progressive then patient experienced severe decline in function, and decline in body weight.[14] Most importantly late-RAD patients including those with late LCNP, do not typically respond well to treatment and experience excess disease morbidity and functional impairment overtime.[14, 41]

Late LCNP may have a significant impact on dysphagia experienced by OPC survivors, many years after treatment and cause extensive functional impairment and result in poor swallowing related QOL. The functional impact of late LCNP has not been studied in a study with substantial numbers of OPC survivors and given that it is an area of concern among late LCNP patients, we investigated the impact of late LCNP on dysphagia and swallowing related QOL among OPC survivors.

Gap in Knowledge/Unmet Need: Previous studies examining late radiation-associated LCNP have mostly been case reports of nasopharyngeal cancer survivors. Few studies have addressed late LCNP among OPC survivors, the largest to date comprising only 3 late LCNP cases in a cohort of 59 OPC survivors.[15]With a rapidly growing pool of OPC survivors who have received curative doses of radiotherapy, there is urgent need to investigate this disabling late effect of therapy. Late LCNP is a debilitating, permanent condition, and can have a profound impact on QOL of OPC survivors yet we know little to predict or understand the continuum of associated toxicities.[14] For the growing numbers of OPC survivors at risk for and experiencing late LCNP, needed to identify risk profiles of those most vulnerable to late LCNP and subsequent late effects to help in the development of more targeted preventive strategies and interventions.

The overall objective of this research plan was to characterize risk and burden of late LCNP among OPC survivors.

This research is expected to contribute to a comprehensive understanding about late LCNP in terms of incidence, predictors of risk, and impact on functional outcomes including swallowing-related QOL, symptom burden, and functional impairment and among OPC survivors.

The contribution of the proposed research will be significant because once we identify predictors of late LCNP and associated late toxicities; we can identify high-risk populations who are most vulnerable for future implementation of targeted preventive interventions to alleviate late effects of cancer treatment among OPC survivors. Also, our study may provide

support for recommendations for ongoing surveillance of late-toxicities experienced by OPC survivors to promote timely treatment of side-effects.

Public Health Significance

This research will support future research of late effects experienced by OPC survivors by providing information about late LCNP which has not been previously studied among a large cohort of more than 2,000 OPC survivors and its impact on morbidity and decline in function among these patients. Late LCNP experienced by OPC survivors may lead to placement of feeding tubes, tracheostomy tubes, and aspiration which can lead to pneumonia. Therefore, patients may be hospitalized and such adverse consequences lead to increase in medical costs.

The results from this study have the potential to inform the development and implementation of ongoing surveillance, risk-reduction, and preventive interventions which could be implemented early and be personalized to meet individual needs to allow for more strategic allocation of resources and lower health care cost.

OPC patients have excellent prognosis in terms of survival therefore de-escalation of treatment may be a viable option to reduce treatment-associated late toxicities like LCNP. Risk-based OPC treatment planning, use of targeted therapies, nerve-sparing RT planning to decrease irradiation of vital structures which play an important role in swallowing, or sequential chemoradiotherapy may help to alleviate late effects like LCNP and improve function among survivors. Knowledge about predictors of late LCNP and its consequent impact on swallowing function and overall symptom severity will allow more effective delineation of de-escalation targets.

Among NPC patients, neuro-nutritional agents, glucocorticoids, and hyperbaric oxygen can be administered early to alleviate functional symptoms and prevent progression of nerve damage and such treatment, if viable, might be suggested to OPC patients with late

LCNP.[44] Further, as among NPC patients, laryngoplasty, tracheostomy, and gastrostomy tube placement may help manage voice hoarseness, respiratory function, and maintain adequate nutritional intake and thereby have the potential to improve QOL in such patients.[19] Similar options can be explored for OPC patients and more informed treatment decisions can be made with better understanding of the continuum of late LCNP and its associated functional implications.

The study identified predictors of LCNP, which can inform future research in terms of reducing treatment exposure. Currently, treatment of OPC does not vary by HPV status and this study has the potential to inform future clinical trials investigating de-escalation of OPC treatment based on HPV status. Further, this study has the potential to inform future screening and surveillance recommendations among OPC survivors, given the delayed progression of late LCNP. As neuropathies may be experienced among patients with other head and neck cancers, findings from this study may be extrapolated to inform survivorship research for such patients. The study will thereby address tertiary cancer prevention among OPC patients and help alleviate disease morbidity experienced by OPC patients over time.

SPECIFIC AIMS

The incidence of oropharygeal cancer (OPC) is increasing by 5% each year and it is projected that by 2030 about half of head and neck cancers (HNC) will be OPC.[1]This phenomenon is attributable to the to the epidemic of HPV-associated OPC which is usually diagnosed in patients who are middle aged, and despite advanced-stage have biologically favorable disease with excellent prognosis for long-term survival. Survivors may experience severe side-effects over-time due to cancer treatment and thereby experience excess morbidity and disability compared to other cancer survivors. It has been estimated that 20%-50% HNC survivors experience disability from treatment toxicities and are unable to work.[2-5] Late lower cranial neuropathies (LCNP) are a rare, but potentially severe late effect induced by damage due to radiotherapy (RT). Fibrosis of nerve tracts or adjacent soft tissues may lead to delayed but progressive neuro-vascular damage and eventually neuropathy which over time causes profound functional impairments.[16] According to a recent report, the incidence of delayed LCNP among 59 OPC survivors was 5% at 5.7years (Hutcheson, et al).[15] While a rare late effect, case reports suggest substantial functional burden including profound impairment in swallowing, speech, voice and shoulder function and overall low quality of life in survivors who develop LCNP.[14-16,19]

Gap in Knowledge/Unmet Need*:* Previous studies examining late radiation-associated LCNP have been case reports or small cohorts of predominantly nasopharyngeal cancer (NPC) survivors. Few studies have addressed late LCNP among OPC survivors. With an ever-growing pool of OPC survivors who have received curative doses of radiotherapy likely sufficient to induce LCNP, there is urgent need to investigate this disabling late effect of

therapy. Late LCNP is a permanent condition and may have a profound impact on quality of life (QoL) of OPC survivors yet we know little to predict or understand the continuum of associated toxicities.[14-16] For the growing numbers of OPC survivors at risk for and experiencing LCNP, we must identify risk profiles of those most vulnerable to LCNP and subsequent late effects to help in the development of more targeted preventive strategies and interventions.

Objective: The *overall objective* of this application was to characterize risk and burden of late LCNP among OPC survivors.

Central Hypothesis: Our *central hypothesis* was that OPC survivors with late LCNP will experience higher levels of functional burden and symptom burden that impact their quality of life (QoL) relative to survivors without LCNP, and that significant predictors of late LCNP can be identified in this study to help target the high-risk populations for risk reduction strategies.

Rationale: The *rationale* for this research was that once we identify predictors of late LCNP and associated burden, we can identify high-risk populations who are most vulnerable for future implementation of targeted risk reduction strategies to alleviate late effects of cancer treatment and improve QoL among OPC survivors.

Our study population comprised a cohort of disease-free OPC survivors diagnosed and treated at MD Anderson Cancer Center, January 2000 -December 2013 with a nested cross-sectional survivorship survey.

Specific aims:

Aim1: To estimate the risk of late lower cranial neuropathies (LCNP) in patients with oropharyngeal cancer (OPC) and identify clinical predictors for late LCNP.

Aim 1(a): To estimate the cumulative incidence of late LCNP among OPC survivors.

Hypothesis: Based on preliminary data, we expected the 5-year incidence rate of late LCNP will be estimated at 5%.

Aim 1(b): To identify clinical predictors for late LCNP among OPC survivors.

Hypothesis for Aim 1(b): We hypothesized that risk of LCNP, will be correlated with tumor subsite and stage, radiation dose, fractionation schedule, smoking status, and systemic therapy.

AIM 2: To compare severity of treatment related symptoms and swallowing-related QoL by LCNP status among oropharyngeal cancer (OPC) survivors.

AIM 2(a): To compare the severity of treatment-related symptoms and subsequent impact on General Functional Impairment (GFI), by LCNP status among oropharyngeal cancer (OPC) survivors.

We assessed the impact of late LCNP on severity of treatment-related symptoms and general functional impairment using the MD Anderson Symptom Inventory Head and Neck Cancer Module (MDASI-HN) survey after end of cancer treatment.

Hypothesis: We hypothesized that LCNP status among OPC survivors, will be associated with higher symptom scores (per mean of top 5 most severe core and head and neck specific scores on MDASI-HN survey) and significantly higher levels of GFI (per mean interference scores on MDASI-HN survey) than those without LCNP.

AIM 2(b): To compare swallowing-related QoL by LCNP status among oropharyngeal cancer (OPC) survivors.

Impact of late LCNP on swallowing-related QOL was assessed using the MD Anderson Dysphagia Inventory (MDADI) survey after end of cancer treatment.

Hypothesis for Aim 2(a): We hypothesized that LCNP status among OPC survivors will be associated with significantly worse swallowing-related QOL (per MDADI survey) than those without LCNP.

Expected Outcomes:

It was anticipated that the aims will yield a comprehensive understanding about late LCNP in terms of incidence, predictors of risk and impact on functional outcomes, symptom burden, functional impairment and QOL among OPC survivors. We hope to inform the development of effective risk reduction and management strategies for this rare but devastating late effect of therapy.

Figure 1: Overall Late LCNP Risk & Burden Study Aims

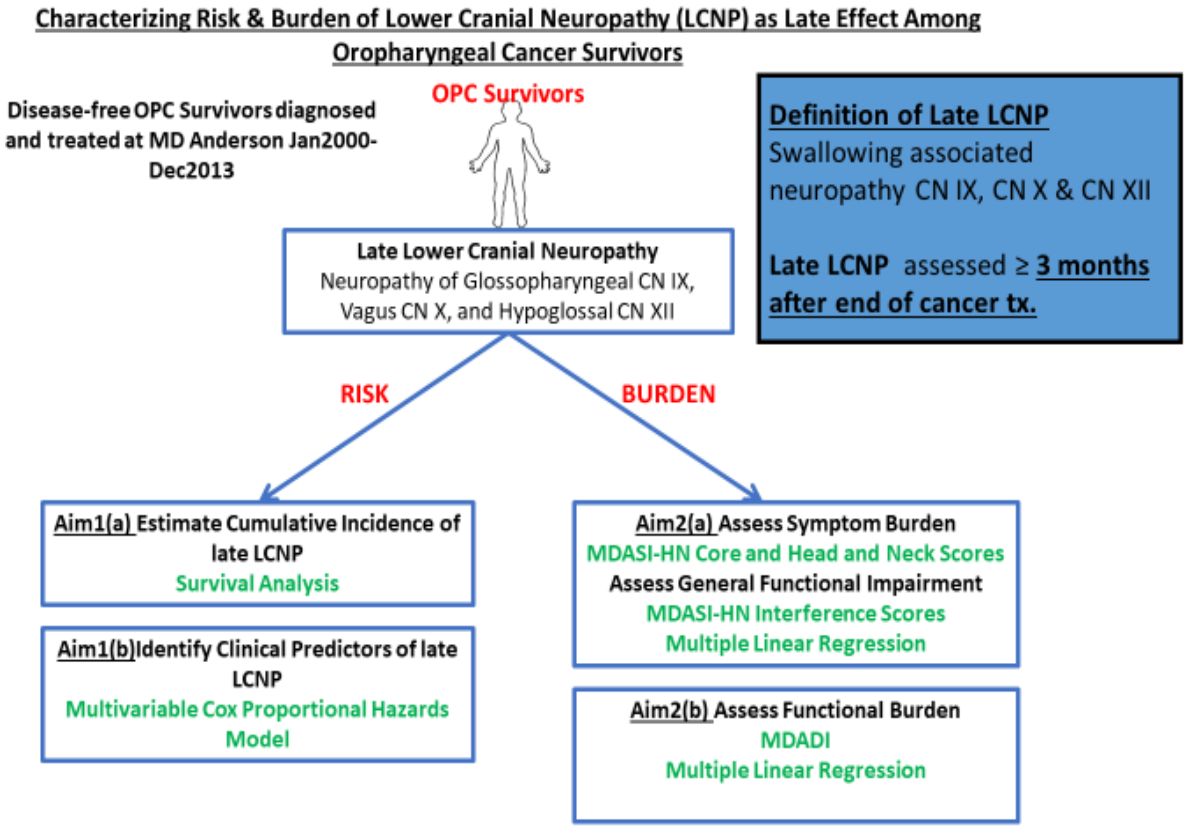

Figure 1: Overall Late LCNP Risk & Burden Study Aims.

OPC – Oropharyngeal Cancer, **LCNP** – Lower Cranial Neuropathy, **MDADI** – MD Anderson Dysphagia Inventory, **MDASI-HN** - MD Anderson Symptom Inventory for Head and Neck Cancers (MDASI-HN)

GENERAL STUDY METHODOLOGY FOR SPECIFIC AIM 1 AND 2

Definition of Late LCNP

Late LCNP was defined as **swallowing-associated neuropathy of glossopharyngeal (IX), vagus (X) and hypoglossal (XII) nerves,** which are critical to the oropharyngeal phase of swallowing mechanism and speech production. The degeneration of these nerves potentially results in substantial amounts of dysphagia and functional impairment, based on case report evidence (Hutcheson, et al).[14-16,18,19] **CN XI or Accessory Nerve palsy** was rare and reports suggested that it occurs less frequently than CN X and CN XII palsy. It has been suggested that this may be due to the course of CN XI, in the posterior part of the neck, which may not receive as much radiation as the anterior part. Further, this nerve may also be protected from radiation damage by the cervical nerve. [28] CN XI palsy was also inconsistently recorded in medical charts. Thereby, CN XI was omitted from LNCP analysis in this research, with the intent to focus on swallowing-associated LCNP.

Late effects of cancer treatment are often defined as severe treatment associated toxicities which occur 3 months or more after end of cancer treatment. [51]

Therefore, **late LCNP** due to treatment in our study was assessed **3 months or more after the end of cancer treatment** to focus on late effects of therapy as opposed to neuropathy which may be tumor associated or an acute effect of treatment.

Descriptive Analysis Methodology: Descriptive statistics (e.g., means, ranges, standard deviations) and graphical methods (box-plots, histograms and scatter plots) were computed to explore relationship between variables of interest. Normality of continuous variables was tested, when normality assumption was met independent T-tests otherwise, Wilcoxon rank-sum test or Kruskal Wallis test was used to test for differences between groups. For categorical variables, contingency tables, chi-square (X^2) test and Fisher's exact test were used.

Clinically important covariates: included age, t-stage, subsite, treatment modality and smoking.

HPV Status: HPV status was not available in about half of the cohort, as HPV testing was not conducted consistently till 2007. But we classified patients as HPV – and HPV + based on test results. Only exploratory analysis of HPV status was conducted; therefore, HPV status information was not taken into consideration for our power analysis estimates.

Analysis Software: Data was be analyzed using the statistical software package Stata and SAS.

Hypothesis Testing: All reported p-values were two-sided and were considered to be statistically significant at p value of < 0.05.

Human Subjects

This dissertation research was a secondary analysis of existing oropharyngeal cancer data. Informed consents were signed by participants prior to participating in the cross-sectional patient reported outcome survey and in the tumor registry data. There were no benefits or risks for study participants in the conduct of the study. Only adults at least 18 years of age were recruited for this study and children were excluded.

Personal identifiers were used by selected study personnel for data abstraction and all study personnel participated in institution approved human subjects training course. Abstracted data was stored on a study database and access to database was protected by passwords. Survey forms were stored in locked cabinets and on a password protected database. Only de-identified data was used for analysis and was stored on encrypted institution approved computers and devices.

METHODS

Research and Methods for Specific Aim 1(a) & 1(b): Cumulative Incidence & Risk Prediction

Study Design

This study was a retrospective cohort study.

Study population

This study included oropharyngeal cancer (OPC) patients diagnosed and treated at MD Anderson Cancer Center, January 2000 - December 2013.

Exclusion criteria

1. Patients who were deceased, had a secondary primary malignancy (SPM) or recurrent malignancy of the head and neck before 3 months of follow-up after end of cancer treatment.
2. Patients diagnosed with LCNP before starting cancer treatment i.e. LCNP at baseline or before treatment.
3. Patients who received cancer treatment with palliative intent.

Research and Methods for Specific Aim 1(a) Cumulative Incidence

Data Collection

Primary Outcome Variable: The primary outcome variable for this aim is late LCNP among all eligible OPC survivors in our study population.

Diagnosis of Lower Cranial Neuropathy (LCNP): LCNP status among patients was assessed by clinical examination of cranial nerves by head and neck surgeon, radiation oncologist and speech pathologist and is recorded in the charts of patients.

Data Abstraction from Medical Records: Medical records were reviewed to identify cases of LCNP. Case status was verified by head and neck specialized physician review. Time to event of LCNP diagnosis was also be collected.

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Variables: Demographic, clinical information, treatment related factors, health behaviors and HPV status were abstracted from medical charts using a structured study forms.

Demographic Variables: included age, sex, race and education.

Clinical Variables: included T and N staging, sub-site, OPC treatment modality, RT dose, mode of RT, RT fractionation schedule, chemotherapy, surgery, lack of solid food diet at baseline (as a surrogate of baseline dysphagia), and smoking status.

Power Analysis

The power analysis of this aim addressed the precision of our cumulative incidence estimate, by calculating 95% confidence intervals using late LCNP event rates between a range of 0.02 – 0.10. An earlier study among 59 OPC survivors, treated on clinical trials at MDACC by Hutcheson et al has suggested a LCNP cumulative incidence of 2.1% at 6-year follow-up of (95% CI: 0.2%,10%) which suggests our assumption to detect a 5- year incidence of LCNP of 5% is reasonable.[7]

On the basis of tumor registry estimates, assuming that 95% OPC patients are alive at 3 months such that late LCNP outcome can be assessed among these patients, as well as loss to follow-up and missing data rate of 20%, [52] we will have a sample size of 2683.

About half of our cohort has missing information for HPV status. As we did not believe HPV status influences risk of late LCNP, only exploratory analysis of HPV status was conducted in our study and was not be the focus of any of our power analysis estimates.

We used the following formula to calculate the 95% confidence interval of our cumulative incidence estimates of 0.02-0.10.

Formula of 95% Confidence Interval for Incidence Proportion

$95\%CI = P \pm 1.96 \sqrt{P(1-P) / N}$
Where P= incidence proportion and N= sample size

Confidence Interval and Precision of Estimate of Incidence N= 2683

LCNP Event Rate	95% Lower Bound CI	95% Upper Bound CI
0.02	.015	.025
0.03	.023	.036
00.04	.032	.047
0.05	.042	.058
0.06	.051	.069
0.07	.061	.079
0.08	.070	.090
0.09	.080	.101
0.10	.096	.104

Literature Review, Research and Methods for Specific Aim 1 (b): Risk Prediction

Literature Review Specific Aim 1

Earlier studies have revealed that age, tumor subsite, tumor stage (T-stage) and pre-treatment swallowing scores as per MDADI may have an impact on swallowing scores as per MDADI overtime. [53-55]Similarly another review among OPC patients treated with transoral robotic surgery, also reported that pre-treatment swallowing function, T-stage, N-stage, primary subsite involving base of tongue and adjuvant chemoradiation may predict swallowing outcomes and toxicity.[56]

Treatment Intensity: HNC patients treated with non-surgical therapy had previously reported, that treatment intensity as per patients treated with less <50 Gy had significantly better swallowing scores on the MDADI, than those treated with higher RT dose or chemoradiation ($p < 0.001$).[57] Therefore patients treated more aggressively with greater treatment intensity or combined modality, may be more likely to develop late toxicities like late LCNP.

Swallowing scores prior to treatment: In a previous study, swallowing scores prior to treatment explained 13% of the variance in long-term swallowing scores among HNC patients.[57] Therefore, patients not eating solid food at baseline (prior to treatment) may have some pre-treatment swallowing dysfunction, which may be tumor-associated and may eventually contribute to development of late LCNP overtime.

Tumor Stage (T-Stage): OPC patients withT1 and T2 tumors, have reported significantly better swallowing scores as per MDADI (+15.9, p=0.0001 and + 10.9, p=0.0049 respectively) than patients with T4 tumors.[53] This may be due more aggressive treatment of advanced OPC tumors, which may have a detrimental impact on long term toxicities like late LCNP and late-RAD.

Smoking: Current smokers have also reported significantly worse swallowing scores as per MDADI (- 9.4 points, p=0.0007) compared to nonsmokers.[53] Further smoking can lead to worse functional outcomes and inferior prognosis overtime, for both HPV positive as well as negative disease.[53] Smokers therefore may experience greater disease morbidity and late treatment -related toxicities like late LCNP.

Age: An earlier study reported that younger HNC patients reported worse swallowing scores overtime.[57] This may be due to higher expectations of younger patients to resume work and daily activities after treatment, which when unmet lead to greater dissatisfaction and higher disease burden. Given the long latency period for late LCNP, these patients may eventually develop late toxicities like late LCNP.

Survival Time: Further long-term survival of OPC patients, may also contribute to higher chances of them developing late LCNP. Survival time will refer to difference between time of diagnosis and time of last follow-up.

In summary, age, T and N staging, sub-site, pre-treatment swallowing dysfunction, smoking and survival time may act as potential confounders, contributing to development of late toxicities like late LCNP. These variables were evaluated and controlled for in our analysis to obtain adjusted effect estimates for predictors of late LCNP in our study.[52, 54, 55, 57]

Effect Modifiers: There was insufficient evidence in literature to suggest any specific effect modifiers, and given that late LCNP was rare, we did not have enough power to explore effect modification in this study. We however conducted exploratory analysis of biologically plausible interaction terms between treatment variables including RT dose, age, survival time and smoking.

Research and Methods

Study Design: Same as Aim 1 a

Study population: Same as Aim 1 a

Exclusion criteria: Same as Aim 1 a

Data Collection

Primary Outcome Variable: Same as Aim 1 a. The primary outcome variable for this aim was late LCNP, among all OPC survivors in our study population.

Definition of Late LCNP: Same as Aim 1 and Aim 2

Diagnosis of Lower Cranial Neuropathy (LCNP): Same as Aim 1 a

Primary Exposure: Radiation therapy (RT) was the exposure of interest for this aim, as most OPC patients receive either RT alone or in combination with systemic therapy and exposure to surgery alone or surgery in combination to adjuvant therapy is rare. RT dose which has been suggested by the literature as one of the main predictors of LCNP was the primary exposure for this aim.[14-16]

Predictors

RT dose, mode of RT, RT fractionation schedule, chemotherapy, surgery, eating solid food at baseline and smoking are some of the variables based on literature review which may influence risk of late LCNP and may act as predictors along with our main predictor RT dose.[15,17,18,42,46] Thereby these variables were assessed in our proposed study and investigated as potential predictors of late LCNP among OPC survivors.

Covariates

Demographic, clinical information, treatment related factors, health behaviors and HPV status were abstracted in Aim 1 a.

Demographic covariates included age, sex, gender, race and education.

Clinical covariates included T stage, sub-site, treatment modality, RT dose, mode of RT, RT fractionation schedule, chemotherapy, surgery, lack of solid food diet at baseline and smoking

Survival Time was defined as the number of years a patient survives after diagnosis.

Power Analysis

The power analysis of this aim addressed the specific hypothesis that risk of LCNP, would be correlated with tumor subsite and stage, radiation dose, fractionation schedule, smoking status, and chemotherapy. A previous study revealed that the event rate of late LCNP among 59 OPC survivors was 5%.[15]

We assumed reasonable tumor regression rates and that 95% OPC patients are alive at 3 months, so late LCNP outcome could be assessed among these patients. We also assumed a loss to follow-up and missing data rate of 20%, [52] therefore we would have a sample size of 2683. Assumptions derived from unpublished pilot data (PA11-0809, PI: Hutcheson), included a standard deviation for radiation dose of 2.59.

A previous study conducted among NPC survivors reported that total radiation dose to nasopharynx above 70Gy may be a significant predictor for cranial neuropathy (RR = 1.961, $p = 0.009$) and lower cranial neuropathy (RR= 3.088, $p < 0.001$).[20] Given the low event rate of late LCNP, retrospective study design, loss to follow-up, and possibility of missing data we assumed we would find a small effect size of 1.4 according to Cohen's conventions for small effects. Therefore, assuming hazard ratios for late LCNP a range of 1.1 – 1.4 we calculated the power for this aim.

As per the reasons stated above we also assumed that the R square or the variation in our primary predictor RT dose explained by the 13 predictors in the cox model would range

from 0.2, 0.3 and 0.4. This would allow us to derive power calculations for this study capturing a range of effect sizes which fit Cohen's conventions for medium and large effect sizes for multiple R square which was a plausible assumption for this model.

Proc Power in SAS with assumptions mentioned above was used for the power calculations and are listed in the table below.

R-square	**Hazard Ratio**	**Power**
0.2	1.1	0.725
0.2	**1.2**	0.998
0.3	1.1	0.667
0.3	**1.2**	0.996
0.4	1.1	0.601
0.4	**1.2**	0.988

Therefore, we observed that at a modest assumption of R-square of the important covariates explaining only 20% of the variation in radiation dose, assuming late LCNP event rate of 5%, loss to follow-up and missing data rate of 20%, standard deviation of radiation dose of 2.59, hazard ratio range of 1.1 – 1.4 with a R-square range of 0.2 – 0.4 with n=2683, we would have 99% power to detect a reasonable hazard ratio of 1.2 for radiation dose and late LCNP

Research and Methods for Specific Aim 2 (a) & (b): Symptom Burden & Functional Burden

Study Design

This study was a cross-sectional survivorship study.

Study population for Aim 2

This study will include a sub-cohort (907) of the population in Aim 1, who responded to a cross-sectional survivorship survey that was conducted among OPC survivors treated at MD Anderson Cancer Center during January 2000 -December 2013.

Key exclusion criteria

1. Patients who were deceased, had a secondary primary malignancy (SPM) or recurrent malignancy of the head and neck preceding the survey administration
2. Patients lost to follow up or refused contact by MD Anderson prior to survey administration
3. Patients whose primary spoken language is not English.
4. Patients diagnosed with LCNP or with clinical signs of LCNP before starting cancer treatment i.e. LCNP at baseline.

Survey Characteristics

Cross-sectional Survey: A cross-sectional patient reported outcome survey was administered to OPC survivors in Fall, 2015, and included the following validated instruments and study-specific items: MD Anderson Dysphagia Inventory (MDADI), MD Anderson Symptom Inventory Head and Neck Cancer Module (MDASI-HN), decisional regret, and adapted patient-reported version of Performance Status Scale for Head and Neck cancer (PSS-HN), EQ5D, and adapted NHANES terminology for head and neck specific health problems (osteoradionecrosis, lymphedema, aspiration, thyroid problems, stricture of throat or esophagus, pneumonia and hospitalization), as well items pertaining to feeding tube, tracheostomy, smoking, and employment status .

MD Anderson Dysphagia Inventory (MDADI) is a validated patient reported outcomes (PRO) survey, with 20 questions that quantify perceived limitations in swallowing ability of OPC patients and their impact on day to day activities of these patients.[58] MDADI was validated among HNC patients and has internal consistency scored by Cronbach's alpha of 0.96 and was documented to have test-rest reliability correlations ranging from 0.69 to 0.88.[58]

The survey provides subscale scores which are comprised of emotional (based on 6 questions), physical (based on 8 questions), and functional scores (based on 5 questions). It also estimates a global summary score (based on 1 question- "My swallowing limits my day to day activities") and composite score (based on 19 questions). The composite MDADI

score is comprised of responses from 19 questions on the survey which are considered to reflect overall swallowing related quality of life.[54, 58-60]

Scoring of MDADI: The questions related to swallowing function are Likert scaled with the options strongly agree, agree, no opinion, disagree and strongly disagree, scored on a scale of 1-5, respectively, with the exception of two questions (E7 and F2) for which reverse scoring is calculated. After summation of response scores, mean is estimated and multiplied by 20 to estimate total score.[54] Total scores range from 20-100 with higher scores reflecting higher perceived swallowing-related QOL.[54, 58-60]We can use MDADI scores as continuous or categorical variables. For categorical variables MDADI scores will be classified in the following categories: ≥80 as optimal, 60-79 as adequate and < 60 as poor.[53]

MD Anderson Symptom Inventory Head and Neck Cancer Module (MDASI-HN) is a validated patient reported survey used to evaluate severity of cancer treatment related symptoms and their subsequent impact on functional status, as well as day to day activities of head and neck cancer patients. MDASI-HN comprises 28-items including 13 questions to assess core symptoms common across all cancers, 9 questions to assess symptoms specific to HNC like presence of mucus, swallowing problems, choking, voice problems, pain, constipation, taste issues, presence of sores and oral problems.[61-64] The head and neck specific items relate to common treatment related toxicity experienced by HNC patients due to radiotherapy or chemoradiotherapy .[62] Further, there are 6 interference questions to assess the impact of symptoms experienced by patient on daily function with respect to “general activity”, “walking”, “work”, “mood”, “relations with other people” and “enjoyment of life”.

The internal consistency reliability for MDASI-HN has been estimated with Cronbach alpha of 0.72 to 0.92.[62]

Scoring of MDASI-HN: MDASI-HN symptom severity items have a range from 0 to indicate "not present" to 10 for "as bad as you can imagine" wherein lower scores on core and site-specific domains indicate better function. Interference items also have a range from 0 to indicate "do not interfere" to 10 for "interfere completely" such that higher scores indicate more limitations experienced by patients and indicate lower QOL.[61-64] Mean subscale scores for core, head and neck and interference domains can be estimated as mean intensity of those specific domains. Mean global score is estimated as mean of scores of all 28 questions on the survey. [61-64]

We can also use symptom and interference scores as categorical variable where scores will be categorized as no symptoms (score=0), mild (1–3), moderate (4–6) and any one item rated as severe (7–10) symptoms, as per Cleeland et al.[64]

Literature Review, Research and Methods for Specific Aim 2 (a): Symptom Burden

We will assess the impact of late LCNP on symptom burden using the MD Anderson Symptom Inventory Head and Neck Cancer Module (MDASI-HN) survey.

Literature Review

Symptom Burden

Symptom burden is a concept which incorporates severity of symptoms experienced by patients and the impact of those symptoms on their day-today life.[65] Symptom burden thereby combines symptom severity and symptom interference (surrogate measure for general functional impairment) reported by a substantial proportion of patients suffering from a specific disease. Patients may experience symptoms due to disease, recurrence or as a consequence of treatment related toxicity, which can be acute and occur during or immediately after treatment.[65] Patients can also suffer from late-toxicities such as late LCNP many years after treatment completion, which can lead to high symptom burden among HNC and OPC survivors. It has been suggested that a complex interplay between patient level, cancer and treatment related factors may contribute symptom burden.[66]

Symptom Burden among HNC and OPC Survivors

HNC patients endure substantial symptom burden, as they often experience debilitating symptoms which may compromise their physical appearance, swallowing, speech, oral health and respiratory function.[65, 67] HNC treatment may lead to multiple

complications including mucositis, dry mouth, dysphagia, choking, speech problems, lack of taste, pain and neurotoxicity among others which can contribute to excessive symptoms, distress, and overall lower quality of life.[68, 69]

Patients may also experience fatigue, emotional distress, feel self-conscious, and have low self-esteem which may contribute to feelings of social isolation.[76, 79] About 22-57% HNC patients experience depression and symptoms of anxiety, indicating high levels of psychological distress.[70, 71] In fact, studies have even reported that HNC patients may have an elevated risk for suicide (four times higher) than the general population.[72]

Thereby, symptoms of distress experienced by HNC patients may have a negative impact on the physical and emotional domains of health-related QOL.[73] Prospective cohort studies among HNC survivors have reported health related quality of life (HRQOL) scores (10 years post-diagnosis) to be significantly lower than their pre-treatment HRQOL scores.[83,84] The link between symptom burden and QOL is important, as studies among HNC patients have reported that QOL domains can predict survival.[76-78] A systematic review reported improved survival among HNC patients, with less psychosocial distress, high self-efficacy and physical function.[79]

Predictors of Symptom Severity

According to previous literature, age, sex, race, T-stage, tumor subsite, radiation dose, fractionation schedule, induction chemotherapy, concurrent systemic therapy, timing of

radiation treatment (definitive versus post-surgery or adjuvant) and smoking are some of the variables associated with treatment associated toxicity and symptom burden.[68,67]

An earlier longitudinal study among HNC patients reported, that pre-treatment MDASI-HN scores (coefficient = 0.55, $p < 0.001$), concurrent chemotherapy (coefficient = 18.77, $p=0.016$), site of primary tumor (coefficient = 5.03, $p=0.016$) and definitive versus adjuvant radiation treatment (coefficient = 15.01, $p=0.044$) in a multivariate model, were significantly associated with MDASI-HN scores at week 5 of radiation treatment.

As most OPC survivors have long-term survival, minimizing severity of treatment related symptoms, are a critical component of OPC treatment today. In our research study we assessed the impact of late LCNP on severity of treatment related symptoms among OPC survivors.

Severity of treatment related symptoms: for our study was defined as, severity of core symptoms common across all cancers and symptoms specific to head and neck cancers and would be correlated with functional impairment measured by MDASI-HN interference scores experienced by survivors as a consequence of cancer treatment.

General Functional Impairment (GFI)

General Functional Impairment (GFI) is defined as diminished of ability of a survivor to take care of himself or herself, manage the household, work, and indulge in activities for relaxation. Thereby GFI can have an adverse impact on the daily lives of cancer survivors.[80]

OPC patients may endure severe treatment related symptoms (symptom severity) overtime, which may have a detrimental impact on GFI and symptom interference scores. For some patients, the impairment is temporary, and with time they return to their normal activity and functional level. But a substantial number of OPC survivors continue to experience these limitations, experience disability and may be unable to return to normal activities including work leading to decline in income.[80]

There is need to understand the impact of long term GFI in the growing pool of OPC survivors, as few studies in the past have investigated it and most of the literature related to GFI is pertaining to its impact on employment.

According to a previous study about 32.9% and 41.9% of HNC patients experienced unemployment and reduction in income respectively.[80] Previous studies among HNC patients report fatigue, pain, problems in speech, eating and facial appearance as reasons that survivors do not return to normal activities including work.[80] Likewise, advanced clinical stage disease, alcohol exposure, and less education are some of the factors associated with disability.[89] Among HNC survivors, socioeconomic factors like education and income particularly are associated with unemployment.[80] Therefore, GFI was a secondary outcome of interest and impact of LCNP on GFI was assessed, using mean MDASI-HN scores from the interference component.

Confounders

According to previous literature age, sex, race, T-stage, tumor subsite, radiation dose, fractionation schedule, induction chemotherapy, concurrent systemic therapy, surgery, eating

solid food at baseline, timing of radiation treatment (definitive versus post-surgery or adjuvant) and smoking were some of the variables associated with treatment associated toxicity and symptom burden.[68,67]

These variables may affect severity of treatment-related symptoms, MDASI-HN scores and can act as potential confounders Therefore these variables along with patients eating solid food at baseline (control for pre-treatment swallowing dysfunction) and survival time were evaluated as confounders and controlled for in multivariate models, to estimate the adjusted association between late LCNP and top 5 mean MDASI-HN and mean MDASI-HN interference scores.

Effect Modifiers: There was insufficient evidence in literature to suggest any specific effect modifiers, and given that late LCNP is rare we did not have enough power to explore effect modification in this study; however, exploratory analysis of biologically plausible interaction terms between treatment variables, age survival time and smoking were assessed.

Research and Methods

Data Collection

Primary Outcome

Mean MDASI-HN symptom scores, which summarize information from all 22 items of core and head and neck specific components, were described in association with late LCNP to reflect overall symptom severity. We also identified a cluster of top 5 most severe symptoms reported by OPC survivors, to identify most important core and head-neck symptoms reported by this population. This methodology was supported by other symptom research studies. Some symptoms may be more commonly reported by this population, be more severe and may have a greater impact on the life of survivors, whereas others may be rare. Thereby overall composite MDASI-HN scores may not be a true reflection of treatment related symptom severity in this population.[81, 82]

Therefore, mean of Top 5 most severe core and head and neck specific symptoms reported, by OPC survivors in this study was the primary outcome to reflect severity of most prevalent treatment-related symptoms in this population.

Primary Exposure: Late LCNP among OPC survivors will be the primary exposure for this aim. Late LCNP was assessed as described earlier. OPC survivors without late LCNP served as the comparison group to test differences in MDASI-HN scores by late LCNP status.

Variables

Covariates for this aim included:

Demographic variables – Age, Sex, Gender, Race, Education

Clinical variables - T and N staging, tumor sub-site, treatment modality, RT dose, mode of RT, RT fractionation schedule, chemotherapy, surgery, patient eating solid food at baseline, smoking and overall modality of treatment.

Survival time will be defined as the number of years a patient survives after diagnosis and will be calculated as the difference between age at diagnosis of OPC and age at time of survey

Secondary Outcomes for Aim 2b

GFI was a secondary outcome of interest, and impact of LCNP on impairment was assessed using mean MDASI-HN scores from the interference component. Covariates for this outcome as suggested by literature included age, education, race, education, T-stage, survival time, alcohol consumption, marital status, BMI and co morbidity.[89] Single item scores of the top 5 most severe reported core and head and neck specific symptoms were also be assessed, and associations of LCNP with these important symptoms were determined. We controlled for the same covariates listed above for primary outcome.

Power Analysis Aim 2 b

The power analysis of this aim addressed the specific hypothesis that among OPC survivors with late LCNP, there would be higher symptom scores (per mean of top 5 most severe core and head and neck specific scores on MDASI-HN survey) than those without late LCNP. Multiple linear regression modelling this association would control for 13 variables including age, sex, race, education, survival time, tumor subsite, T-stage, radiation dose, radiation fractionation schedule, chemotherapy, surgery, smoking, and lack of solid food diet prior to treatment.[68, 67] We assumed a loss to follow-up and missing data rate of 20%[52] for our study, therefore we would have a study sample size of 726. Proc Power in SAS with assumptions mentioned above testing for a two-sided test with $\alpha = 0.05$ was used for the power calculations.

Under a fixed effects model and a conservative assumption of R squared of full model to be 0.10, we had 98% power to detect a R -squared difference for late LCNP as small as 0.02, which according to Cohen's conventions for small, medium and large effects could be classified as a small effect.

Study R square and Cohen's Conventions for Small, Medium, and Large Effects

Cohen's Effects	Cohen's F^2	Cohen's R^2	R^2 for main predictor LCNP	R^2 of full model in study	Power from study
Small	0.02	0.02	0.02	0.10	0.98
Medium	0.15	0.13	0.13	0.30	>0.99
Large	0.35	0.26	0.26	0.30	>0.99

Assumptions: Fixed effects model, Loss to follow-up and missing data rate of 20%[48], sample size n= 726, two-sided test with $\alpha = 0.05$, main tested predictor late LCNP controlling for 13 variables including age, sex, race, education, survival time, tumor subsite, T-stage, radiation dose, radiation fractionation schedule, chemotherapy, surgery, smoking and lack of solid food diet prior to treatment.

Literature Review, Research and Methods for Specific Aim 2 (b): Functional Burden

Literature Review

Dysphagia and Swallowing-related Quality of Life

Dysphagia is difficulty in swallowing and is most commonly reported functional toxicity among OPC survivors.[56,83] This toxicity may occur due to surgery, radiotherapy or chemoradiation.[56,83] Treatment intensification strategies among HNC in recent times have led to enhanced locoregional control and survival.[68] But these aggressive treatments may also contribute to debilitating treatment related toxicities including dysphagia, which can have a devastating impact on the life of HNC patients.[84] About 30-50% HNC patients treated with aggressive non-surgical treatments report dysphagia.[85]

Some patients may develop acute dysphagia which improves overtime, but others may report chronic dysphagia with progressive deterioration.[85] Dysphagia may occur also occur many years after cancer treatment, as a late functional toxicity called late-RAD, discussed earlier.[19] A pooled analysis of 3 RTOG trials of concomitant chemoradiotherapy reported that 35% of OPC survivors reported severe late laryngopharyngeal toxicity.[86] Further, a study using SEER population level data reported 3-year prevalence estimates of about 50% for dysphagia among OPC survivors.[87]

Predictors of Dysphagia

A review among HNC patients reported that total RT dose, fractionation schedule, combined treatment modality, subsite, primary tumor size, age and smoking may contribute to acute and late dysphagia.[84,85] Similarly, another systematic review among OPC patients, reported pre-treatment swallowing function, T-stage, base of tongue tumors and adjuvant chemoradiation as predictors of swallowing function.[56]

Dysphagia-aspiration-related structures (DARS) in the head and neck are vital for swallowing function and RT dose to these structures may contribute to swallowing toxicity.[85] Literature suggests that delivery of RT dose to pharyngeal constrictors, suprahyoid muscles and larynx is associated with chronic dysphagia.[68] It is also suggested that RT dose > 50 Gy to the pharyngeal region, may contribute to chronic dysphagia among OPC survivors.[68] Combined modality treatment, concomitant chemotherapy or targeted therapy, surgery after radiation including DARS regions and smoking have also been reported to contribute to worse swallowing and functional outcomes.[85]

Swallowing related Quality of Life

Given the rising numbers of OPC survivors, swallowing outcomes and speech play a crucial role in quality of life among these survivors.[88] Swallowing impairment among HNC patients can lead to increased risk of impaired airway protection, pneumonia, swallowing insufficiency, low food intake, extended gastrostomy tube dependence, weight loss and malnutrition.[88] Patients may have to modify their diet, need extended meal times, feel self-

conscious to eat in social settings and thereby contribute to social isolation and diminished QOL.[88] Literature suggests that Dysphagia has high correlation with swallowing and Quality of life outcomes over time.[53]

LCNP may have a significant impact on dysphagia experienced by OPC survivors, many years after treatment and cause extensive functional impairment and result in poor swallowing related QOL. The functional impact of LCNP has not been studied in a study with substantial numbers of OPC survivors and given that it is an area of concern among LCNP patients, we investigated the impact of late LCNP on dysphagia and swallowing related QOL among OPC survivors.

Variables in Study

Survival Time: Long-term survival of OPC patients may contribute to higher chances of them developing late toxicities including chronic dysphagia overtime, which may contribute to lower swallowing-related QoL scores on MDADI. Earlier reports indicate that age, tumor subsite, tumor stage, RT dose and MDADI scores prior to cancer treatment may predict MDADI scores at specific time points and longitudinally overtime.[53,55,57] Another review among OPC patients treated with transoral robotic surgery also reported that pre-treatment swallowing function, T-stage, N-stage, primary subsite involving base of tongue and adjuvant chemoradiation may predict swallowing outcomes and toxicity.[56] Additionally, another study among OPC patients treated with bilateral intensity-modulated radiotherapy (IMRT) with systemic therapy, on multivariate analysis revealed that older age; as per 5-year

increase in age (OR= 1.25; 95% CI = 1.04-1.51), pre-treatment diet restriction (OR= 2.78; 95% CI = 1.31-5.88), total IMRT dose; as per 5 Gy increase (OR= 5.11; 95% CI = 1.77-14.81) were significantly associated with increased risk of chronic dysphagia.[66]

T-Stage: OPC patients withT1 and T2 tumors, have reported significantly better swallowing scores as per MDADI (+15.9, p=0.0001 and + 10.9, p=0.0049 respectively) than patients with T4 tumors.[53] This may be due more aggressive treatment of advanced OPC tumors, which may have a detrimental impact on long term toxicities like Dysphagia.

Treatment Intensity: HNC patients treated with non-surgical therapy, have reported that treatment intensity i.e. patients treated with less <50 Gy had significantly better swallowing scores as per MDADI, than those treated with higher RT dose or chemoradiation (p< 0.001).[57]

Combined modality treatment: Concomitant chemotherapy or targeted therapy and surgery after radiation including DARS regions have been reported to contribute to worse swallowing and functional outcomes.[85]

Reconstructive Surgery: Oral cancer and OPC patients who had reconstructive surgery for primary tumors, have also reported significantly worse composite MDADI scores (58.8 versus 79.5, p < 0.01) compared to those who did not get treated with reconstructive surgery.[55]

Age: Oral cancer and OPC patients younger than 60 years have also reported significantly worse physical (65.8 versus 78.4, $p = 0.01$) and emotional subscale (68.3 versus 82.0, $p < 0.01$) scores on the MDADI compared those patients older than 60 years.[55]

OPC Subsite: OPC patients with base of tongue tumors have also reported significantly worse functional subscale scores on MDADI in comparison to patients with oral cancer and OPC patients with tonsillar tumors (66.7, 78.8 and 90.0 respectively, $p<0.01$).[55]

Current smokers*:* Among OPC patients, current smokers have reported significantly worse swallowing scores as per MDADI (- 9.4 points, $p=0.0007$) compared to nonsmokers.[53] Further smoking can lead to worse functional outcomes and inferior prognosis overtime, for both HPV positive as well as negative disease.[53]

Pretreatment Swallowing: Among HNC patients, earlier studies have reported that swallowing scores prior to treatment explained 13% of the variance in long-term swallowing scores. Patient's not eating solid food at baseline i.e., before treatment, may have some pre-treatment swallowing dysfunction, which may eventually contribute to long-term swallowing impairment and dysphagia. [53, 55-57, 85]

Thereby RT dose, Mode of RT, RT fractionation schedule, chemotherapy, surgery, combined modality treatment, age, subsite, eating solid food at baseline, and smoking were some of the variables that could affect swallowing outcomes and can act as confounders.[53, 55-

[57, 85] They were evaluated as confounders and controlled for in multivariate models, to estimate the adjusted association between late LCNP and composite MDADI scores.

Effect Modifiers: There was insufficient evidence in literature, to suggest any specific effect modifiers and given that late LCNP is rare, we did not have enough power to explore effect modification in this study. However exploratory analysis of biologically plausible interaction terms between treatment variables, age survival time and smoking were assessed.

Research and Methods

Data Collection

Primary Outcome: The primary outcome for this aim was mean composite MDADI score reported by OPC survivors and represents swallowing-related QOL. The composite MDADI scores was calculated as mean of responses from emotional, physical and functional components of the survey and will reflect overall swallowing related quality of life.[54, 58-60]

Primary Exposure: Late LCNP among OPC survivors was the primary exposure for this aim, as the goal was to assess the impact of LCNP on swallowing toxicities reported by OPC survivors. Late LCNP was assessed as described earlier. OPC survivors without late LCNP served as the comparison group to test differences in MDADI scores by late LCNP status.

Covariates

Covariates for this aim included;

Demographic Variables – Age, Sex, Gender, Race, Education

Clinical Variables - T and N staging, tumor sub-site, treatment modality, RT dose, mode of RT, RT fractionation schedule, chemotherapy, surgery, patient eating solid food at baseline, smoking

Survival Time was defined as the number of years a patient survives after diagnosis and was calculated as the difference between age at diagnosis of OPC and age at time of survey.

Power Analysis

The power analysis of this aim, addressed the specific hypothesis that among OPC survivors with late LCNP, there would be significantly worse swallowing-related QoL (per MDADI survey) than those without late LCNP. Multiple Linear regression modelling this association would control for 13 variables including age, sex, race, education, survival time, tumor subsite, T-stage, radiation dose, radiation fractionation schedule, chemotherapy, surgery, smoking and lack of solid food diet prior to treatment.[53,55-57,85] We assumed a loss to follow-up and missing data rate of 20%[53] for our study therefore we would have a study sample size of 726.Proc Power in SAS with assumptions mentioned above testing for a two-sided test with $\alpha = 0.05$ was used for the power calculations.

Under a fixed effects model and a conservative assumption of R squared of full model to be 0.10, we would have 98% power to detect a R-squared difference for late LCNP as

small as 0.02 which according to Cohen's conventions for small, medium and large effects could be classified as a small effect.

Cohen's Conventions for Small, Medium, and Large Effects

Cohen's Effects	Cohen's F^2	Cohen's R^2	R^2 for main predictor LCNP	R^2 of full model in study	Power from study
Small	0.02	0.02	0.02	0.10	0.98
Medium	0.15	0.13	0.13	0.30	>0.99
Large	0.35	0.26	0.26	0.30	>0.99

Assumptions: Fixed effects model, Loss to follow-up and missing data rate of 20%[48], sample size n= 726, two-sided test with $\alpha = 0.05$, main tested predictor late LCNP controlling for 13 variables including age, sex, race, education, survival time, tumor subsite, T-stage, radiation dose, radiation fractionation schedule, chemotherapy, surgery, smoking and lack of solid food diet prior to treatment.

Journal Article 1

Title of Journal Article: Risk and Predictors of Late Lower Cranial Neuropathy in Long-term Oropharyngeal Cancer Survivors: A Retrospective Cohort Study

Name of Journal Proposed for Article Submission: To be decided

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Brief Running Title: Risk and Predictors of Late Lower Cranial Neuropathy in Oropharyngeal Cancer

Key Words: Lower cranial neuropathy, oropharyngeal cancer, radiotherapy, late effects, survivorship

Abstract

Background

Lower cranial neuropathy (LCNP) is a rare, but permanent, late effect of radiotherapy (RT) and other cancer therapies. LCNP is associated with excess cancer-related symptoms, worse swallowing-related quality of life (QoL) and long-term feeding tube dependence, aspiration pneumonia, and tracheostomy. The overall objective of this paper is to quantify the cumulative incidence of late LCNP and identify clinical predictors of late LCNP among long-term oropharyngeal cancer (OPC) survivors**.**

Methods

The study population included 2,021 OPC survivors (median survival: 6.8 years) who received primary treatment at MD Anderson Cancer Center from 2000 to 2013. Late LCNP events were defined by neuropathy of the glossopharyngeal (IX), vagus (X) and/or hypoglossal (XII) nerves ≥3-months after cancer therapy. Cumulative incidence of LCNP was estimated using the Kaplan Meir method with adjustment for competing risks using time to event as the underlying metric. Log-rank test was used to assess differences between groups by LCNP status, and multivariable Cox proportional hazard models were fit.

Results

4.4% (n=88) of OPC survivors were diagnosed with late LCNP with median time to LCNP onset after treatment of 5.4 (range: 0.3-14.1; IQR: 1.6-8.5) years post-treatment. Cumulative incidence of LCNP among all OPC survivors was 0.02 (95% CI: 0.02-0.03), 0.06 (95% CI: 0.05-0.08), and 0.10 (95% CI: 0.08-0.13) at 5 years, 10 years, and 18 years of

follow-up, respectively. Multivariable Cox regression identified T4 stage vs T1 stage (HR: 3.82; 95%CI: 1.85-7.86, p<0.001) and accelerated RT fractionation vs standard RT fractionation (HR 2.15, 95%CI 1.34-3.45, p=0.002) independently associated with late LCNP status, adjusting for age, subsite, T-stage, smoking, and therapeutic modality.

Conclusion

While rare in the population overall, risk of late LCNP progressed over time to exceed 10% cumulative risk over survivors' lifetime. Our prediction model identified OPC survivors who had T4 tumors and those who received accelerated fractionation RT treatment as having a higher risk of late LCNP. Further efforts are necessary to investigate the risk and predictors for this disabling late effect of cancer treatment experienced by growing numbers of relatively younger OPC survivors who are expected to survive decades after treatment.

INTRODUCTION

Oropharyngeal cancer (OPC) incidence is increasing by 5% each year, attributable to the epidemic of Human Papilloma virus (HPV)-associated OPC. It is projected that by 2030 about half of head and neck cancers (HNC) will be OPC.[1] In recent decades, HPV-associated OPC has dramatically transformed the OPC patient population such that today's typical OPC patients are middle aged, male, white, non-smokers and non-drinkers, have a high socioeconomic status, and are often diagnosed at a more advanced stage (per AJCC 7th edition).[1-4] As a consequence of modern regimens of organ preserving radiotherapy, favorable biology, and improved prognosis due to better response to treatment, these patients have excellent prognosis and are often expected to live for decades despite advanced stage disease at presentation.[2-4] HPV associated HNC patients have better 3-year (HPV: 82.0% vs. HPV-negative 57.0%) and 5-year (RR=0.40; 95%CI 0.20-1.08) overall survival rates in comparison to HPV negative HNC patients.[2,3] As the lifespan of OPC survivors increase, they are more likely to experience severe side-effects over time due to delayed tumor and cancer treatment-related toxicities. For most part, OPC survivors experience excess morbidity and disability compared to other cancer survivors. These late effects may lead to debilitating problems in critical physiological functional activities including swallowing, eating, breathing, and speaking. In fact, according to a survey study in 2004, 52% of HNC patients of mixed sites experienced disability due to cancer treatment and were unable to work due to these problems.[5]

Lower cranial neuropathy (LCNP) is a rare but permanent and potentially devastating late effect induced by normal tissue injury due to radiotherapy (RT) or surgery and other

HNC therapies. HNC treatment-associated fibrosis of nerve tracts or adjacent soft tissues may lead to delayed but progressive neuro-vascular damage and eventually cranial neuropathy which over time causes profound functional impairments.[6] LCNP can occur unilaterally or bilaterally and can affect glossopharyngeal (IX), vagus (X), accessory (XI), and hypoglossal (XII) nerves which are crucial for oropharyngeal phase of swallowing mechanism, speech production, and shoulder function.[6-10] In a large survey study, OPC survivors with late LCNP reported significantly worse cancer treatment-related symptoms with largest effect size and detrimental impact on swallowing, speech, mucus problems, choking, and fatigue.[11] Further, survivors with late LCNP reported poor swallowing-related quality of life (QoL). Notably, late feeding tube, tracheostomy, and aspiration pneumonia events were almost exclusively seen in survivors who developed LCNP compared to their LCNP-free counterparts. [12]

It is also postulated that LCNP potentially leads to the accelerated functional decline among HNC patients suffering from a severe form of dysphagia which occurs many years post-RT called late RT-associated dysphagia (late RAD).[9] Late RAD is characterized by extreme functional impairment in oropharyngeal phases of swallowing, which causes swallowing inefficiency, oropharyngeal residue, and silent aspiration.[9] Over time, about 85% of OPC survivors with late-RAD develop pneumonia and more than 60% of them require long-term gastronomy tube placement.[9] Overall, literature suggests substantial functional burden including profound impairment in swallowing, speech, voice, and overall low quality of life (QoL) in OPC survivors who develop LCNP.[6-9]

The incidence of late LCNP among 59 OPC survivors was 5% at 5.7years according to an earlier study, [7] however another cohort study among HNC survivors reported 14% cranial neuropathy incidence rates over a 10-year follow-up, suggesting progressively increasing LCNP risk over time in this population.[14] Further, LCNP has delayed occurrence. A previous study among NPC patients reported late LCNP occurrence between 12 to 240 months post-RT treatment thereby highlighting the need for long-term surveillance of late LCNP among HNC and OPC patients.[7-9]

Most OPC patients receive either curative RT treatment alone or in combination with systemic therapy. Definitive surgery or surgery in combination with adjuvant therapy while historically rare is increasing with adoption of transoral robotic surgery methods. Despite this rising popularity of primary TORS for OPC, still the vast majority of modern OPC patients receive RT as definitive or adjuvant therapy. In practice, cranial nerves are historically considered to be relatively resistant to radiation injury but RT-associated cranial nerve injury occurs both at acute and late (months and years after RT treatment) recovery intervals.[7] It is postulated that late LCNP may be caused by peripheral nerve and brainstem injury and RT-associated peripheral nerve injury may occur by axonal degeneration, suppression of Schwann cell proliferation, and fibrosis of connective tissues entrapping nerve fibers. [7]

Total RT dose is most commonly suggested in literature as the chief predisposing factor for late LCNP, but the contributing threshold dose is not known.[7] It has also been suggested that the dose to regions-of interest (ROI) in the RT field including among others the superior pharyngeal constrictor (SPC) region, which comprises minor nerve tracts and the constrictor and longitudinal pharyngeal muscles, which are important for pharyngeal

shortening during swallowing for bolus propulsion into the esophagus may play a more pivotal role in late treatment related toxicity than total RT dose.[15] Previous literature suggests potential risk factors for treatment-associated late LCNP include RT dose, field, mode and fractionation, surgery, systemic therapy, smoking, and individual sensitivity to treatment. [7, 10,16-18] However, previous studies investigating LCNP have predominantly been case series among nasopharyngeal cancer (NPC) survivors and few studies have addressed late LCNP among OPC survivors. The largest to date comprised only 3 late LCNP cases in a cohort of 59 OPC survivors. With a rapidly growing pool of OPC survivors who have received curative doses of radiotherapy, there is urgent need to investigate this disabling late effect of therapy. Late LCNP is a debilitating, permanent condition and can have a profound impact on QoL of OPC survivors, yet we know little about risk and predictors of late LCNP in this population. For the growing numbers of OPC survivors at risk for experiencing late LCNP, there is need to identify risk profiles of those most vulnerable to late LCNP and subsequent late effects to help in the development of more targeted preventive strategies and interventions. Therefore, the overall objective of this study was to quantify the cumulative incidence of late LCNP and identify clinical predictors for late LCNP among long-term OPC survivors. The hypothesis for this study was that that 5-year incidence rate of LCNP would approximate 5% and risk of LCNP would correlate with age, tumor subsite and stage, RT dose, fractionation schedule, smoking status, and systemic therapy.

MATERIALS AND METHODS

Study Design, Eligibility and Consent

All OPC patients (n=3627) who completed treatment with curative intent at MD Anderson Cancer Center (MDACC) between January, 2000 and December, 2013, were assessed for eligibility in this retrospective cohort study. All eligible participants were ≥ 18 years of age at diagnosis, had oropharyngeal squamous cell carcinoma (OPSCC), and at time of new patient registration within the institution had consented to future research participation. Patients who had recurrent HNC, those treated at other institutions, those deceased < 3 months post-treatment, and those with secondary primary malignancy (SPM) or persistent/recurrent malignancy of the head and neck < 3 months post-treatment were excluded. As this study investigated late LCNP as a treatment-associated late-effect, patients with LCNP of any cause at the time of cancer diagnosis or with clinical signs of LCNP (n=168) prior to cancer treatment were also excluded. A total of 2,021 OPC survivors were included in the final study analysis. Details of study participants inclusion and exclusion are presented in Figure 1.

Primary Outcome Variable

The primary outcome variable for this study was late LCNP. LCNP status among patients was assessed by clinical examination of cranial nerves by the head and neck surgeon, radiation oncologist, and/or speech pathologist and was recorded in medical charts. Late LCNP for this study was defined as swallowing associated neuropathy of glossopharyngeal

(IX), vagus (X) and hypoglossal (XII) nerves, which were critical to the oropharyngeal phase of swallowing mechanism and speech production.[19,20] As CN XI palsy was inconsistently recorded in medical charts, it was excluded from LNCP analysis in this study, with the intent to focus on swallowing-associated LCNP.

Late effects of cancer treatment are often defined as severe treatment associated toxicities which occur ≥ 3 months post-cancer treatment ,[21] therefore, late LCNP was defined as onset of swallowing-associated neuropathy of at least one of the glossopharyngeal (IX), vagus (X), and hypoglossal (XII) nerves with minimum onset ≥ 3 months after the end of cancer treatment. Medical records were reviewed to identify cases of LCNP and case status was verified by head and neck specialized physician (R.G.) review. Time to event of LCNP diagnosis and information about other competing events were also collected. Details are presented in an earlier publication.[11]

Clinical and Demographic Variables

Demographic, clinical, treatment-related factors, health behaviors, and HPV status were also abstracted from medical charts using a structured study form. Demographic variables included age and sex; clinical variables included T and N staging (7th edition AJCC), sub-site, HPV status, OPC treatment modality, RT dose, type/mode, and fractionation schedule, chemotherapy, surgery, lack of solid food diet at baseline (as a surrogate of baseline dysphagia), and smoking status at diagnosis. Survival time was calculated as the difference between date of first visit to head and neck clinic and date of LCNP diagnosis or competing event diagnosis or date of last follow-up. RT dose, mode and

fractionation schedule, chemotherapy, surgery, solid food diet at baseline and smoking were some of the variables based on literature review which may influence risk and may act as predictors of late LCNP.[7, 10,16-18] Thereby, these variables were investigated as potential predictors of late LCNP among OPC survivors.

Statistical Analysis

Descriptive statistics were computed to explore relationship between variables of interest. Cumulative incidence of LCNP was calculated using the Kaplan Meier method, with adjustment for competing risks for all OPC survivors using time to event as an underlying metric.

Differences in LCNP risk by co-variables of interest were also assessed and Log-rank test was used to investigate between group differences by LCNP status. Multivariable Cox proportional hazards models were fit regressing LCNP status as the dependent variable on clinical and demographic predictors. Model building followed the purposeful variable selection method of Hosmer and Lemeshow.[22] Univariate analysis was conducted to estimate hazard ratios for the crude effect of each variable of interest. Candidate predictors with $p < 0.25$ on Wald test along with literature-based *a priori* defined clinically important covariates including age, t-stage, subsite, treatment modality, and smoking were entered into multivariable proportional hazards model. Variables that associated with late LCNP (Wald test $p < 0.05$) along with clinically important covariates were entered into the preliminary main effects model. Pruned models were compared to full models using partial likelihood ratio test; change in hazard ratio estimate ≥10% magnitude for each covariate was the threshold for re-entry of variables back into the model. Further, we added variables not

selected in earlier steps into model one at a time, checked the Wald statistic or partial likelihood ratio test and retained variables that made important contributions. Biologically plausible interaction terms and other model building strategies like stepwise regression were also explored. Multicollinearity was assessed using variance inflation factors. The proportional hazard assumptions of the final model were also assessed and the fit of the final model were tested using overall goodness-of-fit χ 2 test. Subgroup analyses were conducted among single versus multimodality treatment groups and surgically treated versus non-surgically treated groups, and those with HPV-associated disease among others. Hazard ratios (unadjusted and adjusted) and corresponding 95%confidence interval (CI) were estimated. All reported p-values were two-sided and were considered to be statistically significant at $p < 0.05$ and statistical analysis was conducted using the STATA software, version 14.0 (StataCorp LP, College Station, TX).

RESULTS

Sample Characteristics

Two thousand twenty-one (n=2,021) eligible OPC survivors with a median survival time of 6.8 (range, 0.3-18.4; IQR: 4.3-10.2) years were included in this study. Table 1 displays the distribution of demographic, tumor, and treatment-related characteristics in the study population. Among study participants, median age at diagnosis was 56 (range, 28-86; IQR: 50-63) years; 86.1% were male, 93.5% had either tonsil or base of tongue tumors, 72% had T1-T2 tumors, 90.3% had nodal involvement, and 89.9% could eat a normal solid-food diet prior to treatment. About 99.0% were treated with RT with a median RT dose of 70 Gy (range, 40-75; IQR: 66-70 Gy) and 60.7% were treated with intensity-modulated radiotherapy split-field technique (IMRT-SF).

Late Lower Cranial Neuropathy

4.4% (88/2,021) OPC survivors were diagnosed with late LCNP with median time to LCNP onset post-treatment of 5.4 years (range, 0.3-14.1; IQR:1.6-8.5). Among LCNP cases, median RT dose was 70 (range, 66-73.5; IQR: 66-72) Gy. However, 73.9% (65/88) of LCNP cases received an RT dose of ≥70Gy in comparison to 52.9% (1,022/1,933) of those without LCNP. 51.1% (45/88) of LCNP cases were treated for T1-T2 tumors, 48.9% (43/88) had T3-T4 tumors, and 89.8% (79/88) reported eating a solid-food diet prior to treatment. All LCNP cases received curative RT, 75% (66/88) were treated with RT in combination with systemic therapy, 37.5% (33/88) received IMRT-SF, and 36.4% (32/88) received accelerated RT fractionation therapy. In total, 7.6% (154/2021) of all survivors and 21.6% (19/88) LCNP

cases received concomitant boost accelerated RT treatment (p <0.001). Lastly, one (1.1%) LCNP case underwent transoral robotic surgery to the primary OPC tumor and 29.5% (26/88) had neck dissection.

Among LCNP cases, CN XII (hypoglossal nerve) neuropathy was most common (78.4%; 69/88). As isolated CN IX neuropathy was hard to detect; CN X/CN IX palsies were combined and 44.3% (39/88) patients had CN X/CN IX neuropathy. Polyneuropathy which included CN X/CN IX palsy and CN XII palsy was diagnosed in 22.7% (20/88) of LCNP cases. Among LCNP cases, 63.6% (56/88) had ipsilateral nerve damage, 9.1% (8/88) had contralateral nerve damage, and 26.1% (23/88) had bilateral nerve damage.

Cumulative Incidence of LCNP

Cumulative incidence of LCNP among all OPC survivors was 0.02 (95% CI: 0.02-0.03), 0.06 (95% CI: 0.05-0.08), and 0.10 (95% CI: 0.08-0.13) at 5 years, 10 years, and 18 years of follow-up, respectively. Overall cumulative incidence has been presented in Figure 2. Table 1 displays the cumulative incidence of late LCNP across demographic, tumor and treatment-related characteristics in the study population over an 18-year follow-up period. Cumulative Incidence of late LCNP increased proportionally with higher T-stage category with highest incidence of 0.26 (95% CI: 0.15-0.42, p=<0.001) among survivors with T4 tumors. Among OPC survivors; cumulative incidence of LCNP among those who did not eat a solid-food diet prior to treatment was 0.42 (95%CI: 0.12-0.91, p=0.086), those treated with multimodality treatment was 0.14 (95%CI: 0.09-0.20, p=0.003), those treated with

accelerated RT fractionation treatment was 0.19 (95%CI: 0.13-0.26, p=<0.001) and those treated with intensity modulated radiotherapy whole-field technique (IMRT-WF) and volumetric-modulated arc therapy (VMAT) was 0.14 (95%CI: 0.09-0.22, p=<0.001).

Risk Factors for LCNP

Univariate analysis identified smoking status, T-stage, single vs multimodality treatment, RT dose, type, and fractionation schedule, and chemotherapy as significantly associated with late LCNP status ($p<0.05$). Multivariable Cox regression identified T4 stage (HR: 3.82; 95%CI: 1.85-7.86, p=0.000) and accelerated RT fractionation (HR 2.15, 95%CI 1.34-3.45, p=0.002) independently associated with late LCNP status, adjusting for age, subsite, T-stage, smoking and therapeutic modality. Results of univariate and multivariate analysis are summarized in Table 2. Further, statistically significant interaction was identified between RT schedule and subsite of primary tumor (p=0.021) but as effect estimates of the model with the interaction term were similar to full regression model without the interaction term, estimates of final statistical model without interaction were reported for ease of clinical interpretation.

Subgroup Analysis: LCNP among those treated with Non-surgical Therapy

Among non-surgically treated patients, chemotherapy was further investigated as a predictor of late LCNP. The majority of non-surgically treated patients (67.6%; 1,342/1,986) received RT in combination with systemic therapy and 31.6% (628/1,986) received single

modality RT. About 52.5% (1,042/1,986) received concurrent chemotherapy, 31.5% (625/1,986) received induction chemotherapy (IC), and 17.3% (344/1,986) received both induction and concurrent chemotherapy. Among those who received induction chemotherapy, 38.7% (242/625) received Induction TPF (docetaxel, cisplatin, and fluorouracil), 5.8% received Induction CTPF (cetuximab, docetaxel, cisplatin, and fluorouracil), 20.2% (126/625) received Induction PCC (paclitaxel, carboplatin, cetuximab) and the remaining survivors received varied induction chemotherapy regimens. Among non-surgically treated patients, Induction TPF chemotherapy (HR: 2.37; 95%CI: 1.28-4.38; p=0.006) and Induction C-TPF (HR: 4.0; 95%CI: 1.22-13.13, p=0.022) were identified in addition to T-stage (model with TPF; HR: 3.72, 95%CI: 1.81-7.65, p=<0.001; model with CTPF; HR: 3.97, 95%CI: 1.92-8.21, p=<0.001) and accelerated RT fractionation (model with TPF; HR: 2.56, 95%CI: 1.55-4.21, p=<0.001, model with CTPF; HR: 2.28, 95%CI: 1.41-3.68, p=0.001) as significantly associated with late LCNP adjusting for the same covariates as the final model.

Validating Model Assumptions

None of the predictors in the final model violated the proportionality assumption of the Cox model except T-stage, but when a Cox model stratified on T-stage was fit, effect estimates for predictors in final model remained unchanged. Further, on inclusion of previously identified interaction RT schedule and subsite of primary tumor, none of the variables violated the proportionality assumption. Therefore, estimates for the unstratified Cox model were reported for ease of clinical interpretation. Goodness-of-fit of the final

model was assessed using the goodness-of-fit $\chi 2$ test which was not significant (p=0.406) and Cox-Snell residuals and in conclusion the final model fit the data well.

DISCUSSION

Late lower cranial neuropathy is a rare but progressive and functionally devastating late toxicity in OPC survivorship.[11,12] Late effects are of great concern among an ever-growing pool of younger OPC survivors with prospects of long-term cure, many of whom are expected to survive decades after treatment. This single-center retrospective cohort study is to our knowledge the first of its kind. The cohort represents the largest (n=2,021) to date among OPC survivors over an 18-year surveillance period and thus provides a high degree of precision in estimates of risk of late LCNP in terms of cumulative incidence and identification of clinical risk predictors of LCNP. Results of this study suggest that risk of late LCNP, though initially small, progressed over time to exceed 10% cumulative risk over survivors' lifetime. Multivariate analysis revealed that T-stage and accelerated RT fractionation treatment are significant risk factors of late LCNP. Further, among non-surgically treated patients, induction TPF chemotherapy with or without cetuximab (C-TPF) were additionally identified as significant risk factors of late LCNP.

The progressively increasing cumulative incidence estimates reported in this study are deeply troubling as the majority of OPC survivors in this study were middle-aged at the time of diagnosis supported by the 50-63 years interquartile range (IQR) for age at diagnosis which is similar to the age distribution of most HPV-positive OPC patients today.[23] This progressive increase in LCNP risk over time is similar to a study among 59 OPC survivors

treated by IMRT, which reported a cumulative risk of 2.1% (95% CI: 0.2-10%), 6.1% (95%CI: 0.9%-19%), and 11.0% (95%CI: 2.4%-28%) at 6-year, 7-year, and 8-year follow-up. [7] Another study among NPC patients also reported a progressive increase in late LCNP cumulative incidence of 5.7%, 17.4%, 27.1%, and 37.3% over a 5, 10, 15 and 20-year follow up respectively.[24] The cumulative incidence estimates in current study are quite precise supported by their narrow 95% confidence intervals and risk estimates increased as expected by disease severity (as per T-stage), use of RT, use of systemic therapy, neck dissection, and increase in treatment intensity with use of multimodality treatment including chemoradiation and accelerated RT fractionation. Tight confidence intervals and expected performance in subgroup stratifications support both accuracy and validity of these cumulative incidence estimates.

The progressive trajectory of LCNP has long-term clinical implications on the functional status of HNC survivors as was suggested by a prospective study among 3 OPC survivors with LCNP, which suggested that LCNP cases could experience severe decline in function over time, as per multiple functional metrics.[7] Long-term deterioration of swallowing function was noted using both patient-reported MDADI scores and clinician-rated modified barium swallow (MBS) scores as per validated Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) criteria, as well as diet score rated on the Performance Status Scale of Head and Neck Cancer (PSS-HN).[7] In fact, survivors with LCNP may be compelled to modify their diet, need extended meal times, feel self-conscious to eat in social settings, be socially isolated, and experience poor QOL.[26] The investigators have previously reported worse cancer treatment-related symptoms, poor swallowing-related QoL, and worse

functional status metrics including long-term feeding tube dependence, lack of normalcy of diet, dietary restrictions in public, weight loss, aspiration pneumonia, and tracheostomy among long-term OPC survivors with late LCNP.[11,12] Further, the devastating impact of cranial neuropathy on the life of LCNP cases was reflected by their qualitative remarks in the present study which suggested, profound distress and suffering with loss of swallowing function to an extent where these patients regretted pursuing any OPC treatment at all. It is also worrisome, that a recent report indicated that OPC incidence is now rising among the older population.[27] These patients are likely to have comorbidities and experience more side-effects with multimodality treatment including concurrent chemoradiation and are also likely to experience bigger deficits in swallowing function overtime and even more poor/diminished QoL. These findings altogether suggest that as OPC survival probabilities continue to improve, the number of survivors at risk of substantial functional morbidity associated with late LCNP grows too. These survivors eventually transition from oncologic management to care of primary care physicians and there is need for increased surveillance to assess and treat late effects.

The results from this multivariate analysis suggest, on an average, OPC patients with T4 stage tumors were 3.8 times more likely to develop late LCNP than those with T1 tumors after adjusting for age, subsite, smoking, therapeutic modality, and RT fractionation schedule. Identification of T-stage as a predictor in this study is plausible given that locally advanced OPC tumors are bulky tumors. As per AJCC 7th edition TNM staging in this study, T3 tumors are > 4cm with possible extension to lingual epiglottis, whereas T4 tumors are even bigger with T4a tumors being moderately advanced invading other head neck sites

possibly including the larynx/tongue muscles/hard palate/ mandible and T4b tumors including very advanced extensive tumors invading the lateral pterygoid muscles, lateral part of the nasopharynx and even the skull base and carotid artery (AJCC 7th edition). In case of larger tumors, the RT treatment planning target volume is more extensive, requiring a relatively larger gross tumor volume, clinical target volume (to incorporate subclinical disease), and additional marginal area (to account for errors).[28] These larger irradiation fields may include neurovascular structures including cranial nerves and adjacent normal tissues, the injury of which may precipitate cranial neuropathy. Additionally patients with T4 tumors may have also have a greater risk of subclinical baseline neve injury by compression of nerve tracts by large tumors.[29-31] According to previous literature primary tumor size among other clinical variables may also contribute to acute and late dysphagia including late-RAD among HNC patients [32,33] and tumor stage may predict swallowing function (as per MDADI scores) at specific time points and longitudinally.[34-36] Another prospective study among 529 HNC patients treated with curative RT which reported T3-T4 vs T1-T2 stage (OR:2.38, 95%CI: 1.36-4.19, p=0.003) was positively significantly associated with grade 2-4 RTOG swallowing dysfunction at 6 months post-treatment.[37] Therefore, tumor stage can not only contribute to late LCNP but also potentially play a role in development of late functional toxicities including late RAD.

Advanced stage cancers are also treated more intensely/aggressively with multimodality treatment regimens including either chemoradiotherapy (CRT) or surgery followed by CRT or chemotherapy. Chemoradiotherapy is regarded as standard of care for locally advanced OPSCC but multimodality treatment regimens can result in acute and

persistent tissue changes and lead to severe acute and late treatment-related toxicities.[38,39] A trial in France demonstrated that multimodality treatment was associated with an increase in grade 3 or 4 acute toxicity though these findings were not statistically significant.[40] Thus, collectively among patients with T4 tumors larger irradiation fields and greater treatment intensification may contribute to higher risk of late LCNP.

In this study, OPC patients treated with accelerated RT fractionation were 2.2 times more likely to develop late LCNP than those who received standard RT fractionation after adjusting for age, subsite, smoking, T-stage, and therapeutic modality. Accelerated RT fractionation treatment regimens incorporate several RT fractions in a day with the goal to shorten total treatment time and also to overcome tumor cell regeneration/repopulation during RT treatment.[41,42] Thereby, accelerated RT fractionation therapy may also include an increase in average RT dose per week above the standard 10 Gy dose per week of conventional RT fractionation which may contribute to an increase in late effects of RT treatment.[28] Further, regeneration/repair in some normal tissues maybe slower and as a consequence of longer half-time for repair; these tissues may be more susceptible to RT-induced injury.[28] Lastly, an increase in RT dose per week may contribute to an increase in early tissue injury like mucositis or other severe and extensive/protracted acute effects which may result in chronic normal tissue injury and consequential late effects.[28]

Pure acceleration, split-course treatment acceleration, accelerated hyper-fractionation, and concomitant boost are some of the strategies used in accelerated RT fractionation therapy.[42] In this study, more than 20% LCNP cases received concomitant boost accelerated RT treatment. Concomitant boost RT technique incorporates initial irradiation of gross tumor

volume and clinical target volume, followed by a second boost RT dose delivered to a smaller clinically identifiable tumor area to ensure the highest RT dose is given to the smallest region to reduce potential of late RT-associated toxicity/morbidity. [42] In this institution concomitant boost RT strategy includes a total RT dose of 72 Gy, given in 42 fractions during 6 weeks.[42,44] During the last/final two weeks of RT treatment, the patient receives twice a day treatment with the second dose administered as boost RT dose.[42,44] However, in a previous phase II Radiation Therapy Oncology Group Trial (RTOG 99-14), advanced HNC patients treated with concomitant boost accelerated RT regimen/strategy with cisplatin had better survival but endured severe acute toxicity and alarmingly higher rates of late toxicities including late gastrostomy tube dependence.[43] Another randomized trial among NPC patients also reported, accelerated hyper-fractionation therapy was associated with significantly higher risk of RT-associated central nervous system injury including damage to cranial nerves, temporal lobe, and brainstem.[44]

Some patients (n=8) in this study also received Danish Head and Neck Cancer Group (DAHANCA) moderate accelerated RT fractionation strategy which incorporated 6 instead of 5 weekly radiation fractions during RT.[45] A previous randomized trial among patients with glottic cancer reported that patients treated with the DAHANCA regimen suffered more frequently from severe acute mucositis even though frequency of late effects were comparable among patients treated with 6 vs 5 RT fractions.[45] It was postulated that effectiveness of RT treatment may be influenced by inherent radio-sensitivity of cells, hypoxia of the tumor microenvironment, and regeneration of stem cells during RT treatment.[45] Another randomized trial among NPC patients, also reported that accelerated hyper-fractionation radiation treatment was associated with higher late LCNP incidence than

conventional fractionation (13.0% vs 8.7%) over a median follow-up of 59.2 months.[44] Finally, the effect estimates in this study for accelerated RT are robust and similar to a previous study among NPC, which reported RT fractionation schedule (RR: 2.91, 95%CI: 1.07-7.91, p=0.036) as a significant predictor of upper cranial nerve neuropathy and but not as a significant predictor of lower cranial nerve neuropathy.[24] In summary, accelerated RT fractionation treatment regimens can contribute to an increase in risk of nerve fibrosis and cranial nerve injury.

Among non-surgically treated patients, the present study identified Induction TPF and Induction C-TPF followed by chemoradiotherapy or RT as risk factors associated with late LCNP. Chemotherapy drugs are cytotoxic and modify radiation sensitivity of cells either by altering their cell-cycle phase or by interfering with repair of radiation initiated double-strand DNA breaks.[46,47] Thus, while enhancing tumor control, they can also contribute to late toxicity like LCNP. A prior study among NPC patients reported that chemotherapy was significantly associated with development of cranial neuropathy (RR=1.42, p=0.021).[24] Another clinical trial among stage III and stage IVB NPC patients revealed that late cranial neuropathy was significantly increased among patients treated with RT and concurrent adjuvant chemotherapy (p=0.042) than those treated with RT only.[48] Similarly, in a previous study 6.3% of HNC patients, who received intra-arterial Cisplatin therapy developed cranial neuropathy shortly after treatment.[49] Thus, while various authors have associated concurrent chemotherapy with LCNP after NPC radiotherapy, the results of this study are, to our knowledge, the first to link induction chemotherapy to elevated risk of LCNP in OPC.

Induction chemotherapy (IC) is a treatment alternative for patients with locally advanced head and neck squamous cell carcinoma (HNSCC) with goals of shrinking tumors, reducing risk of distant metastasis, and organ preservation for operable and inoperable tumors. [51-53] Induction TPF is considered the gold-standard evidence-based IC treatment regimen and is considered superior to PF (cisplatin combined with 5-FU).[52,53] However, the use of IC in case of unresectable disease followed by RT or chemoradiation (CXRT) is controversial. [52,53] TPF may also be more toxic than concurrent chemoradiotherapy and contribute to greater morbidity and death, as some trials have reported IC toxicity-related death rates of 2%-7%.[52] The TPF regimen in the United States includes a combination of 3 drugs, including 3 cycles of docetaxel 75 mg/m^2 combined with cisplatin 100 mg/m^2 and 1000 mg/m^2 5FU infusion for 4 days, for every 3 weeks.[53] Each one of these drugs has it's individual toxicity profile. Cisplatin can contribute to neuropathy, hearing problems, renal toxicity, and cardiovascular adverse events, 5FU can result in severe mucositis and hematological problems, docetaxel can also contribute to neuropathy, erythema and hypotension.[53] In case of CTPF, the cetuximab component can additionally contribute to severe anaphylactic toxic reactions.[53] Therefore, in combination these drugs may contribute to late effects like LCNP. Lastly, IC therapy including drugs like Cisplatin may lead to increased radio-sensitivity to subsequent RT which in turn can play a role in development of late treatment-related toxicity and late LCNP.[54]

The results from this study are of paramount importance in the realm of OPC survivorship as they have the potential to inform/advocate for long-term screening and surveillance recommendations to monitor and treat late effects like LCNP, inform future late

effects research, and advise the development and implementation of targeted risk-reduction and preventive interventions. These strategies could be implemented early and be personalized via risk stratification methods to meet individual needs for symptom management and psychosocial support to allow for more strategic allocation of resources and potentially lower health care cost. Risk-based OPC treatment planning, use of targeted therapies, nerve-sparing RT planning to decrease irradiation of vital structures which play an important role in swallowing, or sequential chemoradiotherapy may help to alleviate late effects like LCNP and improve function among survivors. Knowledge about predictors of late LCNP and its consequent impact on swallowing function and overall symptom severity may also allow more effective delineation of de-escalation targets.

With more than 2,000 OPC survivors, this is to our knowledge, the largest retrospective cohort study to date to estimate risk of late LCNP and identify clinical predictors of late LCNP. However, there are limitations to acknowledge. Study participants had varying survival time and may be susceptible to survival bias. As a consequence of the long latency period for late LCNP development, risk would be highest among survivors with greater survival time. Nonetheless, consistently precise and robust effect estimates on late LCNP were identified which varied across clinical and demographic covariates as expected. The low event rate of late LCNP and loss-to-follow-up among survivors may also have contributed to low statistical power to identify additional potential predictors like RT dose among others. But the substantial study sample of OPC survivors, allowed for identification of possibly the most impactful predictors of LCNP. There may be some misclassification of study variables due to the retrospective study design but as study results varied as would be

expected by clinical and demographic variables their impact on study results is likely to be minimal. HPV testing had also not been conducted in about half of the cohort, therefore accurate estimates of risk based on HPV status in study population could not be assessed. However, sensitivity analysis of study results by HPV status did not have an impact on effect estimates for late LCNP, suggesting study results were valid and accurate. As this study was conducted at a tertiary care cancer center and there were small numbers of surgical patients there may be some limitations to generalizability of study results to more diverse populations. Further, late LCNP risk may have been underestimated in this study, as LCNP diagnosis was primarily via clinical signs of loss of motor function only and did not take into account loss of sensory function. Further, CN XI palsy was excluded to focus on swallowing associated late LCNP only. Isolated CN IX palsies were not detected in this study. Therefore, actual risk of LCNP among OPC survivors may most likely be higher than reported in our study. Lastly, individual susceptibility and impact of genetic predictors on LCNP could not be assessed and should be addressed by future studies assessing the risk of late LCNP.

It is of utmost importance going forward to investigate evidence-based risk identification and early risk reduction strategies for late effects detection and management. Effective screening interventions, may consider the use of patient-reported outcomes tools like MD Anderson Dysphagia Inventory (MDADI) and MD Anderson Symptom Inventory – Head and Neck module (MDASI-HN) among others for surveillance and detection of late effects. Potential treatment for late LCNP also needs to be investigated in prospective clinical trials. Future studies need to further assess the role of dose to organs at risk (including the salivary glands, pharyngeal constrictors, cricopharyngeal muscle, base of tongue, supraglottic and glottic larynx and other critical structures), induction chemotherapy, and transoral

robotic surgery in development of late effects like LCNP.[55] Further, it is crucial that HNC treatment selection must take into account long-term treatment-related morbidity and should be prioritized based on individual patient preferences to reduce disease burden due to late effects. Better RT techniques need to be developed to modify dose delivery and less toxic chemotherapy agents need to be investigated. Treatment de-intensification strategies need to be explored which maintain cure and prevent late effects.

CONCLUSION

While rare in the population overall, quantitative estimates of lifetime risk of late LCNP over an almost 18-year follow-up into OPC survivorship demonstrate that one out of 10 OPC survivors middle-aged at time of diagnosis are likely to develop late LCNP. The progressively increasing risk of late LCNP of 2%, 6%, and 10% at 5, 10, 18-year follow-up also indicates that risk of LCNP overtime is much higher than previously believed. The potential impact of late LCNP on the life of OPC survivors is devastating as late LCNP and accompanying late-RAD is refractory to treatment, life-long, and permanent. In this study patients with big bulky tumors had large irradiation fields possibly including cranial nerves, they were likely to be treated most aggressively with multimodality treatment regimens including, IC, RT, and systemic therapy, thereby they were more likely to develop late LCNP. In summary, the long-term treatment-related burden of OPC is becoming more apparent, there is urgent need to find ways to treat cancer, minimize late effects like LCNP and improve QoL among OPC survivors.

TABLES

Table 1: Patient Characteristics (N=2,021)

Variables	All patients (n=2021)	LCNP (n=88)	No LCNP (n=1,933)	P-value**	Cumulative Incidence	Log rank Test p value
Age at diagnosis, median (range), IQR	56 (28-86), (50-63)	57(33-80) (51-63)	55(28-86) (50-63)	0.734		
Survival time, median (range), IQR yrs	6.8(0.3-18.4) (4.3-10.2)	5.4(0.3-14.1) (1.6-8.5)	6.8(0.3-18.4) (4.4-10.3)	**< 0.001**		
RT Dose, Gy median (range), IQR	70(40-75), (66-70)	70(66-73.5) (66-72)	70(40-75) (66-70)	**< 0.001**		
RT Fractions (range), IQR	33(15-44), (28-43)	33(30-43) (32-40.5)	33(15-44) (30-33)	**< 0.001**		
Sex				0.429		0.399
Female	281(13.9)	15(5.3)	266(94.7)		0.096 (0.055-0.165)	
Male	1740(86.1)	73(4.2)	1667(95.8)		0.098 (0.073-0.132)	
Primary Site				0.453		0.6418
Tonsil	944(46.7)	40(4.2)	904(95.8)		0.101 (0.0678-0.152)	
Base of Tongue	945(46.8)	45(4.8)	900(95.2)		0.100 (0.070- 0.142)	
Others	132(6.5)	3(2.3)	129(97.7)		0.039 (0.012-0.128)	
T classification				**< 0.001**		**< 0.001**
1	686(33.9)	18(2.6)	668(97.4)		0.046(0.027-0.077)	
2	770(38.1)	27(3.5)	743(96.5)		0.087 (0.049-0.151)	
3	358(17.7)	20(5.6)	338(94.4)		0.178 (0.109-0.283)	
4	207(10.2)	23(11.1)	184(88.9)		0.259 (0.154-0.417)	
N classification (AJCC 7th Ed)				0.212		**0.0445**
N0	196(9.7)	6(3.1)	190(96.9)		0.082 (0.031-0.207)	
N1+2a	510(25.2)	16(3.1)	494(96.9)		0.052 (0.030-0.088)	
2b+3	968(47.9)	46(4.8)	922(95.2)		0.127 (0.084-0.188)	
2c	347(17.2)	20(5.8)	327(94.2)		0.127 (0.075- 0.211)	
HPV status				**0.007**		0.681
Negative	110(5.4)	6(5.5)	104(94.6)		0.142 (0.054-0.345)	
Positive	817(40.4)	22(2.7)	795(97.3)		0.080 (0.033-0.175)	
Unknown	1094(54.2)	60(5.4)	1034(94.5)		0.098 (0.073-0.131)	
Smoking				0.559		0.087
Never	861(42.6)	39(4.5)	822(95.5)		0.101 (0.065-0.154)	
Former	842(41.7)	33(3.9)	809(96.1)		0.088 (0.059-0.131)	
Current	294(14.6)	16(5.4)	278(94.6)		0.131 (0.070-0.240)	
Missing	24(1.2)	0(0)	24(100.0)		0.000	
Solid Food pre-Tx						0.086
Yes	1816(89.9)	79(4.4)	1737(95.6)	1.000	0.092 (0.070-0.121)	
No	205(10.1)	9(4.4)	196(95.6)		0.421 (0.116- 0.912)	
Treatment Group				0.102		**0.003**
Single Modality	647(32.0)	21(3.3)	626(96.8)		0.060 (0.038-0.094)	
Multimodality	1374(68.0)	67(4.9)	1307(95.1)		0.136 (0.090-0.201)	
Treatment Group				0.397		**0.029**
RT alone	628(31.1)	21(3.3)	607(96.7)		0.061 (0.039-0.095)	
Surgery alone	19(0.9)	0(0.0)	19(100.0)		0.000	
RT plus systemic	1342(66.4)	66(4.9)	1276(95.1)		0.136 (0.091-0.201)	

Variables	All patients (n=2021)	LCNP (n=88)	No LCNP (n=1,933)	P-value**	Cumulative Incidence	Log rank Test p value
Surgery +adjuvant RT &Chemo	32(1.6)	1(3.1)	31(96.9)		0.032 (0.005-0.208)	
Radiotherapy				1.000		0.447
No	21(1.0)	0(0.0)	21(100.0)		0.000	
Yes	2000(99.0)	88(4.4)	1912(95.6)		0.099 (0.075-0.128)	
Chemotherapy				0.082		**0.002**
No	656(32.4)	21(3.2)	635(96.8)		0.060 (0.038-0.093)	
Yes	1365(67.5)	67(4.9)	1298(95.1)		0.136 (0.091-0.201)	
Surgery				1.000		0.865
No	1986(98.3)	87(4.4)	1899(95.6)		0.098 (0.075-0.128)	
Yes- Robotic	35(1.7)	1(2.9)	34(97.1)		0.029 (0.004-0.191)	
Neck Dissection				0.454		0.779
No	1500(74.2)	62(4.1)	1438(95.9)		0.091 (0.067-0.123)	
Yes	521(25.8)	26(5.0)	495(95.0)		0.110 (0.067-0.175)	
RT Schedule				**< 0.001**		**< 0.001**
Standard Fractionation	1681(83.2)	56(3.3)	1625(96.7)		0.071 (0.047-0.107)	
Accelerated	319(15.8)	32(10.0)	287(90.0)		0.187 (0.132-0.260)	
Missing (Pt. Without RT)	21(1.0)	0(0.0)	21(100.0)		0.000	
RT Type				**< 0.001**		**< 0.001**
3d Conformal	234(11.6)	24(10.3)	210(89.7)		0.174 (0.118-0.251)	
IMRT-SF	1227(60.7)	33(2.7)	1194(97.1)		0.073 (0.041-0.129)	
IMRT- WF+VMAT	377(18.7)	25(6.6)	352(93.4)		0.136 (0.085-0.215)	
Proton	36(1.8)	2 (5.6)	34(94.4)		0.056 (0.014-0.204)	
IMRT Ipsi	126(6.2)	4 (3.2)	122 (96.8)		0.052 (0.018-0.145)	
Missing (Pt. without RT)	21(1.0)	0(0.0)	21(1.0)		0.000	

Abbreviations: IQR, interquartile range, T, tumor; RT, radiotherapy; IMRT-SF, Intensity modulated radiotherapy split-field technique; IMRT-WF, Intensity modulated radiotherapy whole-field technique; IMRT-Ipsi, Intensity modulated radiotherapy ipsilateral treatment; VMAT, Volumetric-modulated arc therapy

Bold denotes statistical significance at p value < 0.05

TABLE 2: Univariate & Multivariate Cox Proportional Hazards models for Late LCNP (N=2021)

Variables	Univariate Analysis HR (95%CI)	P Value	Multivariate Analysis HR (95%CI)	P Value
Age at diagnosis, median (range)	1.02 (1.00- 1.04)	0.117	1.02 (0.99-1.04)	0.163
RT Dose, Gy median (range)	1.24 (1.14- 1.36)	**< 0.001**		
RT Fractions	1.11 (1.07- 1.16)	**< 0.001**		
Sex		0.412		
Female	Reference		Reference	
Male	0.79 (0.45-1.37)	0.400		
Primary Site		0.624		
Others	Reference		Reference	
Tonsil	1.42 (0.44-4.58)	0.560	1.89 (0.58-6.17)	0.292
Base of Tongue	1.62 (0.50-5.21)	0.420	1.85 (0.57-6.05)	0.309
T classification, AJCC 7th Ed		**< 0.001**		
1	Reference		Reference	
2	1.53 (0.84-2.78)	0.161	1.12 (0.60-2.10)	0.727
3	2.72 (1.44-5.14)	0.002	1.59 (0.76-3.31)	0.218
4	6.10 (3.29-11.33)	< 0.001	3.82 (1.85-7.86)	**< 0.001**
N classification, AJCC 7th Ed.		**0.040**		
N0	Reference		Reference	
N1+2a	0.85 (0.33-2.17)	0.733		
2b+3	1.56 (0.67-3.66)	0.302		
2c	2.01 (0.81-5.00)	0.134		
HPV status		0.706		
Negative	Reference		Reference	
Positive	0.67 (0.27-1.66)	0.386		
Unknown	0.72 (0.31-1.67)	0.439		
Smoking		**0.038**		
Never	Reference		Reference	
Former	0.85 (0.53-1.35)	0.493	0.76 (0.47-1.22)	0.253
Current	1.74 (0.97-3.11)	0.064	1.57 (0.86-2.86)	0.143
Solid Food pre-Tx		0.117		
Yes	Reference		Reference	
No	1.82 (0.91-3.66)	0.091	1.16 (0.56-2.41)	0.685
Treatment Group		**0.002**		
Single Modality	Reference		Reference	
Multimodality	2.09 (1.27-3.44)	0.004	1.35 (0.77-2.37)	0.299
Treatment Group		**0.018**		
RT alone	Reference		Reference	
Surgery alone	0.00	1.000		
RT plus systemic	2.06 (1.25-3.39)	0.004		
Surgery +adjuvant RT &Chemo	2.02 (0.27-15.09)	0.494		
Chemotherapy		**0.002**		
No	Reference		Reference	
Yes	2.13 (1.30-3.50)	0.003		
Surgery		0.868		
No	Reference			
Yes- Robotic	1.19 (0.16-8.57)	0.865		
Neck Dissection		0.780		
No	Reference			

Variables	Univariate Analysis HR (95%CI)	P Value	Multivariate Analysis HR (95%CI)	P Value
Yes	1.07 (0.67-1.69)	0.779		
RT Schedule		**0.000**		
Standard Fractionation	Reference		Reference	
Accelerated	2.53 (1.63-3.92)	0.000	2.15 (1.34-3.45)	**0.002**
RT Type		**< 0.001**		
3d Conformal	Reference			
IMRT-SF	0.32 (0.19-0.55)	< 0.001		
IMRT- WF +VMAT	0.96 (0.54-1.70)	0.888		
Proton	1.33 (0.31-5.77)	0.701		
IMRT Ipsi	0.33 (0.11-0.94)	0.039		

Abbreviations: IQR, interquartile range, T, tumor; RT, radiotherapy; IMRT-SF, Intensity modulated radiotherapy split-field technique; IMRT-WF, Intensity modulated radiotherapy whole-field technique; IMRT-Ipsi, Intensity modulated radiotherapy ipsilateral treatment; VMAT, Volumetric-modulated arc therapy

Statistical significance p value < 0.25 after Univariate Analysis

Statistical significance p value < 0.05 after Multivariate Analysis

Bold denotes statistical significance at p value < 0.05

Figure 1. Consort flow chart showing study participant screening and eligibility criteria

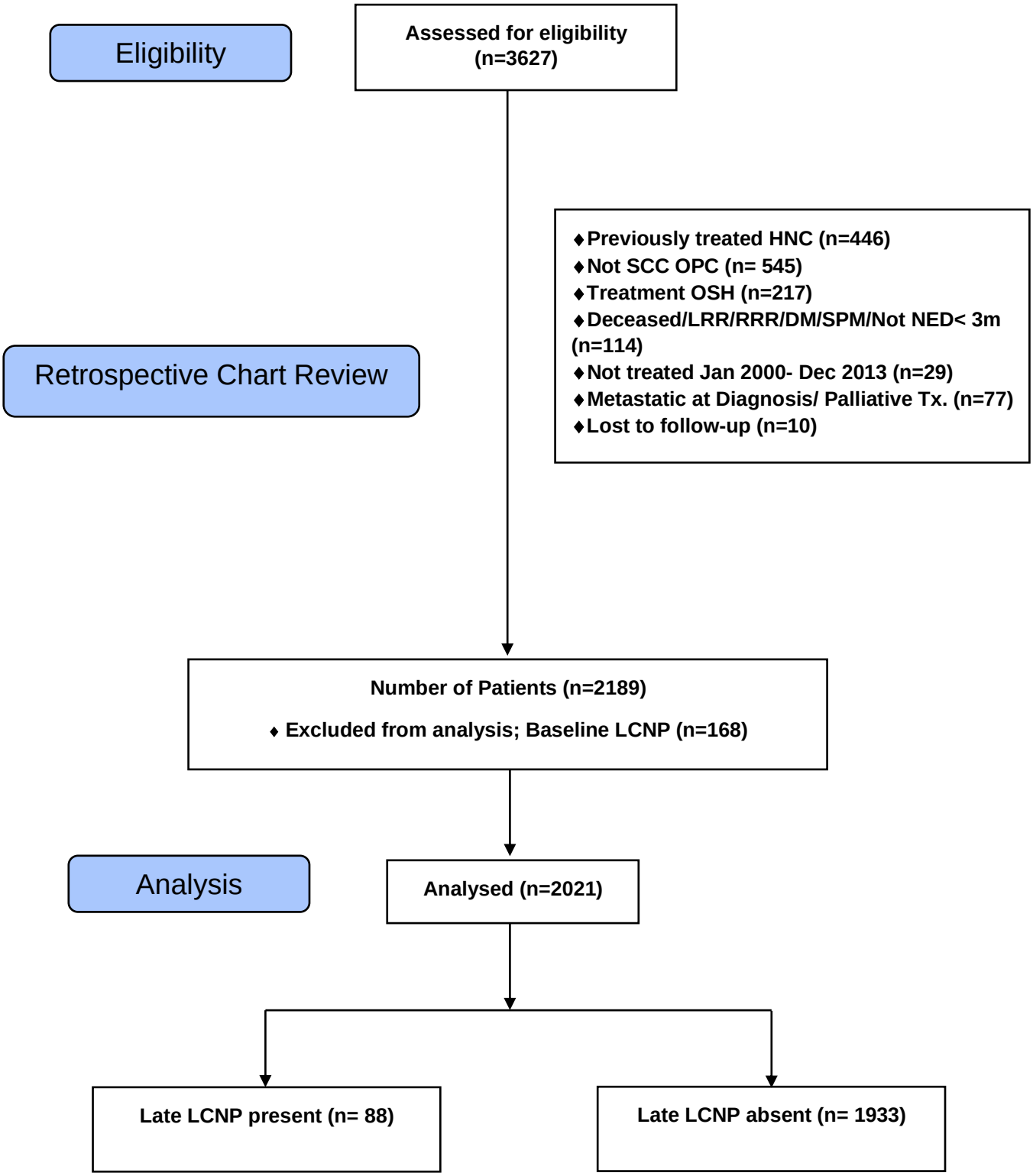

Figure 1. Consort flow chart showing study participant screening and eligibility criteria.

Abbreviations:

OPC, oropharyngeal carcinoma, SCC, squamous cell carcinoma, OSH, outside hospital; SPM, second primary malignancy; LRR, locoregional recurrence; RRR, regional recurrence; DM, distant metastasis; NED, no evidence of disease; LCNP, lower cranial neuropathy.

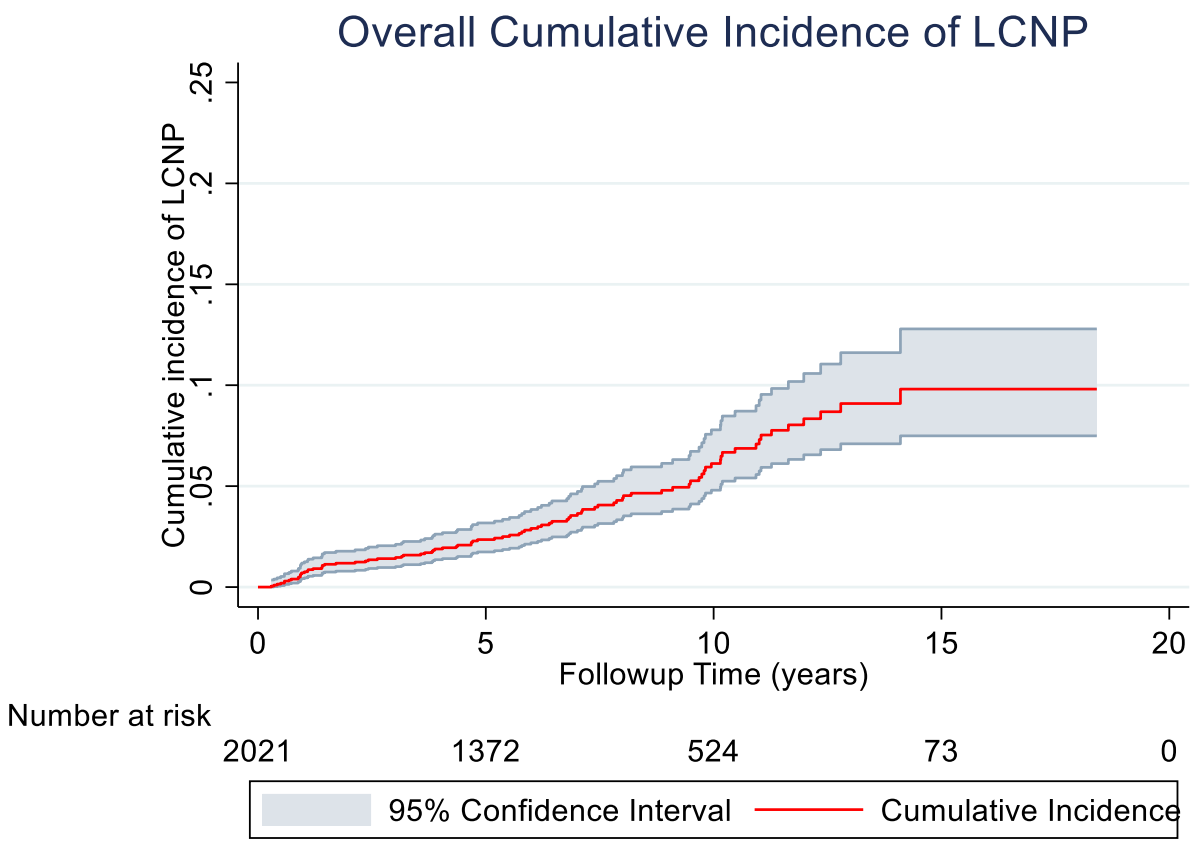

Figure 2: Overall Cumulative Incidence of Late LCNP in OPC survivors over an 18-year surveillance period (n=2,021)

Figure 3: Adjusted Risk of Late LCNP stratified by T-Stage

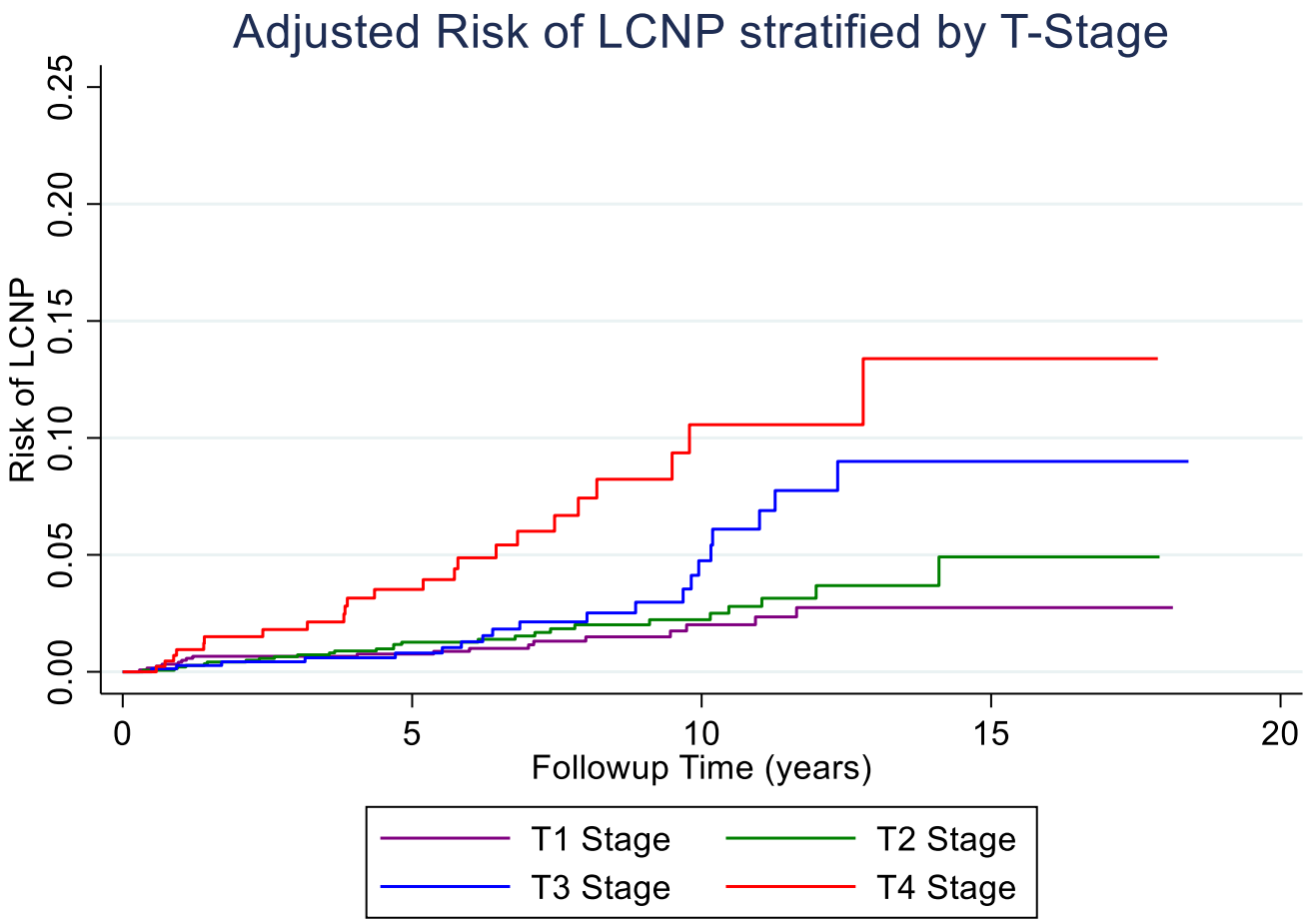

Figure 3. Adjusted Risk of Late LCNP stratified by RT T-Stage. Regression model adjusted for age, subsite, T-stage, smoking and therapeutic modality. Abbreviations: T, tumor; LCNP, lower cranial neuropathy.

Figure 4: Adjusted Risk of Late LCNP stratified by RT Fractionation

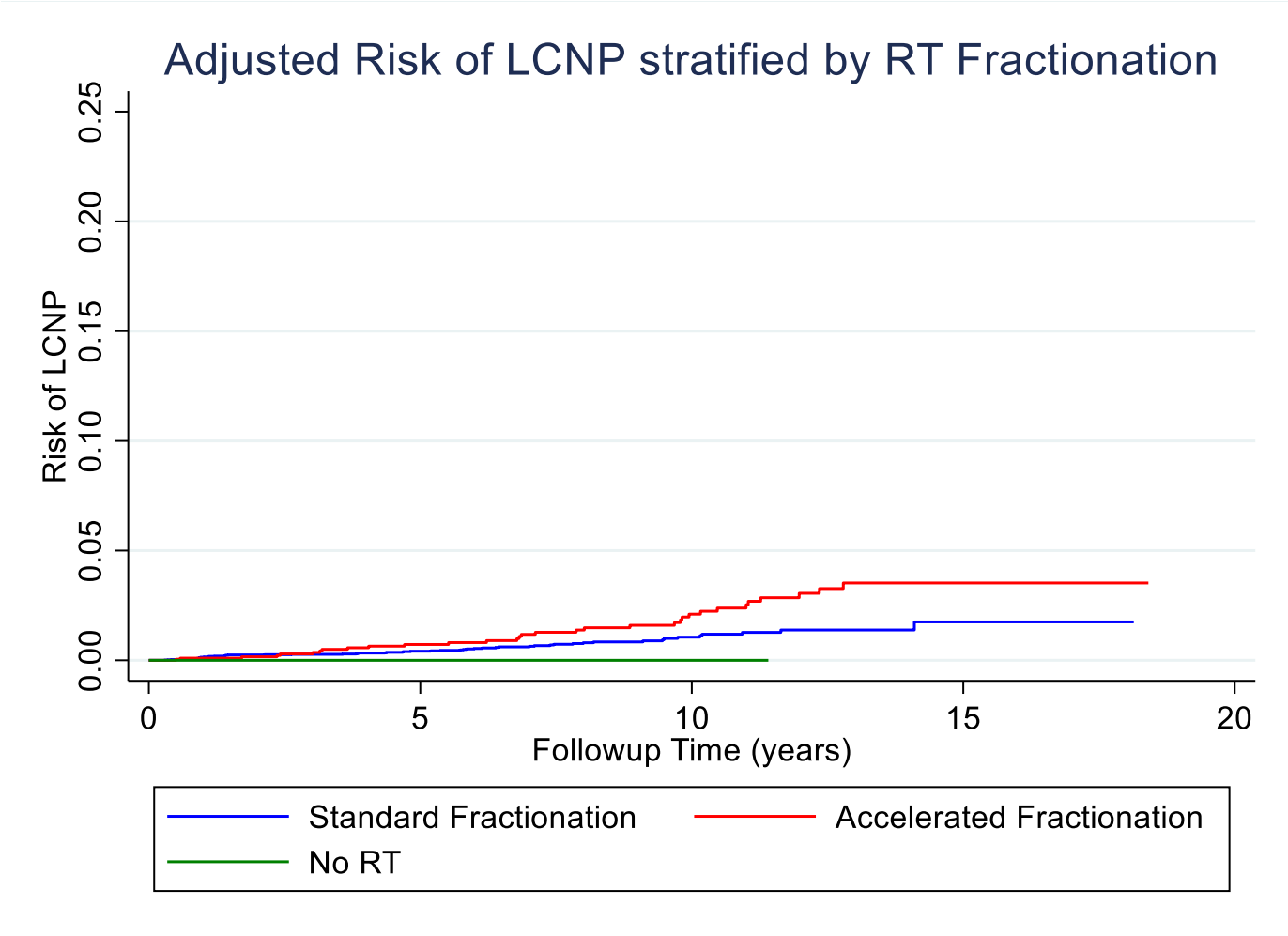

Figure 4. Adjusted Risk of Late LCNP stratified by RT Fractionation. Regression model adjusted for age, subsite, T-stage, smoking and therapeutic modality. Abbreviations: RT, radiotherapy; LCNP, lower cranial neuropathy.

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Journal Article 2

Title of Journal Article: Symptom Burden Associated with Late Lower Cranial Neuropathy in Long-term Oropharyngeal Cancer Survivors

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Key Points

Question What is the impact of late lower cranial neuropathy (LCNP) on severity of cancer treatment-related symptoms and general functional impairment (GFI) among long-term oropharyngeal cancer (OPC) survivors?

Findings In this large cross-sectional survey (n=889), OPC survivors with late LCNP reported significantly worse cancer treatment-related symptoms.

Meaning Further efforts are necessary to lessen symptom burden associated with this disabling late effect of cancer treatment experienced by OPC survivors.

Abstract

IMPORTANCE: Lower cranial neuropathy (LCNP) is a rare but potentially disabling late effect of radiotherapy (RT) and other head and neck cancer therapies. Survivors who develop late LCNP may experience profound functional impairment with deficits in swallowing, speech, and voice.

OBJECTIVE: To investigate the impact of late LCNP on severity of cancer treatment-related symptoms and their subsequent impact on general functional impairment (GFI) among oropharyngeal cancer (OPC) survivors. Impact of late LCNP on single item scores of the most severe symptoms was also assessed. We hypothesized that late LCNP status among OPC survivors would be associated with significantly worse symptom scores and GFI.

DESIGN: Cross-sectional survey analysis among 889 OPC survivors nested within a retrospective cohort of OPC survivors treated during January 2000 -December 2013.

SETTING: MD Anderson Cancer Center

PARTICIPANTS: Eligible survey participants were disease-free and completed OPC treatment ≥1-year prior to survey.

EXPOSURE: Late LCNP defined by onset ≥3-months after cancer therapy.

MAIN OUTCOME: The primary outcome variable was the mean of the top 5 most severely scored symptoms from MD Anderson Symptom Inventory Head and Neck Cancer Module (MDASI-HN) out of all 22 core and HNC-specific symptoms. Secondary outcomes included mean MDASI-HN interference scores and single item scores of the most severe symptoms. Multivariate models regressed MDASI-HN scores on late LCNP status adjusting for clinical covariates.

RESULTS: Overall, 4% (n=36) of 889 OPC survivors (median survival time: 7 years)

developed late LCNP.

Late LCNP was significantly associated with worse mean top 5 MDASI-HN symptom scores (coefficient, 1.54; 95%CI, 0.8, 2.2) adjusting for age, survival time, sex, therapeutic modality, T-stage, subsite, type of radiotherapy, smoking, and normal diet prior to treatment. Late LCNP was also associated with single item scores for difficulty swallowing/chewing (coefficient, 2.25; 95%CI, 1.3, 3.1), mucus (coefficient, 1.97; 95%CI, 1.0, 2.9), fatigue (coefficient, 1.35; 95%CI, 0.4, 2.2), choking (coefficient, 1.53; 95%CI, 0.6, 2.4), and voice/ speech symptoms (coefficient, 2.3; 95%CI, 1.6, 3.0) in multivariable models. However late LCNP was not significantly associated with mean interference scores after correction for multiple comparisons.

CONCLUSION AND RELEVANCE: In this large survey study, OPC survivors with late LCNP reported significantly worse cancer treatment-related symptoms demonstrating the impact of late LCNP on both symptom severity and burden.

Introduction

The incidence of oropharyngeal cancer (OPC) is increasing by 5% annually in the United States.[1] It is projected that by 2030 half of head and neck cancers (HNC) will be OPC.[1] This phenomenon is attributable to the epidemic of human papillomavirus (HPV)-associated OPC, which is usually diagnosed in middle age.[1-4] HPV-disease is biologically favorable with excellent prognosis for long-term survival despite advanced-stage cancer.[2-4] Despite excellent prognosis, survivors may experience severe side-effects of cancer treatment impacting critical functions like speech, breathing, and swallowing.

Late lower cranial neuropathies (LCNP) are a rare, but potentially severe late effect induced by damage due to radiotherapy (RT) and other cancer therapies. Lower cranial nerves include glossopharyngeal (IX), vagus (X), accessory (XI) and hypoglossal (XII) nerves, which are critical to the oropharyngeal phases of swallowing, shoulder function, and speech, respectively.[5-9] Fibrosis of nerve tracts or adjacent soft tissues can lead to delayed, typically progressive, neuro-vascular damage and eventually neuropathy which over time causes profound functional impairments.[5] According to a recent single institution report, the incidence of delayed LCNP among 59 OPC survivors was 5% at 5.7 years.[6]

Although a rare late effect, case reports suggest profound functional impairments and overall low quality of life (QOL) among LCNP cases.[5-8]Symptom burden is defined as severity of symptoms experienced by patients and the impact of those symptoms on day-to-day life.[10] Patients may experience symptoms due to disease, recurrence, or as a consequence of treatment-related toxicity.[10] Late toxicities, such as late LCNP, conventionally persist or

occur ≥ 3 months after treatment completion but may develop even years later.[11]

General functional impairment (GFI) is defined as a diminished ability to take care of oneself, manage the household, work, and indulge in activities for relaxation.[12] Thus, GFI can adversely impact the daily lives of survivors.[12] Treatment-related symptoms may have detrimental impact on GFI marked by symptom interference scores. For some patients, the impairment is temporary, and with time they return to normal activity and function. However, a substantial number of OPC survivors continue to experience limitations, disability, and may be unable to return to normal activities including work leading to a long-term economic impact.[12-13]

Previous studies examining late radiation-associated LCNP have been case reports or small case series or cohorts of predominantly nasopharyngeal cancer (NPC) survivors. In OPC, severe symptoms have been described among LCNP cases, but the late LCNP and symptom relationship has yet to be quantified, nor has impact on GFI.[7, 8] For the growing numbers of OPC survivors at risk for experiencing LCNP, it is critical to quantify the impact of late LCNP on severity of cancer treatment-related symptoms and GFI to inform development and implementation of targeted strategies for late effect surveillance and management.

The purpose of this analysis was to investigate the severity of cancer treatment-related symptoms (per primary endpoint of top 5 MDASI-HN symptom mean) and their subsequent impact on GFI (per secondary endpoint of mean MDASI-HN interference score) by late LCNP status among OPC survivors. Impact of late LCNP on overall mean symptom burden single item scores of most severe symptoms, and categorical ratings of top 5

symptoms was also assessed to explore impact on diverse symptom metrics. We hypothesized that late LCNP status would be associated with significantly worse symptom scores and GFI.

Methods

Patient Eligibility

An IRB-approved cross-sectional patient-reported outcome (PRO) survey was conducted among survivors of a retrospective cohort of OPC survivors treated at MD Anderson Cancer Center (MDACC) between January, 2000 and December, 2013. Eligible participants were ≥ 18 years of age at diagnosis, completed OPC treatment ≥ 1 year prior to survey, and consented to future research participation at new patient registration within the institution. Deceased patients, those who had a secondary primary malignancy (SPM) or recurrent malignancy of the head and neck prior to survey, and those whose primary language was not English were excluded. Patients with LCNP of any cause at the time of cancer diagnosis or with clinical signs of LCNP before starting cancer treatment were also excluded. Details of survey administration and response have been published previously.[14]

OPC Treatment

Institutional practices regarding OPC treatment during the time period of this study have been previously described.[15] Standard of care treatment during the current study time period for stage I/II OPC was definitive radiation and for patients with locally advanced OPC

(III/IV) was definitive chemoradiation.[15-17] During 2000-2006, both IMRT and 3D conformal radiation technique were routinely used, but after 2006 IMRT became the primary modality of treatment.[15] The recommended radiation dose for small volume primary tumors was 66 Gy and for more advanced tumors was 70-72 Gy.[15] For treatment of primary tumors and nodes in the upper neck region predominantly IMRT approach was used, whereas for nodes in the lower neck anterior beam technique with laryngeal and or full midline block was used. Further, for treatment of primary tumors and the neck region when split-field IMRT was not possible whole-field IMRT technique was used. Individual extent of primary disease and pre-existing comorbidities were taken into account to decide whether patients would receive systemic therapy or not. Definitive surgery via transoral resection to primary site was rare but after 2009, a small number of patients were treated with Transoral robotic surgery (TORS) with adjuvant therapy based on pathologic features.[15-17]

Demographic and Clinical Variables

Age at diagnosis, sex, race, education, smoking history, and HPV/p16 status were abstracted from electronic medical records. Clinical and treatment data abstracted included subsite of primary OPC tumor, tumor and nodal stage (AJCC version VII), treatment modality, RT dose, modality and fractionation, surgery, chemotherapeutic regimen, and ability to eat solid food at baseline (surrogate for baseline dysphagia). Survival time was calculated as the difference between age at diagnosis and age at time of survey.

Survey Items

The MD Anderson Symptom Inventory Head and Neck Cancer Module (MDASI-HN) is a 28-item validated PRO instrument that evaluates symptom severity and interference in HNC patients. MDASI-HN includes 13 questions to assess core symptoms common across all cancers and 9 questions to assess HNC-specific symptoms. MDASI-HN symptom severity item scores range from 0 "not present" to 10 "as bad as you can imagine." MDASI-HN also includes 6 interference questions to assess the impact of symptoms on daily function with respect to general activity, walking, work, mood, relations with other people, and enjoyment of life. These item scores range from 0 "do not interfere" to 10 "interfere completely," such that higher scores indicate more limitations and lower QOL.[14-21] Symptom and interference scores are commonly classified as: 0 "no symptom"; 1-3 "mild"; 4-6 "moderate" and 7-10 "severe" symptoms.[22] Mean subscale scores have been shown to be internally consistent (Cronbach alpha: 0.72-0.92).[14-21]

Primary Exposure

Late LCNP was assessed during surveillance and rehabilitation visits by clinical examination of cranial nerves by head and neck surgeons, radiation oncologists, and speech pathologists, and recorded in medical charts. Late LCNP was defined as onset of swallowing-associated neuropathy of at least one of the glossopharyngeal (IX), vagus (X), and hypoglossal (XII) nerves with minimum onset ≥ 3 months after the end of cancer treatment. Three months is considered the start of late toxicity interval as per the NCI – Common Toxicity Criteria Manual, "Late radiation effects are defined as effects that occur 90 days and

onwards after initiation of RT treatment."[11] For this reason, we elected to code any onset of LNCP after 3 months and up until the survey response as a late LCNP. Polyneuropathy was present in some patients with LCNP but there was no standard method to document degree of neuropathy in medical charts. Medical records were reviewed to identify LCNP cases. Physical examination reports were reviewed in detail. Objective methods such as endoscopy and radiographic swallow studies were not universally available for such a large study sample but were reviewed in detail when available. CT and MRI were used to verify LCNP, but they were not a requirement for case status assessment. Case status was verified through independent review of a head and neck surgeon with review of surveillance CT and MRI to rule out malignancy or other sources of neuropathy. Electromyography was not routinely used.

Primary Outcome: The primary outcome variable for this study was the mean of the top 5 most severely scored symptoms out of all 22 core and HNC-specific symptoms. This methodology, reported in the MDASI user guide and previous symptom research studies, serves as an estimate of the severity of the most impactful and prevalent symptoms reported by this population.[23-26]

Secondary Outcome: Results of the MDASI-HN can be summarized in various ways. Therefore, four secondary outcomes of the MDASI-HN were evaluated to fully explore the impact of late LCNP on symptom burden. Secondary outcomes included: 1) overall mean of 22 symptom items, 2) mean interference, 3) single item scores of the top 5 most severe symptoms, and 4) categorical ratings of top 5 symptoms.

Overall mean symptom scores summarize all 22 items of core and HNC- specific symptoms to reflect overall symptom severity. Mean interference serves as a marker of GFI with sub-domains of activity-related interference (using item scores related to general activity, work, and walking) and psychosocial-related interference (using item scores related to mood, relations with other people and enjoyment of life). Single item scores of the top 5 most severe symptoms, while extant in our primary endpoint (mean of top 5) were evaluated to reflect impact of LCNP on individual symptoms to provide insight on particular functional domains where LCNP had the greatest negative impact that might be helpful to focus supportive care efforts for this population. Finally, categorical ratings were examined to allow ease of clinical interpretation to identify proportions of patients experiencing high grade symptoms (supplementary analysis).[22]

Statistical Analysis

Descriptive and univariate analyses were first performed. For the primary outcome, mean top 5 MDASI-HN symptoms, multiple linear regression was next used to investigate associations between LCNP status and MDASI-HN scores, controlling for age, sex, race, T-stage, subsite, RT dose, fractionation, and modality, chemotherapy, surgery, eating solid food at baseline, survival time, and smoking, which according to previous literature, are co-factors that associate with toxicity and symptom burden.[27, 28]

Model building followed the purposeful variable selection method of Hosmer and Lemeshow.[29] Candidate predictors with $p < 0.25$ on univariate Wald test were entered into multivariable models and removed stepwise ($p > 0.2$). Age, T-stage, subsite, treatment

modality, and smoking were *a priori* retained as clinically important covariates and included in all models. Coefficients (unadjusted and adjusted) and corresponding 95% confidence interval (CI) were estimated. Impact of late LCNP on secondary outcomes were evaluated using multiple regression methods adjusting for the same variables as the primary outcome analysis. All data were analyzed without imputation for missing information. Given our consideration of multiple MDASI-HN parameters as symptom burden outcomes, analysis of all twelve primary and secondary outcomes including top5 mean, overall 22-item mean, mean interference including activity-related and psychosocial domains, individual scores for top 5 symptoms, voice and categorical ratings was corrected for multiple comparisons. After Bonferroni correction (α=0.05/12), statistical significance was conferred at $p < 0.004$. Statistical analysis was conducted using the STATA software, version 14.0 (StataCorp LP, College Station, TX).

Results

Sample Characteristics

889 eligible survivors were included in the final analytic sample with a median survival duration at time of survey of 7.0 years (range: 1-16). OPC survivors were mostly white (92%, 821/889), male (84%, 753/889), and had higher than high school education (72%, 637/889). Almost all were treated with RT (99%, 881/889), and few were treated with definitive surgery (3%, 24/889).

Late Lower Cranial Neuropathy

Overall, 4% (n=36) of OPC survivors were diagnosed with late LCNP and these cases had longer survival (median, 10.5 years). The median time to onset among LCNP cases in our study was 5.25, (range: 0.25 to 12.3) years after RT. Among late LCNP cases, 58% (22/36) had T1-T2 tumors, 42% (15/36) received accelerated RT, 25% (9/36) were treated with 3-D conformal RT and 64% (23/36) received IMRT-SF and almost all could functionally eat a normal diet prior to treatment.

Median RT Dose among respondents with LCNP was slightly higher (70 Gy, range: 60-72 Gy) in comparison to those without late LCNP (69.3 Gy, range: 40-73 Gy). 68% (605/889) of respondents received chemotherapy and rate of LCNP was slightly higher among respondents who received chemotherapy (risk difference; 0.26, 95% CI: -2.6, 3.0) in comparison to those who did not.

Treatment-related Symptom Burden (Mean of Top 5 symptoms)

The mean of each of the top 5 most severe symptoms reported by OPC survivors are summarized in Table 1 and included in descending order: dry mouth (mean 3.9± 2.9), swallowing/chewing (mean 2.6±2.8), mucus (mean 2.3±2.4), fatigue (mean 2.0± 2.5), and choking (mean 2.0± 2.6). Overall treatment-related symptom burden among all survivors was low (mean 2.6, median 2.0, range 0-10). Late LCNP cases reported significantly worse mean treatment-related symptom scores compared to those without LCNP (LCNP: 4.5 vs. no LCNP: 2.5, mean difference; -2.0; 95%CI, -2.7, -1.3).

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Unadjusted univariate analyses showed survival time, T-classification, therapeutic modality, chemotherapy, RT dose, fractionation, and modality, and smoking had significant associations with mean scores. Multiple linear regression identified that late LCNP was significantly associated with worse mean top 5 MDASI-HN symptom scores (Coefficient, 1.54; 95%CI, 0.8, 2.2, adjusted R^2, 0.08) adjusting for age, survival time, sex, therapeutic modality, T-stage, subsite, RT modality, smoking, and normal diet prior to treatment.

Overall Mean (22-item) MDASI-HN

LCNP cases reported significantly worse mean overall 22-item mean scores compared to those without LCNP (LCNP: 2.4 vs. no LCNP: 1.4, mean difference; -1.0; 95%CI, -1.5, -0.5). Late LCNP remained significantly associated with worse overall 22-item mean scores (Coefficient, 0.75; 95%CI, 0.2, 1.2,) after multivariable adjustment.

GFI/ Mean Interference

Late LCNP was not significantly associated with worse mean interference scores after multivariable adjustment and correction for multiple testing. Impact of late LCNP on individual domains of interference scores categorized as activity-related and psychosocial-related was also not statistically significant after correction for multiple comparison.

Individual Top 5 Symptoms and Voice/Speech Symptom

Individual symptoms that were most severe among late LCNP cases, in rank order of means, included difficulty swallowing/chewing (LCNP: 5.5 vs. no LCNP: 2.5, mean difference;-2.9; 95%CI, -3.9,-2.0), dry mouth (LCNP: 4.9 vs. no LCNP: 3.8, mean difference;

-1.0; 95%CI, -2.0,-0.4), mucus (LCNP: 4.7 vs. no LCNP: 2.3, mean difference; -2.5; 95%CI, -3.4,-1.5), voice/speech (LCNP: 4.4 vs. no LCNP: 1.3, mean difference; -3.1; 95%CI, -3.9,-2.3) and choking (LCNP: 4.1 vs. no LCNP: 1.9, mean difference; -2.1; 95%CI, -3.0,-1.3).

Late LCNP was significantly associated with worse mean swallowing/chewing scores (coefficient, 2.25; 95%CI, 1.3, 3.1adjusted R^2, 0.10), mucus problems (coefficient, 1.97; 95%CI, 1.0, 2.9, adjusted R^2, 0.07), fatigue (coefficient, 1.35; 95%CI, 0.4, 2.2, adjusted R^2, 0.03), and choking/coughing (coefficient, 1.53; 95%CI, 0.6, 2.4, adjusted R^2, 0.07) adjusting for the same variables as the primary outcome analysis. However, late LCNP was not significantly associated with worse dry mouth after multivariable adjustment. As late LCNP can include vocal cord paralysis and/or lingual paralysis (with associated impact on voice and speech production), the impact of late LCNP on voice/speech was assessed in exploratory post hoc analysis despite its exclusion from the top 5 items in the overall sample. Late LCNP was independently associated with worse mean MDASI-HN voice scores (Coefficient, 2.3; 95%CI, 1.6, 3.0, adjusted R^2 – 0.17) after multivariable adjustment.

Among LCNP cases, a higher proportion reported severe (LCNP: 20% vs no LCNP: 5%) and moderate (LCNP: 40% vs no LCNP: 15%) symptoms. Additionally, among LCNP cases, severe scores (≥7) were reported by 43% (15/35) for swallowing/chewing symptoms and 37% (13/35) for voice/speech problems. Among 35 late LCNP cases, 6 patients rated difficulty swallowing, 4 rated voice/speech problems, 4 rated choking, and 3 rated mucus as 10 of 10 severity, the worst possible score on MDASI-HN (Supplementary Figure 1).

Discussion

This large cross-sectional survivorship survey yields a comprehensive, quantitative assessment of the significant impact of late LCNP on cancer treatment-related symptoms and their subsequent impact on GFI among OPC survivors. Survey results in almost 900 OPC survivors treated during 2000-2013 indicated that, although overall treatment-related symptom burden among all survivors was low, the small subgroup of late LCNP cases (4%) reported significantly worse treatment-related symptom severity. While the impact of late LCNP is clinically recognized, prior studies have yet to quantitatively estimate the burden of this late effect.

Our results suggest, on average, mean of top 5 MDASI-HN items is 1.54 points worse among survivors with LCNP compared to those without LCNP, even after adjusting for age, survival time, sex, therapeutic modality, T-stage, subsite, RT modality, smoking, and normal diet prior to treatment. This reflects a moderate effect size of LCNP on most prevalent symptoms in this survivor population. The adjusted R^2 of the model suggested that late LCNP explained 8% of the variation in top 5 MDASI-HN mean after accounting for the effects of other covariates. This modest/moderate adjusted R^2 for a single exposure may reflect the variability of nerve paresis effects on symptoms among survivors due to their cross-sectional sampling along the continuum of nerve paresis (partial through complete denervation) as progressive deterioration over time is characteristic of late LCNP.[30] That is, LCNP cases responded to the survey from 2 to 16 years after treatment, a timeframe during which the clinical course of LCNP was likely to vary. This observation is consistent with

previous case reports suggesting that functional status of cases approximated the trajectories of their neuropathies.[7] That is, as late LCNP remained clinically stable, physiologic impairment remained steady and, as late LCNP progressed, coincident severe decline in function and body weight occurred.[7]

OPC treatment may lead to multiple local symptoms in the treatment field including dry mouth, dysphagia, mucositis, choking, speech problems, and lack of taste, among others, which can contribute to excessive distress and lower QOL.[27, 31] The top 5 symptom means reported by our study population predominantly featured similar local head and neck specific side effects (4/5, except fatigue). Given their central role in daily functioning, it is not surprising that late LCNP cases also reported higher levels of GFI that highly correlated with symptom severity but this relationship was not statistically significant after multiple comparison correction. Interestingly, among individual components of the interference domain, late LCNP seemed to be more strongly associated with activity-related interference but not psychosocial-related scores, but this relationship was not statistically significant. These findings may perhaps suggest a more lasting impact of LCNP on activity as opposed to emotional distress. It is speculated that psychosocial distress associated with late effects may attenuate over time as patients learn to cope with the emotional distress associated with physical impairment. Similarly, a previous study investigating QOL among oral cancer patients per the Functional Assessment of Cancer Therapy-Head and Neck (FACT-H&N) demonstrated significantly improved emotional scores in the same time that functional scores deteriorated between 1 month and 6 months after treatment.[32] The authors attributed this to a

"response shift" which they described as emotional adaptation to decline in physical functioning and improved coping with the "new normal" level of functioning.[32] These trends are also consistent with results of a study among HNC patients using the MD Anderson Dysphagia Inventory (MDADI), which reported better scores for the emotional versus functional component.[33]

Overall, late LCNP most strongly associated with worse swallowing/chewing and speech/voice symptoms, with LCNP explaining 10% and 17% of the variation in these scores, respectively. These findings agree with those reported by a longitudinal study among 57 OPC survivors wherein 3 LCNP cases experienced severe decline in swallowing function over time, as per patient-reported MDADI scores, clinician-rated radiographic dysphagia grades (DIGEST), and standard diet scales (PSS-HN).[6] Late LCNP also strongly associated with worse mucus and choking scores in the present survey, which may reflect symptoms associated with swallowing effects of LCNP. Inefficient swallows described previously in LCNP cases impact the ability to effectively clear food and liquids through the oropharynx, including mucus.[7] Mucus accumulation can lead to unpleasant symptoms of gagging and choking. This may also reflect aspiration of food and liquids during swallowing as previously reported in 100% of cases with neuropathy mediated late radiation-associated dysphagia (late-RAD) comprised largely of long-term OPC survivors >5-years post-treatment.[34]

Lower cranial nerves are critical to the oropharyngeal phase of swallowing as well as voice and speech production.[5-9] CN IX palsy may lead to swallowing problems by way of loss of function of the stylopharyngeus muscle and loss of pharyngeal sensation, whereas CN X injury can cause paralysis of the pharyngeal constrictors and/or vocal cords (depending on the branch), and thereby contribute to dysphagia as well as voice impairment. Neuropathy of CN XII results in tongue paresis, atrophy, and fibrillations with implications also to swallowing and speech precision.[5-9] Therefore, the specific patterns of symptom burden detected in this survey align with the clinical impact of specific LCNPs among OPC patients.

Fatigue is widely prevalent in HNC survivors but was also reported with greater severity among LCNP cases, which may be because of late LCNP-associated mucus problems that could exacerbate sleep disturbance.[35] LCNP-associated swallowing dysfunction can also contribute to long-term micronutrient deficiency and complications like anorexia, malnutrition, anemia, and cachexia. Cachexia especially has been linked in past studies to functional limitations and fatigue.[36] Furthermore, lack of association between late LCNP and dry mouth is expected, given that dry mouth is not a consequence of lower cranial nerve injury and is instead caused by RT-induced hypofunction of salivary glands.[37]

With approximately 900 OPC survivors, this study is the first to quantitatively estimate the impact of late LCNP on treatment-related severity of symptoms. There are, however, limitations to acknowledge. Cross-sectional survey administration led to respondents with varying survival time and survival bias. Given the long latency period for late LCNP development, risk is highest among responders with greater survival time. For this reason, survival time was accounted for in all regression models. The small number of events

is a limitation inherent to studies of LCNP, as it is known to be a rare late effect. Nonetheless, consistently robust effect estimates on study outcomes were identified that reflect expected outcomes from clinical observations. This study was conducted in a tertiary care cancer center making it subject to referral bias that can limit generalizability of results to other hospitals and communities, but sample characteristics are common of modern OPC in the US, therefore, impact of this issue is expected to be negligible. The largest threat to validity is the possibility of misclassification. Late LCNP ascertainment may be incomplete due to loss to follow-up, missing chart details, or differential follow-up among patients displaying mild cranial neuropathy symptoms insufficient to merit return to clinic for late LCNP. Therefore, exposure misclassification in this study would most likely lead to under-reporting of LCNP and consequently to underestimation of LCNP impact on symptom burden. Thus, if misclassification was substantial, actual coefficients for LCNP and symptom burden may be higher than reported in this study. With cross-sectional survey, degree or time course of LCNP was not standard in all cases. There was, for instance, no standard method to document degree of neuropathy in medical records. Likewise, the impact of LCNP on diet and other functional parameters was not assessed and will be investigated in future publications. We also did not obtain detailed validated measures of anxiety and depression and therefore the impact of late LCNP on these domains need to be investigated in future studies using other more robust measures.

Symptom burden can be reflected by many parameters of the MDASI-HN. Each of the MDASI-HN outcomes we report in this analysis is described in the MDASI user guide as options to report findings from the instrument. It is important to acknowledge, however, that the top 5 mean MDASI-HN metric has not been evaluated for validity in a dedicated

publication. It is, however, supported by both the MDASI user manual and by expected performance relative to clinical and demographic classifiers in this report and other publications. [23-26]Evaluation of individual items as a secondary endpoint also suggested that late LCNP had a greatest negative impact on difficulty swallowing, speech, mucus problems, choking, and fatigue symptoms among OPC survivors. For this reason, the functional translation of late LCNP may lead to placement of feeding tubes, tracheostomy tubes, aspiration, and pneumonia, as has been described in smaller series with more objective metrics.[6-8]Smaller series, however, fail to include non-LCNP controls such that effect sizes from these more objective metrics are not available in current literature. It is our hope that these survey-based quantifications offer initial progress toward quantifying the impact of this rare but devastating late effect of treatment.

This research can inform development of supportive care interventions among OPC survivors to target these symptom domains through personalized speech and swallowing therapy and nutritional consultations and such implications need to be assessed in future studies. Given the high degree of symptom burden, the authors support the integration of interdisciplinary supportive care early to potentially attenuate or slow the functional impact of LCNP. Diverse symptoms likely merit involvement of speech pathologists, oral oncologists, physiatrists, physical therapists, nutrition, and oncology nursing among others to optimize outcomes. Targeted and individualized treatments must take into consideration patient perspectives and routine symptom screening using validated PROs such as MDASI-HN in patients with LCNP may also be of value to prioritize areas for intervention.

Conclusions

In this large survey study, late LCNP cases reported significantly worse cancer treatment-related symptoms, and worse symptoms associated with motor functions of the upper aerodigestive tract (swallowing, voice), demonstrating the relevance of late LCNP to both symptom severity and QOL. Among LCNP cases, a higher proportion reported severe (LCNP: 20% vs no LCNP: 5%) and moderate (LCNP: 40% vs no LCNP: 15%) symptoms. There is a clear need for long-term surveillance of late LCNP among HNC and OPC patients, particularly in light of epidemiologic trends that suggest growing numbers of OPC survivors at risk of late effects in immediate years ahead.[6-8] Further, efforts are necessary to lessen symptom burden associated with this disabling late effect among OPC survivors.

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Table 1: Patient Characteristics 889 (N=889), Top 5 mean MDASI-HN:

Variables	No. of Patients	LCNP Rate (%)	Top 5 mean MDASI-HN Score (+/-Standard Deviation) All patients (n=906)
Age at diagnosis, median (range)			56 (32-84)
Survival time, median (range)			7(1-16)
Radiation Dose, Gy. median (range)			70 (40-73)
Sex			
Female	136 (15.3)	5(3.7)	2.81 ± 2.3
Male	753 (84.7)	31(4.1)	2.57 ± 2.1
Education			
≥Highschool	168(18.9)	8(4.8)	2.95 ± 2.4
>Highschool	637(71.7)	27(4.2)	2.49 ± 2.1
Missing	84(9.4)	1(1.2)	2.86 ± 2.3
Race			
Others	59(6.6)	3(5.0)	2.79 ±2.7
White	821(92.4)	32(3.9)	2.60 ± 2.1
Missing	9(1.0)	1(11.1)	2.44 ± 1.7
Primary Site			
Tonsil	438(49.3)	17(3.8)	2.58 ± 2.2
Base of Tongue	451(50.7)	19(4.2)	2.64 ± 2.2
T classification			
1	334(37.6)	8(2.4)	2.37 ±2.1
2	345(38.8)	13(3.8)	2.52 ±2.1
3	131(14.7)	8(6.1)	2.89 ±2.3
4	79(8.9)	7(8.9)	3.56 ±2.5
N classification			
N0	81(9.1)	3(3.7)	2.58 ±2.3
N1+2a	236(26.5)	7(2.9)	2.48 ±2.2
2b+3	429(48.3)	19(4.4)	2.50 ±2.0
2c	143(16.1)	7(4.9)	3.16 ±2.4
HPV status			
Negative	56(6.3)	2(3.6)	2.37 ±1.9
Positive	429(48.3)	9(2.1)	2.46 ±2.1
Unknown	404(45.4)	25(6.2)	2.80 ±2.3
Smoking			
Never	409(46.0)	16(3.9)	2.49 ±2.1
Former	422(47.5)	17(4.0)	2.64 ±2.1
Current	58(6.5)	3(5.2)	3.22 ±2.5
Solid Food pre-Tx			
Yes	879(98.9)	35(4.0)	2.56 ±1.8
No	10(1.1)	1(10.0)	2.61 ±2.2
Treatment Group			
Single Modality	278(31.3)	11(4.0)	2.34 ±2.1
Multimodality	611(68.7)	25(4.1)	2.73 ± 2.2
Treatment Group			
RT alone	270(30.4)	11(4.1)	2.38 ±2.1
Surgery alone	8(0.9)	0	0.80 ±0.7
RT plus systemic	596(67.0)	23(3.9)	2.73 ±2.2

Surgery plus adjuvant	15(1.7)	2(13.3)	2.64 ±2.3
Radiotherapy			
No	8(0.9)	0	0.80 ±0.8
Yes	881(99.1)	36(4.1)	2.62 ±2.2
Chemotherapy			
No	284(32.0)	11(3.9)	2.34 ±2.1
Yes	605(68.0)	25(4.1)	2.73 ±2.2
Surgery			
No	865(97.3)	34(3.9)	2.63 ±2.2
Yes	24(2.7)	2(8.3)	1.91 ±2.0
Neck Dissection			
No	665(74.8)	27(4.1)	2.64 ±2.2
Yes	224(25.2)	9(4.0)	2.52 ±2.2
RT Schedule			
Standard Fractionation	778(88.3)	21(2.7)	2.54 ±2.1
Accelerated	95(10.8)	15(15.8)	3.40 ±2.4
Missing	8(0.9)	0	1.76 ±1.9
RT Type			
3d Conformal	50(5.7)	9(18.0)	4.34 ±2.6
IMRT-SF	675(76.6)	23(3.4)	2.63 ±2.1
IMRT- WF	33(3.8)	1(3.0)	2.72 ±2.3
Proton	23(2.6)	1(4.4)	2.14 ±1.6
IMRT Ipsilateral	100(11.3)	2(2.0)	1.8 ±1.6

Abbreviations: T, tumor; RT, radiotherapy; MDASI-HN, MD Anderson Symptom Inventory Head and Neck Cancer Module (MDASI-HN

Table 2. Top 5 MDASIHN Univariate and Multivariate Regression (n=889)

Variables	Univariate Analysis Coefficient (95%CI)	Multivariate Analysis Coefficient (95%CI)
Late LCNP		
No	Reference	Reference
Yes	2.00 (1.28, 2.72) ***	1.54 (.82, 2.27) ***
Age at diagnosis	0.001 (-.02, .02)	0.007 (-.01, .02)
Survival Time	0.06 (.02, .09) *	0.02 (-.03, .06)
Radiation Dose	0.10 (.04, .15) *	
Sex		
Female	Reference	Reference
Male	-0.24 (-.64, .16)	-0.32 (-.71, .08)
Education		
≤Highschool	Reference	Reference
>Highschool	-0.46 (-.83 -.09) *	
Missing	-0.09 (-.66, .48)	
Race		
Others	Reference	Reference
White	-0.20 (-.78, .39)	
Missing	-0.35 (-1.87, 1.18)	
Primary Site		
Tonsil	Reference	Reference
Base of Tongue	0.07 (-.22, .36)	-0.08 (-.38,.23)
T classification		
1	Reference	Reference
2	0.15(-.17, .48)	0.007 (-.33,.35)
3	0.52 (.08, .96) *	0.06 (-.42, .54)
4	1.19 (.65, 1.73) ***	0.73 (.16,1.30) **
Smoking		
Never	Reference	Reference
Former	0.14 (-.15, .44)	0.12 (-.18,.41)
Current	0.73 (.12, 1.33) *	0.62 (.03, 1.22) **
Solid Food pre-Tx		
Yes	Reference	Reference
No	0.06 (-1.29, 1.42)	0.60 (-.64,1.85)
Treatment Group		
Single Modality Tx.	Reference	Reference
Multimodality Tx.	0.40 (.09, .71) *	0.17 (-.20, .53)
Radiotherapy		
No	Reference	
Yes	1.83 (.32,3.33) *	
Chemotherapy		
No	Reference	Reference
Yes	0.40 (.09, .70) *	
Surgery		
No	Reference	Reference
Yes,	-0.72 (-1.61, .18)	
Neck Dissection		
No	Reference	Reference
Yes	-0.11 (-.46,.22)	
RT Schedule		
Standard Fractionation	Reference	Reference
Accelerated	0.85 (.39, 1.32) ***	

Missing	-0.77 (-2.27, .74)	
RT Type		
3d Conformal	Reference	
IMRT-SF	-1.71 (-2.33, -1.10) ***	-1.34 (-2.02, -.66) ***
IMRT- WF	-1.62 (-2.55, -.68) *	-1.33 (-2.29, -.38) **
Proton	-2.20 (-3.25, 1.15) ***	-1.76 (-2.89, -.63) **
IMRT-Ipsilateral	-2.54 (-3.27, -1.81) ***	-2.06 (-2.89, -1.23) ***

Abbreviations: T, tumor; RT, radiotherapy; MDASI-HN, MD Anderson Symptom Inventory Head and Neck Cancer Module (MDASI-HN)

* Statistical significance p value < 0.05 after Univariate Analysis

** Statistical significance p value < 0.05 after Multivariate Analysis

*** Statistical significance p value < 0.001

FIGURE 1: Consort flow chart

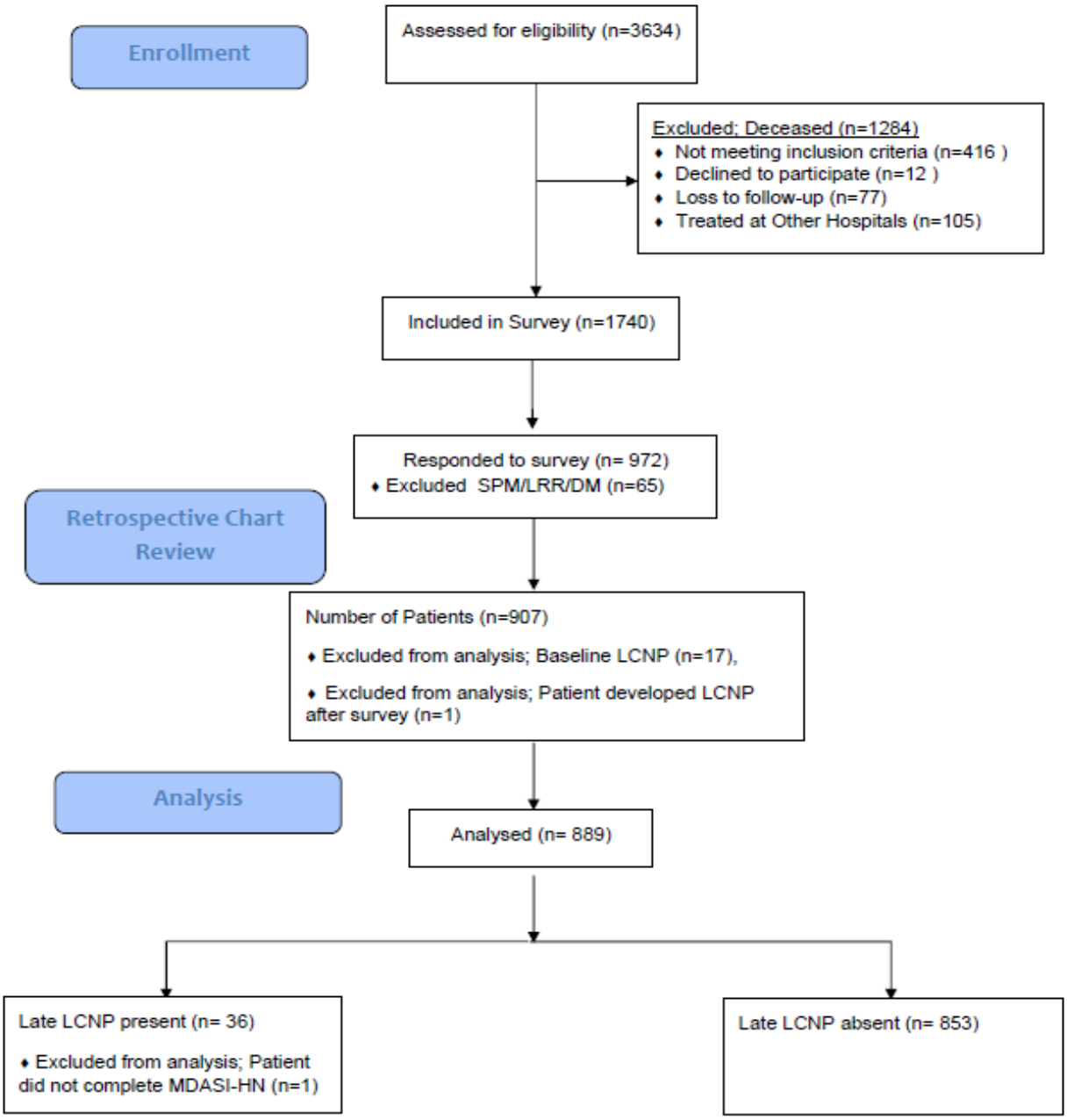

Figure 1. Consort flow chart showing study participant recruitment and eligibility criteria. Abbreviations: SPM, second primary malignancy; LRR, locoregional recurrence; DM, distant metastasis; LCNP, lower cranial neuropathy; MDASI-HN, MD Anderson Symptom Inventory Head and Neck Cancer Module (MDASI-HN)**.**

Figure 2: Crude/Unadjusted Difference in means of individual MDASI-HN symptom severity by Late LCNP status.

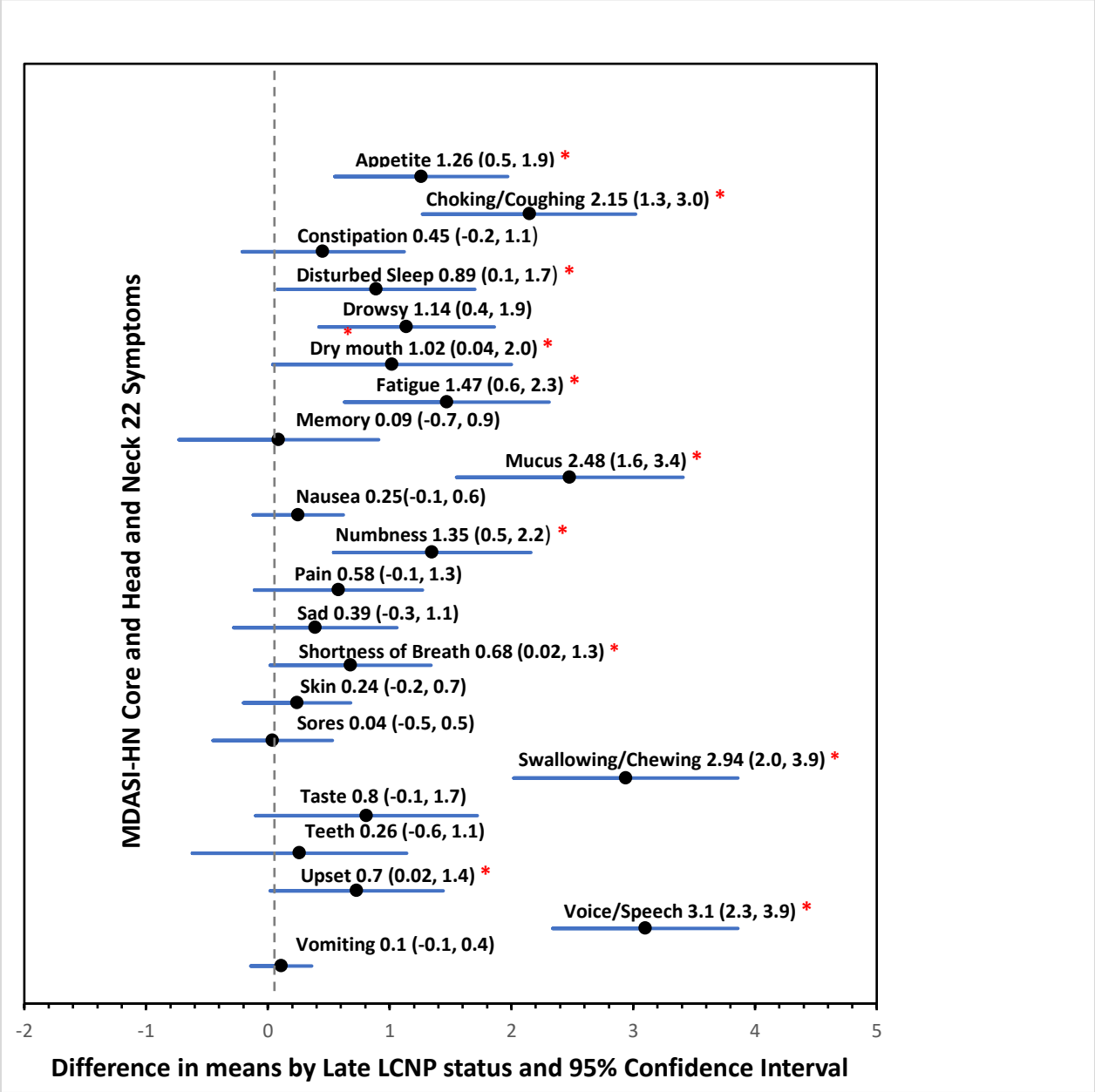

Figure 2. Crude/Unadjusted Difference in means of individual MDASI-HN symptom severity by Late LCNP status. Darkened circles represent estimate of difference in means and bars represent 95% Confidence Intervals. * Denotes statistical significance conferred if 95% confidence for the estimate did not include the null value. Abbreviations: MDASI-HN, MD Anderson Symptom Inventory Head and Neck Cancer Module (MDASI-HN); LCNP, lower cranial neuropathy.

Figure 3: Multivariate Adjusted Coefficients for Late LCNP and MDASI-HN Scores.

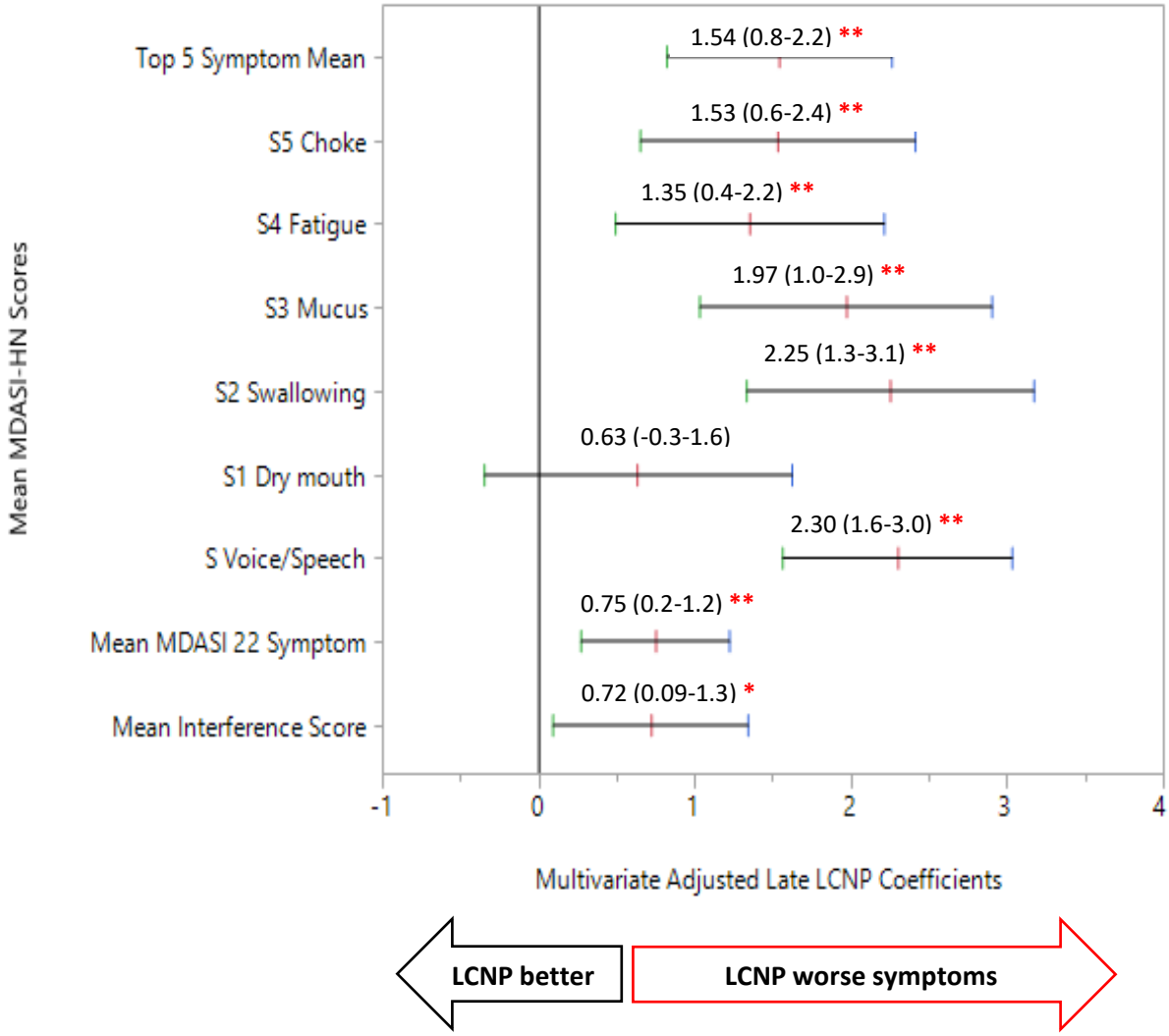

Figure 3. Multivariate Adjusted Coefficients for Late LCNP and MDASI-HN Scores.
All regression models adjusted for age, survival time, sex, therapeutic modality, T-stage, subsite, RT modality, smoking, and normal diet prior to treatment. * Denote statistically significant in multivariate model before multiple comparison correction. ** Denote statistically significant in multivariate model after multiple comparison correction ($p < 0.004$). Abbreviations: MDASI-HN, MD Anderson Symptom Inventory Head and Neck Cancer Module (MDASI-HN); LCNP, lower cranial neuropathy.

JOURNAL ARTICLE 3

Title of Journal Article: Swallowing-related outcomes associated with Late Lower Cranial Neuropathy in Long-term Oropharyngeal Cancer Survivors: A Cross-Sectional Survey Analysis

Name of Journal: Head & Neck (August 2019)

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Key Words: Oropharyngeal cancer, lower cranial neuropathy, radiotherapy, dysphagia, survivorship

With permission from *Head & Neck*, this chapter was excerpted in its entirety from the following journal article: Aggarwal, P, Zaveri, JS, Goepfert, RP, 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: 3880– 3894. References in this chapter are formatted according to the journal style.

Abstract

Background: The purpose of this study was to quantify the association of late lower cranial neuropathy (late LCNP) with swallowing-related quality of life (QOL) and functional status among long-term oropharyngeal cancer (OPC) survivors.

Methods: Eight hundred eighty-nine OPC survivors (median survival time: 7 years) who received primary treatment at a single institution between January, 2000 – December, 2013 completed a cross-sectional survey (56% response rate) that included the MD Anderson Dysphagia Inventory (MDADI) and self-report of functional status. Late LCNP events ≥3-months after cancer therapy were abstracted from medical records. Multivariate models regressed MDADI scores on late LCNP status adjusting for clinical covariates.

Results: Overall, 4.0% (n=36) of respondents developed late LCNP with median time to onset of 5.25 years post-treatment. LCNP cases reported significantly worse mean composite MDADI (LCNP: 68.0 vs. no LCNP: 80.2, $p<0.001$). Late LCNP independently associated with worse mean composite MDADI (β= -6.7, p=0.015, 95%CI: -12.0, -1.3) as well as all MDADI domains after multivariate adjustment. LCNP cases were more likely to have a feeding tube at time of survey (OR= 20.5; 95%CI, 8.6 to 48.9), history of aspiration pneumonia (OR= 23.5; 95%CI, 9.6 to 57.6), and tracheostomy (OR= 26.9; 95%CI, 6.0 to 121.7).

Conclusions: In this large survey study, OPC survivors with late LCNP reported significantly poorer swallowing-related QOL and had significantly higher likelihood of poor

functional status. Further efforts are necessary to optimize swallowing outcomes to improve QOL in this subgroup of survivors.

INTRODUCTION

Swallowing is a complex and multifaceted neuromuscular process that involves 5 cranial nerves (CN) and almost 30 muscles in the upper aero-digestive tract. Patients with oropharyngeal cancer (OPC) receive local treatments, radiotherapy (RT), and/or surgery, to this functionally critical region that can cause chronic dysphagia with adverse impact on swallowing-related quality of life (QOL). [1-6] Dysphagia is one of the most impactful and prevalent functional toxicities reported in approximately 30-50% of survivors. [7-10] Prior analysis of this OPC survivorship found that, among 22 symptoms queried, the severity of dysphagia symptoms most strongly associated with decisional regret about cancer treatment.[11] The rising incidence of highly curable HPV-associated OPC leads to greater numbers of OPC survivors at risk of dysphagia with great impetus to understand factors that associate with poor swallowing outcomes and adversely impact QOL in this growing population. Dysphagia also leads to excessive morbidity, negatively impacting functional status and health of OPC survivors. Impaired airway protection can lead to aspiration pneumonia, and inefficient bolus clearance may result in low food intake, extended gastrostomy tube dependence, weight loss, and malnutrition.[12] Patients with dysphagia often modify their diet, need extended meal times, feel self-conscious to eat in social settings, and thereby experience social isolation and diminished QOL.[12]

Radiation-associated dysphagia is typically linked with soft tissue injuries including inflammation, edema, fibrosis, and stricture.[13] Acute tissue injury results from cell depletion and inflammation that contribute to edema, erythema, and mucositis of the oropharyngeal region.[13,14] Late RT injury is defined classically as 3 months or more after cancer treatment,

and may represent persistence of early injury (i.e., “consequential late effects”) or new damage linked to excessive collagen accumulation, microvascular damage, and overproduction of pro-fibrotic growth factors β (TGF-β1) resulting in fibrosis and atrophy.[14,15] The superior pharyngeal constrictor (SPC) region comprises minor nerve tracts and the constrictor and longitudinal pharyngeal muscles, which are important for pharyngeal shortening and constriction during swallowing for safe and efficient bolus propulsion into the esophagus.[16] Irradiation to this region, specifically the mean SPC region dose, has been reported in numerous studies to be associated with chronic and late radiation associated dysphagia (late-RAD).[16-19] Thereby dysphagia may occur as consequence of reduced base of tongue retraction and elevation of larynx, inadequate retroflexion of epiglottis, pharyngeal transit delay, and inadequate swallowing muscle action.[14]

Surgical treatment for OPC including tongue resection involving geniohyoid or mylohyoid muscles, mandibulotomy-related genioglossus injury and loss of occlusion, lateral soft palate resection may also cause muscle and nerve injury and contribute to dysphagia.[13] Site and extent of tumor resection thereby contribute to severity of dysphagia.[13] Reports also suggest that head and neck (HNC) patients treated with surgery followed by post-operative RT may experience cumulative effects and more accelerated effects of RT.[6, 13, 20] This may contribute to additional decline in swallowing function due to diminished oropharyngeal swallow efficiency. [6, 13, 20]

Lower cranial neuropathies (LCNP) are a rare, but permanent late effect of HNC treatment that injures the glossopharyngeal (IX), vagus, (X), accessory (XI), and/or hypoglossal (XII) nerves.[1, 21-24] These nerves (except XI) play a pivotal role in the

oropharyngeal swallowing mechanism and thereby their damage can contribute to profound functional impairment in terms of dysphagia often with co-existing problems in speech and voice and shoulder impairment.[1, 16, 21-25] A previous study among 59 OPC survivors treated with intensity modulated radiotherapy (IMRT) reported a 5% incidence rate of late LCNP at median follow-up of 5.7 years (range: 4.6-7.6 years).[1] Among LCNP cases, onset of neuropathy preceded quantifiable, clinically significant decline in both patient-reported (per MD Anderson Dysphagia Inventory; MDADI) and clinician-rated (per Modified Barium Swallow Study; MBS) swallowing function.[1] Likewise, the investigators recently published a large survey of 889 long-term OPC survivors in which LCNP was significantly associated with excess symptom burden and had the greatest impact on swallowing/ chewing and voice/speech symptoms among the 22 symptom items rated using the MD Anderson Symptom Inventory Head and Neck Cancer Module (MDASI-HN), a validated multi-symptom survey instrument.[26]

Previous literature also specifically implicates LCNP as a major contributor to late radiation associated dysphagia (late-RAD).[21, 22] Patients with late RAD often have clinically detectable LCNP with unilateral paralysis, muscle wasting leading to atrophy of lingual and pharyngeal musculature with clinical series supporting a prominent role of nerve injury in the functional decline experienced by these patients.[25] A series of 29 HNC survivors with late-RAD reported that 48% of cases had clinically-detectable cranial neuropathies, and cranial nerve XII and X palsies were most common.[25] Several small published series and case reports consistently describe severe problems in swallowing, eating, and extreme functional impairment in pharyngeal phase of swallowing among survivors with late LCNP, with

associated swallowing inefficiency, pharyngeal residue, and silent aspiration. [1, 16, 21-25] Consequently, about 85% of OPC survivors with late-RAD develop pneumonia and more than 60% require long-term gastrostomy tube placement highlighting the possible extreme functional relevance of late LCNP if it indeed is a driver of late dysphagia.[16, 22]

The previous literature and prior analysis of symptom burden suggests a strong association between late LCNP and the severity of dysphagia, however the nature of this association has not been comprehensively evaluated or quantified in a large population of survivors. Few studies have addressed late LCNP among OPC survivors, as most of the published literature on LCNP has been comprised of case reports or studies primarily conducted among nasopharyngeal cancer (NPC) survivors.[27, 28] Studies suggest that risk of cranial nerve damage increases over time [1, 22, 28] and as survival probabilities improve for OPC, there is an ever-growing pool of OPC survivors who have received surgery and/or curative doses of radiotherapy sufficient to induce LCNP. Therefore, there is urgent need to understand to our fullest ability the functional impact of this disabling late effect of therapy. Thus, the purpose of this analysis was to quantify the association of late LCNP with swallowing-related QOL using the MDADI and functional status metrics. We hypothesized that late LCNP among OPC survivors would be associated with significantly worse swallowing-related QOL (per MDADI survey scores) and LCNP status would relate to differences in functional status metrics.

MATERIALS AND METHODS

Study Design, Eligibility and Consent

This cross-sectional survey was conducted in 2015 among a cohort of OPC survivors who received primary cancer treatment at MD Anderson Cancer Center (MDACC) between January, 2000 and December, 2013. An institutional review board-approved patient-reported outcome (PRO) survey was administered to eligible OPC survivors in the cohort who were ≥ 18 years of age at diagnosis, completed their treatment at least 1 year prior to survey administration, and consented to the study. Exclusion criteria were: patients who were deceased, those with second primary malignancy (SPM) or recurrent head and neck cancer tumors preceding survey, and those whose primary spoken language was not English. For this analysis, patients diagnosed with LCNP or with clinical signs of LCNP prior to initiation of OPC treatment were excluded. The survey items included in this analysis were the MDADI, a patient-reported adaptation of the Performance Status Scale for Head and Neck cancer (PSS-HN) with questions on normalcy of diet and public eating, as well as self-report of aspiration pneumonia, current feeding tube status, and current weight. A previous publication provides details of survey administration and response.[7]

MD Anderson Dysphagia Inventory (MDADI)

The MD Anderson Dysphagia Inventory (MDADI) is a 20-item validated patient reported outcomes (PRO) instrument that quantifies perceived limitations in swallowing ability and their impact on day to day activities.[29] MDADI provides subscale scores which are comprised of emotional (6 questions), physical (8 questions), and functional components

(5 questions). It also estimates a global summary score (based on 1 question- "My swallowing limits my day to day activities") and a composite score (based on 19 questions excluding the global item).[29-32]

Scoring of MDADI: The questions related to swallowing function are Likert scaled with the options of 'strongly agree', 'agree', 'no opinion', 'disagree', or 'strongly disagree', scored on a scale of 1-5, respectively, with the exception of two questions (E7 and F2) for which reverse scoring is calculated. After summation of response scores, mean is estimated and multiplied by 20 to estimate total score.[33] Total scores range from 20-100 with higher scores reflecting higher perceived swallowing-related QOL. [12, 29, 32, 33] MDADI scores can be analyzed as continuous or categorical variables with scores classified in the following categories: ≥80 as optimal, 60-79 as adequate and <60 as poor.[10] MDADI was validated among HNC patients and has internal consistency scored by Cronbach's alpha of 0.96 and was documented to have test-rest reliability correlations ranging from 0.69 to 0.88.[29]

Performance Status Scale for Head and Neck (PSS-HN) Adaptation

An adapted version of the PSS-HN, a validated, clinician-rated interview-based measure of performance status among HNC patients was included in the survey instrument.[1] The scale was adapted for patient-reported administration and comprised of questions pertaining to the survivor's diet level and public eating experience.[1] Normalcy of diet options included the following: full diet no restriction, full diet with liquid assist, solid food but avoid some hard to eat foods, soft chewable foods, non-chewable or pureed foods, drink warm and

cold liquids only, or nothing orally only use a feeding tube. Public eating was coded as the following: no restriction of place, food, or companion, no restriction of place, restrict diet in public, eat only in the presence of selected person in selected places, only eat at home with selected persons, or always eat alone.

Primary and Secondary Outcomes

The primary outcome for this study was mean composite MDADI score which serves as an estimate of overall swallowing-related quality of life.[29-33] The secondary outcomes for analysis included the emotional, physical and functional subscale and the global MDADI scores as well as self-reported functional status metrics including current feeding tube status, normalcy of diet, public eating, history of aspiration pneumonia, current weight, understandability of speech, and current tracheostomy. Chart abstracted functional data included baseline weight to calculate percent change in weight between weight at time of survey and pre-treatment weight, and history of dilations due to presence of stricture. Current feeding tube status, aspiration pneumonia history, and current tracheostomy were coded as binary variables. Change in weight was calculated as baseline weight minus current weight and percent change in weight was calculated as change in weight divided by baseline weight. Survey questions on functional status metrics have been listed in Appendix 2.

Primary Exposure

Late LCNP was the primary exposure for this analysis. Late LCNP case status was ascertained by detailed review of medical records of survivors as previously described.[26] For

this study late LCNP was defined as clinical evidence of neuropathy of at least one of the glossopharyngeal (IX), vagus (X), and hypoglossal (XII) nerves ≥ 3 months after the end of cancer treatment.[26] The time period was defined considering the NCI-Common Toxicity Manual's definition of late radiation effects as occurring 90 days and onwards after RT therapy initiation.[34]

Clinical and Demographic Variables

Demographic variables including age at diagnosis, sex, race, and education, and clinical variables including primary tumor subsite, tumor and nodal staging (AJCC version VII), treatment modality, chemotherapy, surgery, neck dissection, RT dose, fractionation, and modality were abstracted from the electronic medical records. Pre-treatment diet (ability to eat solid foods) was also collected as a surrogate variable for presence of baseline dysphagia. Survival time for this population was estimated as the difference between age of diagnosis and age at the time of the survey. History of pharyngoesophageal dilation was used as a surrogate variable for stricture which can contribute to dysphagia and act as a confounder in our analysis.

Statistical Analysis

Demographic, clinical, and treatment variables and distribution of MDADI scores by these variables were summarized using descriptive statistics and univariate analysis. With a rare event leading to small case numbers for our primary exposure (LCNP), imputation of MDADI scores was conducted to minimize loss of statistical power due to skipped or missing MDADI items. Imputation used the mean of responses to MDADI items among

those patients who responded to that specific item (mean score among non-missing on that item).[35] Post-hoc sensitivity analysis was conducted to assess the impact of imputed, missing MDADI responses on study results.

Multiple linear regression was used to investigate the association between late LCNP and MDADI scores controlling for confounders following model building strategies using the purposeful variable selection method.[36] Age, subsite, T-stage, treatment modality and smoking based on previous literature were defined *a priori* as clinically important variables and retained for adjustment in all models. Variance inflation factor was used to assess collinearity among variables. Biologically plausible interaction terms were also assessed using the likelihood ratio tests and were considered statistically significant when *p*-values were < 0.05. Adequacy and fit of model were assessed using R squares, adjusted R squares, and Chi-square goodness of fit tests. Coefficients (univariate and multivariate adjusted) for impact of late LCNP on MDADI scores and their 95% confidence intervals (CI) were estimated. As secondary analyses, the relationships between late LCNP and functional status metrics were assessed according to their distributions using the Fisher's exact test, Wilcoxon rank-sum test, and Kruskal Wallis test. All reported p-values are two-sided and considered statistically significant at p-value of ≤ 0.05. Statistical analysis was conducted using the STATA software, version 14.0 (StataCorp LP, College Station, TX).

RESULTS

Sample Characteristics

A total of 889 eligible OPC survivors with a median survival time 7.0 (range, 1-16) years were included in the analysis. Table 1 displays the distribution of demographic, tumor, and treatment-related characteristics in the study population. The patient characteristics of this study population have been described fully in an earlier publication.[19] Briefly, 84.7% were male, 92.4% were white, 71.7% were educated beyond high school, 76.4% had been treated for T1-T2 tumors, 98.9% could eat a normal solid-food diet prior to treatment, 99.1% were treated with RT of which 76.6% were treated with intensity-modulated radiotherapy split-field technique (IMRT-SF), and median radiation dose was 70 Gy (range, 40-73 Gy). Definitive surgery was rare (2.7%).

Late Lower Cranial Neuropathy

Overall, 36 (4.0%) OPC survivors were diagnosed with late LCNP with median time to LCNP onset after treatment of 5.3 (range, 0.3-12.3) years. Among them, 21 (58.3%) of LCNP cases had been treated for T1-T2 tumors, 35 (97.2%) reported eating a normal solid-food diet prior to treatment, all 36 of them received RT, 23 (63.9%) were treated with RT in combination with systemic treatment, 2 (5.6%) had surgery to the primary OPC tumor, 9 (25.0%) had neck dissection, and 23 (63.9%) were treated with IMRT-SF. Median time from LCNP onset to survey completion was 2.7 (range, 0.1-14.0) years. Among patients without LCNP, composite MDADI scores had a mean of 80.1±16.3 and median of 83.2, (range, 26.3-100) whereas LCNP cases had a mean of 68.0±17.4 and median of 67.4 (range, 36.8-97.9). Among LCNP cases, CN XII palsy was most common and present in 86.1% (31/36) of

LCNP cases. Isolated IX nerve palsy was difficult to ascertain, rather those with pharyngeal paresis were included as CN IX/X nerve palsy and 50% (18/36) of LCNP cases had CN IX or/and CN X neuropathy. Polyneuropathy was also present among 36.1% (13/36) of LCNP cases.

MDADI composite scores

The MDADI composite scores reported by OPC survivors are summarized in Table 1. Lowest (worse) scores were reported by patients with T4 tumors (68.7 ± 18.9) and those treated with 3-dimensional conformal RT technique (67.8 ± 20.4), whereas the highest (better) scores were reported by patients who did not receive RT (89.9 ± 9.4) and those treated with proton therapy (87.5 ± 11.3). Unadjusted univariate analyses demonstrated that survival time, education, T-classification, smoking, therapeutic modality, chemotherapy, RT dose, fractionation, and modality, and stricture had significant associations ($p<0.25$) with composite MDADI scores. Composite MDADI scores were also significantly different based on patient-reported diet levels at the time of survey ($p< 0.001$).

Late LCNP cases reported significantly worse composite MDADI scores compared to those without LCNP (LCNP: 68.0 ± 17.4, 95%CI, 62.1 to 73.9 vs. no LCNP: 80.2 ± 16.3, 95%CI, 79.1 to 81.3, $p< 0.001$). Multiple linear regression identified that late LCNP was significantly associated with lower (worse) composite MDADI scores (coefficient, -6.7; 95%CI, -12.0 to -1.3; p value = 0.015; adjusted R^2, 0.13) after adjusting for age, survival time, sex, education, subsite, T-stage, smoking, therapeutic modality, RT modality, solid food diet prior to treatment, and stricture. These results have been summarized in Table 2.

When MDADI composite scores were categorized, 38.9% (14/36) LCNP cases had poor swallowing scores (MDADI<60) in comparison to 12.9% (110/853) patients without LCNP (OR= 4.3; 95%CI, 2.2 to 8.6).

MDADI Subscale Scores

Late LCNP cases reported significantly lower (worse) scores on all MDADI subscales and on global MDADI scores. The associations remained significant in multiple linear regression models after adjusting for significant covariates. These results are summarized in Table 3. Additionally, global MDADI scores were also highly correlated with composite MDADI scores (Spearman's rho = 0.8, p<0.001).

Figure 1 summarizes multivariate adjusted coefficients for late LCNP and MDADI Scores

We also compared composite MDADI scores among patients without LCNP, LCNP IX/X only, LCNP XII only and polyneuropathy illustrated in Figure # 2. Lowest (worst) mean scores and least variability of scores were reported by LCNP cases with polyneuropathy which may be suggestive of worsening swallowing function with more cranial nerve injury indicating a dose-response relationship. Of great concern was that LCNP cases with polyneuropathy, reported a drop of 18.2 in mean scores in comparison to patients without late LCNP with about half of them reporting poor composite scores indicating a clinically meaningful reduction in MDADI scores but this was not statistically significant.

Sensitivity analysis was also conducted including RT dose and HPV status in final models for all MDADI scores and as the effect estimates for late LCNP remained unchanged therefore these variables were excluded. Results are presented in Appendix Table 2 and Table 3.

Functional status metrics

LCNP status also significantly associated with ($p \leq 0.001$) worse functional outcomes and health metrics reported by the patient or chart abstracted at the time of survey as detailed in Table 4. LCNP cases were more likely to have a current feeding tube (OR= 20.5; 95%CI, 8.6 to 48.9), history of aspiration pneumonia (OR= 23.5; 95%CI, 9.6 to 57.6), tracheostomy (OR= 26.9; 95%CI, 6.0 to 121.7), and were more likely to have undergone dilation for stricture (OR= 12.3; 95%CI, 4.2 to 36.3) than patients without LCNP. LCNP cases were also more likely to report restricted oral diets at the time of survey (LCNP: OR= 3.5; 95%CI, 1.5 to 8.3). Mean percentage of reported weight loss from baseline weight to weight at time of survey was also significantly higher among LCNP cases than patients without LCNP (LCNP: mean 11.7% vs. no LCNP: 6.0%, p=0.002).

DISCUSSION

Late LCNP is rare with reports of incidence ranging from 3.7% to 25.6%. However, another cohort study reported 14% incidence of LCNP in 10-year survivors of HNC, suggesting that risk increases over time.[37]Our previous report confirmed high symptom burden among OPC survivors who developed LCNP, with largest effect sizes (coefficient, 2.3 of 10) on swallowing-related symptoms.[26] This phenomenon is also clinically recognized, but previous work has failed to quantify the impact of LCNP on individual swallowing domains and functional metrics. This large single-center cross-sectional survivorship survey study among OPC survivors provides a comprehensive evaluation and found significant associations with moderate effect size between late LCNP and overall swallowing-related

quality of life, domain-specific swallowing function, as well as functional status metrics related to swallowing.

Overall, swallowing-related quality of life among all 889 OPC respondents suggested most survivors perceived acceptable levels of functioning (as per composite MDADI means of 79.7 ± 16 and 55.2% of survivors reported composite scores ≥80), but the small group of survivors (n=36) with late LCNP reported a clinically meaningful reduction of > 10 points difference relative to survivors without LCNP in univariate analyses.[38] This meaningful reduction was observed for all summary and domain-specific MDADI scores. After multivariate adjustment for clinical covariates, on an average, composite MDADI scores were 6.7 points lower (worse) among late LCNP cases versus those without late LCNP. The adjusted R^2 demonstrated that late LCNP explained 13% of the variation in composite MDADI scores after accounting for the effect of other covariates, which according to Cohen's criteria is a moderate effect.[39] This moderate effect size is consistent with effect estimate for the impact of LCNP on patient-reported MDASI-HN swallowing/chewing symptoms (coefficient, 2.3 of 10) reported in an earlier study and may in part reflect the subjective nature of PROs that likely vary with individuals' overall contentment and satisfaction with life and functional abilities.[12, 13, 40]

Late LCNP was also significantly associated with all domain-specific MDADI subscale scores. Late LCNP cases experienced the greatest deterioration of physical subscale scores which represent patient perception of swallowing ability; LCNP explained 10% of the variation in this domain controlling for important confounders. Previous studies have also

reported lowest MDADI scores on the physical subscale among HNC patients.[10, 38] Further, among late LCNP cases, the least impact of nerve injury was on the emotional subscale scores. Emotional subscale scores reflect psychological response to diminished swallowing ability and functional subscale scores reflect the impact of swallowing impairment on daily functioning and activities.[32] Previous studies among HNC patients have reported the highest subscale scores in the functional domain and substantial recovery of emotional MDADI scores over time.[10, 40] This may be indicative of adjustment and adaptation to a decline in swallowing function overtime.[40]

It is generally believed that PRO instruments may underestimate the prevalence of dysphagia.[41, 42] For this reason, we also explored the relationship between LCNP with other functional status measures of swallowing ability. As expected, late LCNP status was also significantly associated with worse functional status metrics including current feeding tube status, normalcy of diet, public eating, self-reported history of aspiration pneumonia, weight-loss since diagnosis, understandability of speech, tracheostomy, and esophageal dilations due to presence of stricture. Thereby late LCNP was consistently associated with substantial functional morbidity among OPC survivors. These results are not surprising given the degree of swallowing dysfunction previously reported among long-term OPC survivors in earlier case reports that suggested that treatment-related LCNP may play a major role in late RAD, and precipitate delayed but extreme oropharyngeal impairment as recorded by MBS studies.[1, 21, 22] These observations also align to numerous reports of significant swallowing dysfunction caused by lower cranial nerve deficits among populations due to traumatic injury, vascular causes, and infection, documented primarily in case reports.[43-47]

Approximately one-third (28.6%) of late LCNP patients in our study, reported having a feeding tube at the time of survey. High rates of gastrostomy dependence among LCNP cases again support a high prevalence of dysphagia in this population. In an earlier study among OPC patients with advanced stage treated with concurrent RT and chemotherapy, feeding tube use had the maximum impact on QOL (-30 points compared to controls) evaluated by SF36 and HNQOL.[48] Late LCNP cases also had significantly higher rates of aspiration pneumonia (32.3% LCNP versus 2.0% no LCNP), which support association with high dysphagia-related morbidity. Similarly, a study using SEER data among HNC patients treated with chemoradiation reported 23.8% five-year rates of aspiration pneumonia.[49] Additionally, as late LCNP occurs many years after treatment with a tendency for silent aspiration, symptoms of LCNP may be missed due to lack of adequate surveillance among OPC survivors. This may further enhance risk of aspiration pneumonia and contribute to debilitating functional morbidity with increased feeding tube dependence, hospitalization, weight loss, and life-threatening complications.

Overall, late LCNP with accompanying dysphagia is a clinical condition of great concern as it does not typically respond well to treatment. With progressive long-term functional decline with aspiration and recurring aspiration-pneumonia, long-standing feeding tube dependence and elective laryngectomy may be required.[1, 16, 21, 22, 50] Therefore, risk-reduction and management of late effects like LCNP, late-RAD and associated functional toxicities need to be prioritized in contemporary OPC treatment and management. That is, providers should be alerted that survivors found to have a new IX, X, or XII nerve palsy in

routine surveillance likely merit return to the speech pathologist for instrumental swallowing evaluation, counseling, and therapy as well as interdisciplinary consideration of risk reduction strategies for aspiration that preserve oral intake but diminish pneumonia risk. This research may also help to provide benchmarks for novel interventions and surveillance efforts. Routine PRO administration coupled with instrumental examination using fiberoptic endoscopic evaluation of swallowing (FEES) and MBS may also help identify patients in need of more intense, targeted therapy.[50] Multi-disciplinary supportive treatment including routine swallowing and speech assessment, risk-based treatment planning, swallowing and nutritional therapy, counselling to improve coping skills, and guidance in effective meal preparation may help to attenuate the impact of late LCNP-associated swallowing impairment, diminish life-threatening complications, and enhance swallowing-related QOL.[50]

This study is the first to quantify the association between late LCNP and swallowing-related quality of life in a study population of almost 900 OPC survivors finding the hypothesized significant associations. However, there are limitations to acknowledge. Complete case analysis was not feasible as 126/889 (14.2%) respondents returned surveys with skipped or missing MDADI items. Thus, complete case analysis would have contributed to attrition of approximately one-third of LCNP cases that would have substantially diminished power in our study that focused on a rare event like LCNP. Therefore, we imputed missing MDADI scores for 27% (10/36) of late LCNP patients. The validity of our imputed results is supported by sensitivity analyses finding similar effect size estimates using imputed vs non-imputed data (Appendix: Table 1). Imputed composite MDADI scores and

non-imputed composite MDADI scores by LCNP status have also been presented as Supplementary figure # 1 and their distribution is similar which was expected given imputation was conducted using scores from non-missing items only. Post-imputation, unadjusted means and accompanying standard deviations of composite, global, emotional, physical, and functional scores were similar to estimates of means and standard deviations of an earlier study among HNC patients.[38] Further, consistency of results with previous literature was demonstrated as survivors in our study treated with multimodality treatment versus single modality, those who did not receive chemotherapy versus those who did, those treated with accelerated RT versus standard fractionation, those who received conventional 3D conformal RT versus IMRT/ proton therapy and current smokers versus never smokers reported significantly worse composite scores and those with early stage versus more advanced stages reported significant positive trend for better swallowing scores [5, 8-10, 33, 50] These results indicate that our primary outcome variable, composite MDADI variable consistently performed well and showed expected variation across clinical and tumor-related factors. Large and statistically significant differences in functional metrics by LCNP status also support our findings of high functional morbidity among LCNP cases. Our study results also support a previous survey analysis in this study population, which used complete case analysis of MDASI-HN, with low attrition of cases due to missing data and demonstrated a strong impact of LCNP on swallowing, choking, mucus, fatigue, and voice symptoms.[26]

Our study may also be subject to limitations inherent to cross-sectional PRO survey collection including survival bias, which we tried control by including survival time in all our multivariate models. MDADI and PSS-HN scores prior to late LCNP diagnosis were not

available to fully control for subtle differences in baseline function. Rather, oral diet at baseline was included as a covariate in analysis; among LCNP cases all but one could eat a solid food diet pre-treatment suggesting functional baseline swallow in the vast majority of LCNP cases. Further, chart abstraction of the LCNP case status precluded the ability to identify sensory deficits associated with LCNP as clinical documentation focused on motor deficits. We suspect that inclusion of sensory deficits of late LCNP might have led to higher number of late LCNP cases detected. Several factors may limit generalizability of these results. Given that few patients in our study received definitive surgery, our study results may have less application to OPC patients treated with primary surgery. Our study population was treated at a single tertiary cancer care institution and thus demographic characteristics may limit generalizability to other more varied populations. However, the study population demographics are similar to those expected among OPC patients across the US. Finally, it was beyond the scope of this work to identify predictors of late LCNP as would be necessary avoid this severe late functional toxicity. However, a recent cohort study among 10-year survivors identified an association between primary tumor site, RT dose, chemotherapy, and post-RT neck dissection as clinical predictors of cranial neuropathy on univariate analysis.[37] Predictors of LCNP will be addressed in future work by the authors, as well.

CONCLUSIONS

In this large cross-sectional analysis, OPC survivors with late LCNP had significantly lower (worse) swallow-related QOL as per MDADI scores with significantly higher likelihood of adverse functional status metrics like dietary restrictions, nutritional impairment, weight-loss, decline in public food consumption with possible consequences of social isolation, aspiration pneumonia, long-term feeding tube dependence, and tracheostomy. These data support and quantify the detrimental relationship of late LCNP with swallowing-related measures.

Table 1: Patient Characteristics (N=889), late LCNP rate, and mean composite MDADI scores

			Composite MDADI Score ± Standard Deviation)	
Variables	**All Patients (n=889)**	**Patients with LCNP (n=36)**	**All patients (n=889)**	**P-value [a, b]**
Continuous Variables				**P-value [a]**
Age at diagnosis, median (range)	56 (32-84)	57 (42-72)	rho = -0.034	0.306
Survival time, median (range)	7 (1-16)	10.5 (2-16)	rho = -0.076	0.023
Radiation Dose, Gy. median (range)	70 (40-73)	70 (60-72)	rho = -0.201	< 0.001
Categorical Variables	**All Patients n (%)**	**n (%) Patients with LCNP**	**All patients (n=889)**	**P-value [b]**
Sex				0.443
Female	136 (15.3)	5(3.7)	78.3 ±17.5	
Male	753 (84.7)	31(4.1)	79.9 ±16.3	
Education				< 0.001
≤Highschool	168(18.9)	8(4.8)	75.6 ±16.7	
>Highschool	637(71.7)	27(4.2)	80.9 ±15.9	
Missing	84(9.4)	1(1.2)	78.6 ±18.9	
Race				0.983
Others	59(6.6)	3(5.0)	78.5 ±20.0	
White	821(92.4)	32(3.9)	79.8 ±16.2	
Missing	9(1.0)	1(11.1)	78.4 ±19.3	
Primary Site				0.200
Tonsil	438(49.3)	17(3.8)	80.3 ±16.4	
Base of Tongue	451(50.7)	19(4.2)	79.1 ±16.6	
T classification				< 0.001
1	334(37.6)	8(2.4)	82.6 ±15.2	
2	345(38.8)	13(3.8)	80.8 ±15.7	
3	131(14.7)	8(6.1)	75.8 ±17.0	
4	79(8.9)	7(8.9)	68.7 ±18.9	
N classification				0.007
N0	81(9.1)	3(3.7)	79.9 ±16.1	
N1+2a	236(26.5)	7(2.9)	81.8 ±14.7	
2b+3	429(48.3)	19(4.4)	80.1 ±16.4	
2c	143(16.1)	7(4.9)	74.7 ±18.9	
HPV status				0.033
Negative	56(6.3)	2(3.6)	80.9 ±16.8	
Positive	429(48.3)	9(2.1)	81.0 ±15.9	
Unknown	404(45.4)	25(6.2)	78.1 ±17.0	
Smoking				< 0.001
Never	409(46.0)	16(3.9)	81.4 ±16.2	
Former	422(47.5)	17(4.0)	79.0 ±16.3	
Current	58(6.5)	3(5.2)	72.5 ±17.9	

Variables	All Patients (n=889)	Patients with LCNP (n=36)	Composite MDADI Score ± Standard Deviation) All patients (n=889)	P-value [a, b]
Solid Food pre-Tx				0.846
Yes	879(98.9)	35(4.0)	79.9 ±14.0	
No	10(1.1)	1(10.0)	79.7 ±16.5	
Treatment Group				< 0.001
Single Modality	278(31.3)	11(4.0)	83.2 ±14.3	
Multimodality	611(68.7)	25(4.1)	78.1 ±17.2	
Treatment Group				0.001
RT alone	270(30.4)	11(4.1)	83.0 ±14.4	
Surgery alone	8(0.9)	0	89.9 ±9.4	
RT plus systemic	596(67.0)	23(3.9)	78.1 ±17.3	
Surgery plus adjuvant	15(1.7)	2(13.3)	78.4 ±14.2	
Radiotherapy				0.068
No	8(0.9)	0	89.9 ±9.4	
Yes	881(99.1)	36(4.1)	79.6±16.5	
Chemotherapy				< 0.001
No	284(32.0)	11(3.9)	83.0 ±14.3	
Yes	605(68.0)	25(4.1)	78.1 ±17.2	
Surgery				0.403
No	865(97.3)	34(3.9)	79.6 ±16.6	
Yes	24(2.7)	2(8.3)	83.0 ±13.8	
Neck Dissection				0.431
No	665(74.8)	27(4.1)	79.9 ±16.5	
Yes	224(25.2)	9(4.0)	79.0 ±16.5	
RT Schedule				0.002
Standard Fractionation	778(88.3)	21(2.7)	80.3 ±16.1	
Accelerated	95(10.8)	15(15.8)	73.5 ±18.3	
Other	8(0.9)	0	78.3 ±24.3	
RT Type				< 0.001
3d Conformal	50(5.7)	9(18.0)	67.8 ±20.4	
IMRT-SF	675(76.6)	23(3.4)	79.6 ±16.1	
IMRT- WF	33(3.8)	1(3.0)	74.7 ±17.8	
Proton	23(2.6)	1(4.4)	87.5 ±11.3	
IMRT Ipsilateral	100(11.3)	2(2.0)	84.9 ±14.3	
Dilation/ Stricture				< 0.001
No	873 (98.2)	31(3.6)	80.0 ± 16.3	
Yes	16 (1.8)	5(31.3)	61.0 ± 14.6	

Abbreviations: T, tumor; RT, radiotherapy; MDADI, MD Anderson Dysphagia Inventory (MDADI); rho, Spearman rho; pre-Tx, pre-treatment; 3d Conformal, Three Dimensional (3D) Conformal Radiation Therapy; IMRT-SF, Intensity-modulated radiation therapy with split field technique; IMRT-WF, Intensity-modulated radiation therapy with whole field technique. [a] P-value for Continuous Variables and Composite scores calculated using Spearman Test. [b] P-value for Categorical Variables and Composite scores calculated using Kruskal Wallis Test.

Table 2: Univariate and Multivariate Regression: Composite MDADI[a] (N=889)

Variables	Univariate Analysis Coefficient (95%CI)	P value	Multivariate Analysis Coefficient (95%CI)	P value
Late LCNP				
No	Reference		Reference	
Yes	-12.2 (-17.6, -6.7)	**< 0.001**	-6.6 (-12.0, -1.3)	**0.015**
Age at diagnosis	-0.1 (-0.2, 0.1)	0.328	-0.1 (-0.2, 0.1)	0.275
Survival Time	-0.4 (-0.7, -0.1)	**0.009**	-0.2 (-0.6, 0.1)	0.151
Radiation Dose	-1.1 (-1.5, -0.7)	**< 0.001**		
Sex				
Female	Reference		Reference	
Male	1.6 (-1.4, 4.6)	0.305	2.3 (-0.6, 5.2)	0.119
Education				
≤Highschool	Reference		Reference	
>Highschool	5.3 (2.5, 8.1)	**< 0.001**	4.2 (1.5, 6.9)	**0.002**
Missing	3.0 (-1.3, 7.3)	0.167	2.8 (-1.4, 7.0)	0.196
Race				
Others	Reference			
White	1.3 (-3.1, 5.7)	0.556		
Missing	-0.1 (-11.7, 11.5)	0.987		
Primary Site				
Tonsil, soft palate, & pharyngeal wall	Reference		Reference	
Base of tongue & GPS	-1.2(-3.4, 1.0)	0.282	-1.1 (-3.4, 1.2)	0.334
T classification				
1	Reference		Reference	
2	-1.8 (-4.2, 0.6)	0.139	-1.1 (-3.6, 1.5)	0.407
3	-6.9 (-10.1, -3.6)	**< 0.001**	-3.3 (-6.8, 0.3)	0.069
4	-14.0 (-17.9, -10.0)	**< 0.001**	-9.9 (-14.1, -5.8)	**< 0.001**
Smoking				
Never	Reference		Reference	
Former	-2.4 (-4.6, -0.1)	**0.039**	-1.6 (-3.8, 0.5)	0.141
Current	-8.9 (-13.4, -4.3)	**< 0.001**	-7.0 (-11.4, -2.7)	**0.001**
Solid Food pre-Tx				
Yes	Reference		Reference	
No	-0.2 (-10.5, 10.1)	0.965	-2.1 (-12.0, 7.8)	0.675
Treatment Group				
Single modality Tx.	Reference		Reference	
Multimodality Tx.	-5.1 (-7.4, -2.8)	**< 0.001**	-2.7 (-5.4, -0.1	**0.046**
Radiotherapy				
No	Reference			
Yes	-10.4 (-21.9, 1.1)	**0.077**		
Chemotherapy				
No	Reference			
Yes	-4.9 (-7.2, -2.6)	**< 0.001**		
Surgery				

Variables	Univariate Analysis Coefficient (95%CI)	P value	Multivariate Analysis Coefficient (95%CI)	P value
No	Reference			
Yes,	3.5 (-3.2, 10.1)	0.310		
Neck Dissection				
No	Reference			
Yes	-0.9 (-3.4, 1.6)	0.497		
RT Schedule				
Standard Fractionation	Reference			
Accelerated	-6.9 (-10.4, -3.4)	**< 0.001**		
Missing	-2.0 (-13.5, 9.4)	0.731		
RT Type				
3d Conformal	Reference		Reference	
IMRT-SF	11.8 (7.2, 16.4)	**< 0.001**	8.1 (3.1, 13.1)	**0.002**
IMRT- WF	6.9 (-0.2, 14.0)	**0.057**	5.9 (-1.3, 13.0)	0.107
Proton	19.7 (11.7, 27.7)	**< 0.001**	14.4 (6.0, 22.9)	**0.001**
IMRT-Ipsilateral	17.1 (11.6, 22.5)	***< 0.001***	9.9 (3.8, 16.0)	**0.002**
Stricture/Dilation				
No	Reference			
Yes	-19.0 (-27.1, -10.9)	**< 0.001**	-13.1 (-21.1, -5.2)	**0.001**

Abbreviations: T, tumor; RT, radiotherapy; MDADI, MD Anderson Dysphagia Inventory (MDADI); rho, Spearman rho; pre-Tx, pre-treatment; 3d Conformal, Three Dimensional (3D) Conformal Radiation Therapy; IMRT-SF, Intensity-modulated radiation therapy with split field technique; IMRT-WF, Intensity-modulated radiation therapy with whole field technique. Statistical significance p value < 0.25 after Univariate Analysis. Statistical significance p value < 0.05 after Multivariate Analysis. [a]Missing values imputed.

Table 3: MDADI Scores by late LCNP Status (N=889)

	Mean ± SD (95%CI)			Analysis Coefficient (95%CI)		
MDADI SCORES[a]	**Patients with LCNP (n=36)**	**Patients without LCNP (n=853)**	**P value**	**Univariate (95%CI)**	**Multivariate (95%CI)**	**P value**
Composite	68.0 ± 17.4 (62.1 to 73.9)	80.2 ±16.3 (79.1 to 81.3)	**< 0.001**	-12.2 (-17.6 to -6.7)	- 6.7 (-12.0 to -1.3)	**0.015**
Global	65.1 ± 28.9 (55.3 to 74.8)	81.3 ± 23.2 (79.8 to 82.9)	**< 0.001**	-16.3 (-24.1 to -8.4)	-9.1 (-17.0 to -1.3)	**0.023**
Emotional	70.1±19.2 (63.6 to 76.5)	81.0±16.4 (79.9 to 82.1)	**< 0.001**	-10.9 (-16.5 to -5.4)	-5.9 (-11.4 to -0.3)	**0.038**
Physical	62.5±18.0 (56.4 to 68.6)	75.9±19.0 (74.6 to 77.2)	**< 0.001**	-13.5 (-19.8 to -7.1)	-7.7 (-14.0 to -1.3)	**0.018**
Functional	74.4±20.7 (67.4 to 81.4)	86.0±16.1 (84.9 to 87.1)	**< 0.001**	-11.6 (-17.1 to -6.1)	-6.0 (-11.4 to -0.6)	**0.028**

Abbreviations: MDADI, MD Anderson Dysphagia Inventory (MDADI); LCNP, lower cranial neuropathy. Multiple linear regression models adjusted covariates including, age, survival time, sex, education, subsite, T-stage, smoking, therapeutic modality, RT modality, solid food diet prior to treatment, and stricture. The regression model for global scores adjusted for an additional variable, neck dissection. [a]Missing values imputed.

Table 4: Functional Status Metrics by late LCNP status (n=889)

Variables	Patients with LCNP n (%)	Patients without LCNP n (%)	P-value	Crude OR (95%CI)
Current Feeding Tube			**< 0.001**	
No	25 (71.4)	819 (98.1)		Reference
Yes	10 (28.6)	16 (1.9)		**20.5 (8.6 to 48.9)**
Normalcy Diet			**< 0.001**	
Full Diet no restrictions	6 (18.2)	357 (43.7)		Reference
Full Diet with liquid assist	8 (24.2)	315 (38.5)		**3.5 (1.5 to 8.3)**
Solid food but avoid some hard to eat foods	10 (30.3)	96 (11.7)		
Soft chewable foods	2 (6.1)	33 (4.0)		
Non-chewable or pureed foods	1 (3.0)	3 (0.4)		
Warm and cold liquids	2 (6.1)	10 (1.2)		
Not eat or drink anything by mouth	4 (12.1)	4 (0.5)		
Public Eating			**< 0.001**	
No restriction of place/ food/companion	8 (25.8)	582 (70.3)		Reference
No restriction of place, but restrict diet in public	14 (45.2)	191 (23.1)		**6.8 (3.1 to 15.1)**
In presence of selected person in selected places	7 (22.6)	36 (4.3)		
Only eat at home with selected persons	1 (3.2)	14 (1.7)		
Always eat alone	1 (3.2)	5 (0.6)		
Aspiration Pneumonia			**< 0.001**	
No	21 (67.7)	741 (98.0)		Reference
Yes	10 (32.3)	15 (2.0)		**23.5 (9.6 to 57.6)**
Weight loss			**0.050**	
No	4 (11.4)	202 (24.4)		Reference
Yes	31 (88.6)	626 (75.6)		**2.5 (0.9 to 6.9)**
Change in Weight; mean, median (range)[a]	22.9, 16.8(14.2,87.8)	13.3, 9.4(103.1,164.6)	**0.005**	
% Change in Weight; mean ± SD, median, (range)[b]	11.7±10.4, 9.9(-7.9,33.4)	6.0 ±10.7, 5.1(-96.4, 43.4)	**0.002**	
Understandability of Speech			**< 0.001**	
Always understandable	6 (17.6)	528 (63.3)		Reference
Understandable most of the time	16 (47.1)	269 (32.3)		**8.1 (3.4 to 19.2)**
Usually understandable	3 (8.8)	19 (2.3)		
Difficult to understand	8 (23.5)	17 (2.0)		
Never understandable	1 (2.9)	1 (0.1)		
Tracheostomy			**0.001**	
No	31 (91.2)	834 (99.6)		Reference
Yes	3 (8.8)	3 (0.4)		**26.9(6.0 to 121.7)**
Dilation/ Stricture			**< 0.001**	
No	31 (86.11)	842 (98.71)		Reference
Yes	5 (13.89)	11 (1.29)		**12.3 (4.2 to 36.3)**

P values estimated by Fishers Exact Test. [a, b] P values estimated by Wilcoxon Rank-Sum Test. Odds Ratio for normalcy of diet calculated with full diet no restrictions as reference category and all other categories collapsed. Odds Ratio for public eating calculated with no restriction of place/ food/companion as reference category and all other categories collapsed. Odds Ratio for

understandability of speech calculated with always understandable as reference category and all other categories collapsed.

Figure 1: Multivariate Adjusted Coefficients for Late LCNP and MDADI scores

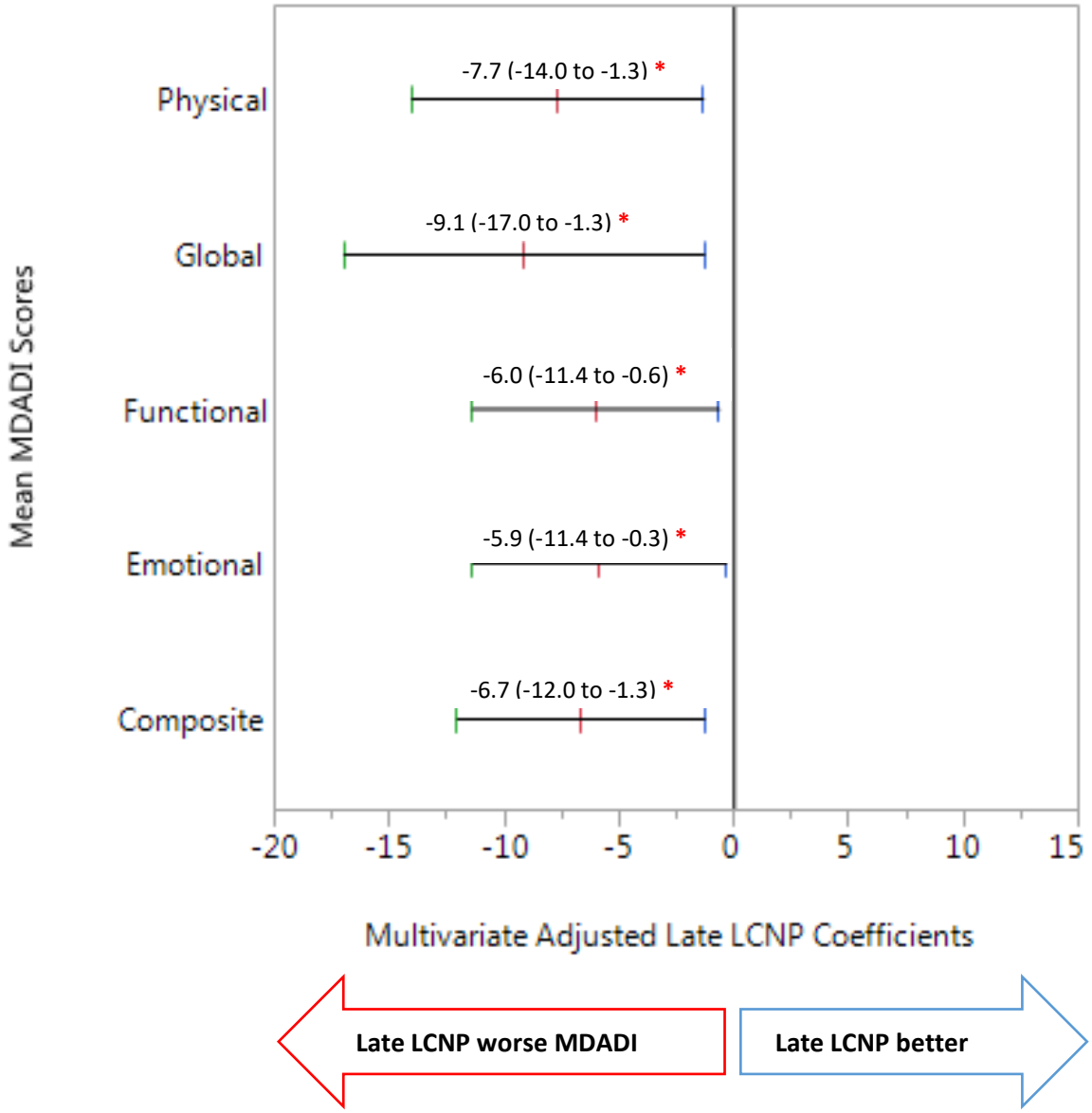

Figure 1. Multivariate Adjusted Coefficients for Late LCNP and MDADI Scores. Multiple linear regression models adjusted for age, survival time, sex, education, subsite, T-stage, smoking, therapeutic modality, RT modality, solid food diet prior to treatment, and stricture. The regression model for global scores adjusted for an additional variable, neck dissection.

Abbreviations: MDADI, MD Anderson Dysphagia Inventory (MDADI); LCNP, lower cranial neuropathy.

FIGURE 2: Imputed composite MDADI scores by Type of LCNP

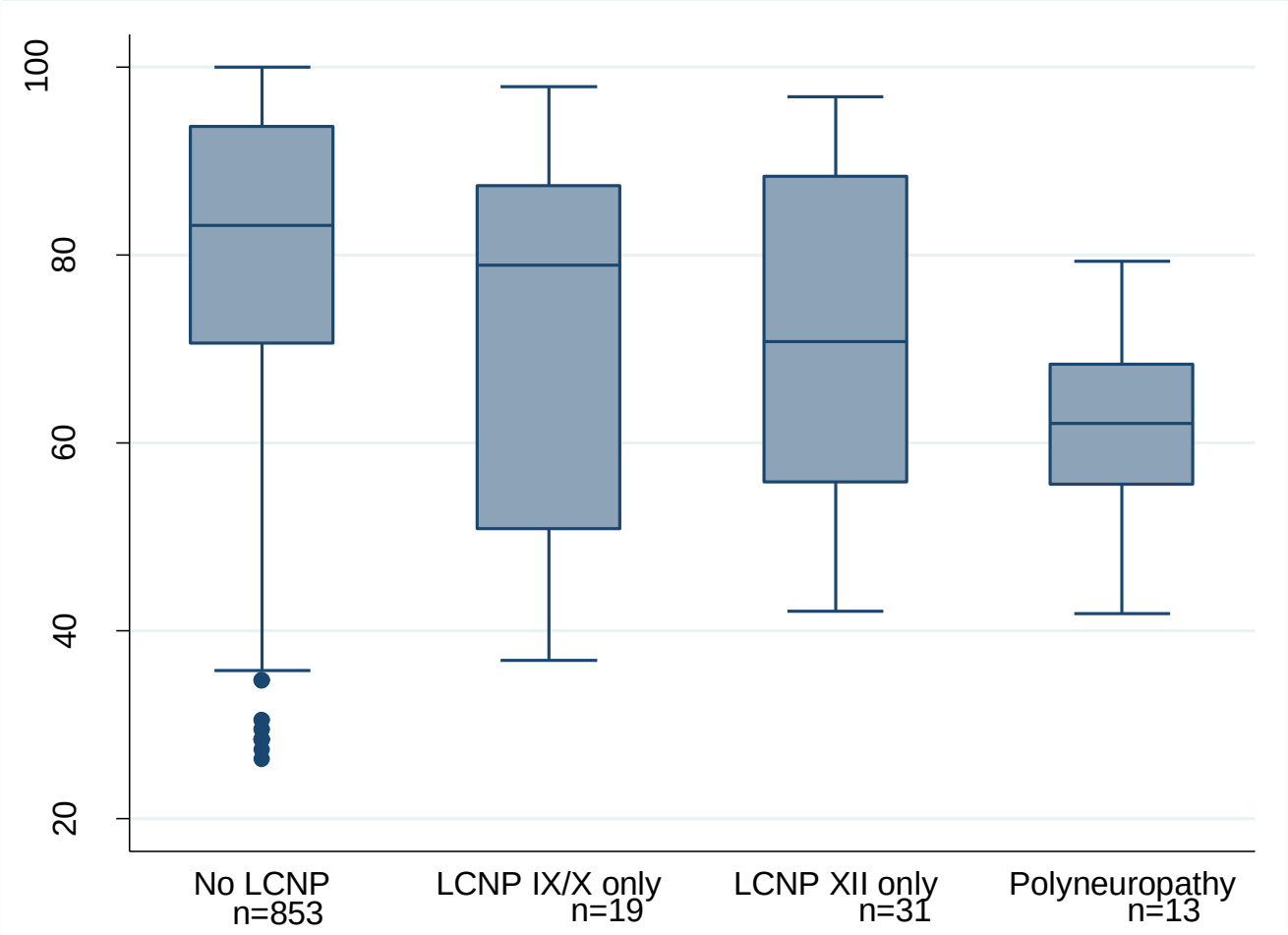

Figure 2. Imputed composite MDADI scores among patients without LCNP, LCNP IX/X only, LCNP XII only and polyneuropathy. Polyneuropathy included LCNP cases with both CN XII and CN IX/X palsy. Patients without LCNP had higher (better) scores than LCNP cases, but lowest (worst) mean scores and least variability of scores were reported by LCNP cases with polyneuropathy.

Abbreviations: MDADI, MD Anderson Dysphagia Inventory (MDADI); LCNP, lower cranial neuropathy; IX/X, Glossopharyngeal or Vagus Nerve; XII Hypoglossal Nerve.

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CONCLUSION

The results of this study clearly establish late LCNP as a serious treatment-related toxicity among long-term OPC survivors and was associated with significantly worse cancer treatment-related symptoms and significantly worse swallow-related QOL.

While rare in the population overall, quantitative estimates of lifetime risk of late LCNP over an almost 18-year follow-up into OPC survivorship demonstrate that one out of 10 OPC survivors middle-aged at time of diagnosis are likely develop late LCNP. The progressively increasing risk of late LCNP of 2%, 6%, and 10% at 5, 10, 18-year follow-up also indicates that risk of LCNP overtime is much higher than previously believed. The potential impact of late LCNP on the life of OPC survivors is devastating as late LCNP and accompanying late-RAD is refractory to treatment, life-long, and permanent. Our prediction model enabled identification of OPC survivors who had T4 tumors and those who received accelerated fractionation RT treatment as having higher risk of late LCNP. In this study patients with big bulky tumors, had large irradiation fields possibly including cranial nerves, were likely to be treated most aggressively with multimodality treatment regimens including, IC, accelerated RT, and systemic therapy, thereby they were more likely to develop late LCNP.

In the large cross-sectional survey analysis, late LCNP cases reported significantly worse cancer treatment-related symptoms, and worse symptoms associated with motor functions of the upper aerodigestive tract (swallowing, voice), demonstrating the relevance of late LCNP to both symptom severity and QOL. Among LCNP cases, a higher proportion reported severe (LCNP: 20% vs no LCNP: 5%) and moderate (LCNP: 40% vs no LCNP: 15%) symptoms.

OPC survivors with late LCNP also reported had worse swallow-related QOL as per MDADI scores with significantly higher likelihood of adverse functional status metrics like dietary restrictions, nutritional impairment, weight-loss, decline in public food consumption with possible consequences of social isolation, aspiration pneumonia, long-term feeding tube dependence, and tracheostomy.

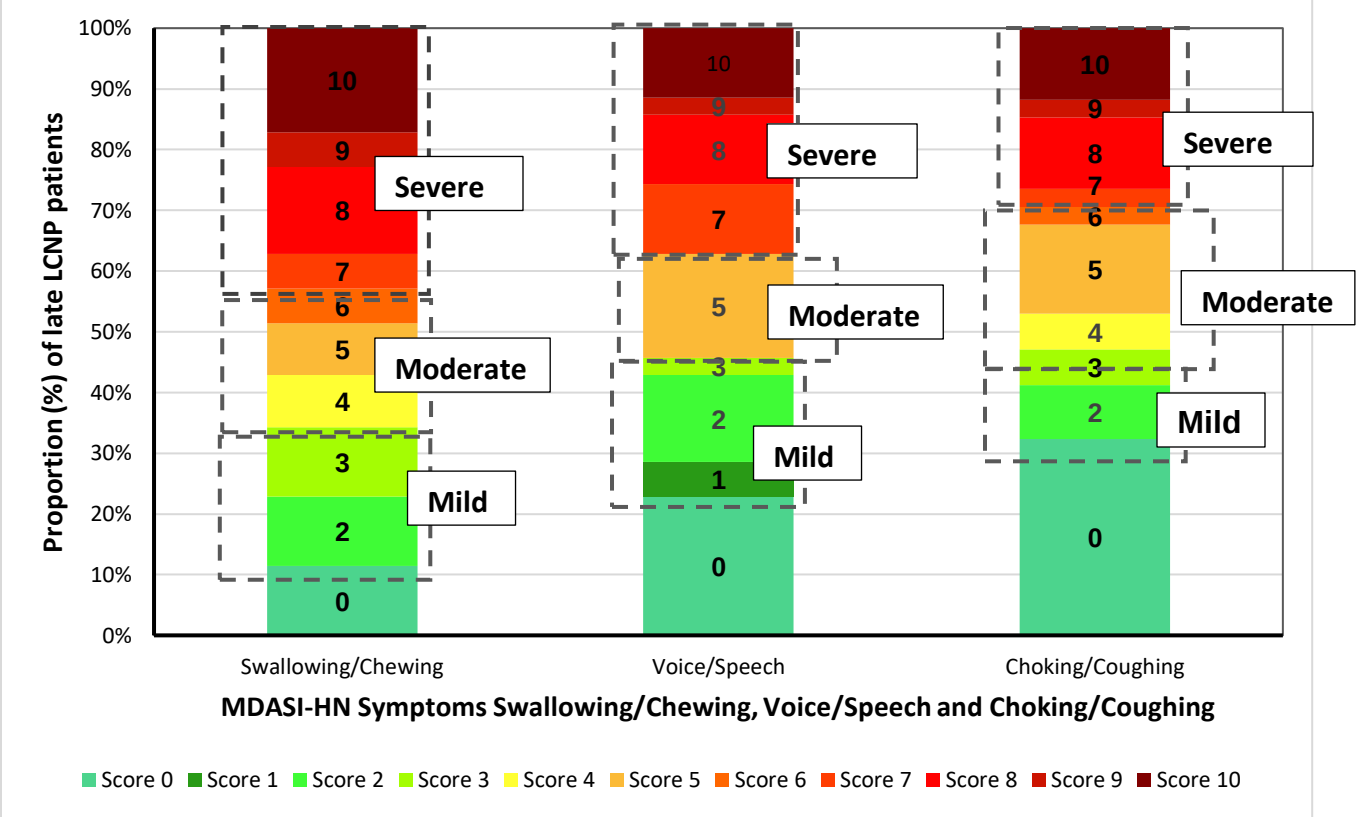
Future studies need to further assess the role of dose to ROI (regions of interest involving critical structures), IC, and transoral robotic surgery in development of late effects like LCNP. Better RT techniques need to be developed to modify dose delivery and less toxic chemotherapy agents need to be investigated. Treatment de-intensification strategies need to be explored which maintain cure and prevent late effects. There is also a clear need for long-term surveillance of late LCNP among HNC and OPC patients, particularly in light of epidemiologic trends that suggest growing numbers of OPC survivors at risk of late effects in immediate years ahead.[6-8] Further, efforts are necessary to address severity of treatment-related symptoms and optimize swallowing outcomes to improve QoL among growing numbers of relatively younger OPC survivors, who are expected to survive decades after treatment. Finally, the long-term treatment-related burden of OPC is becoming more apparent, there is need to find ways to treat cancer and minimize toxicity.

APPENDIX

FIGURES

Journal Article 2

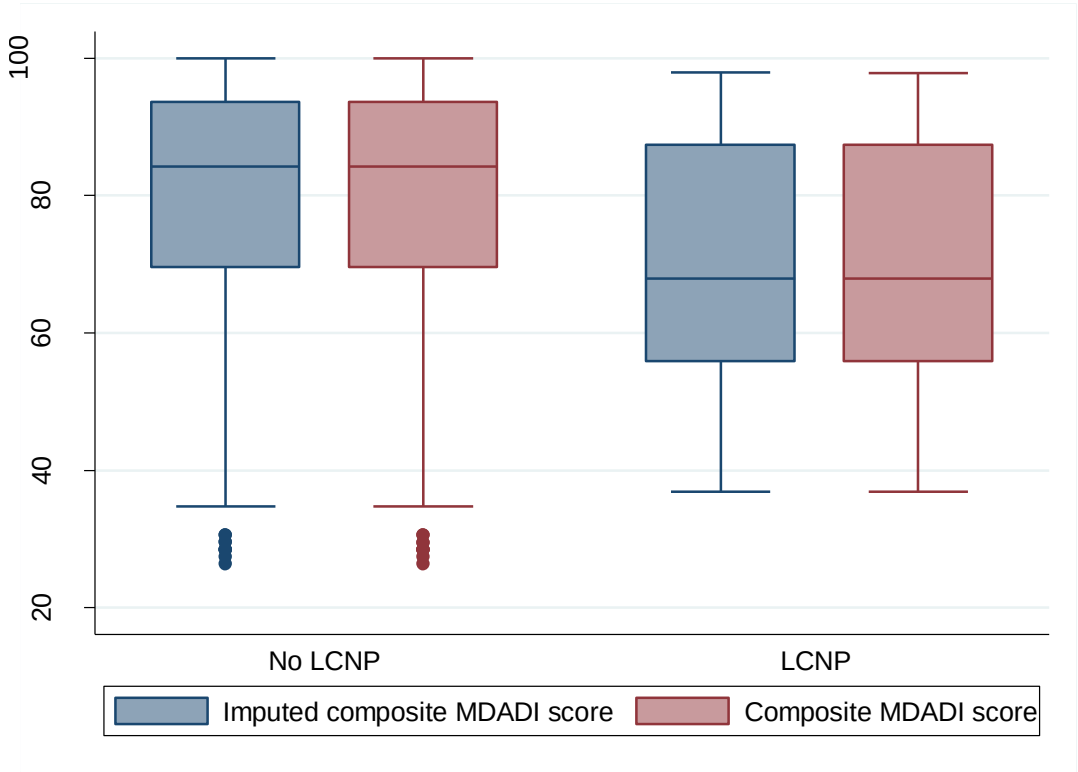
Supplementary Figure 1: MDASI-HN Scores for Swallowing/Chewing, Voice/Speech and Choking/Coughing for late LCNP cases (n=35)



Supplementary Figure 1. MDASI-HN Scores for Swallowing/Chewing, Voice/Speech and Choking/Coughing for late LCNP cases (n=35). Symptom are classified as: 0 "no symptom"; 1-3 "mild"; 4-6 "moderate" and 7-10 "severe" Abbreviations: MDASI-HN, MD Anderson Symptom Inventory Head and Neck Cancer Module (MDASI-HN); LCNP, lower cranial neuropathy.

Journal Article 3

SUPPLEMENTARY FIGURE 1: Imputed composite MDADI scores and non-imputed composite MDADI scores by LCNP status



Supplementary Figure 1: Imputed composite MDADI scores and non-imputed composite MDADI scores by LCNP status. Distribution of imputed composite and non-imputed composite MDADI scores by LCNP status was very similar which was expected given that imputation was conducted using scores from non-missing items only. Further, there was expected decline in both imputed composite and non-imputed composite MDADI scores among LCNP cases in comparison to those without LCNP. This along with our sensitivity analysis in Appendix 1, Table 1 show that imputed and non-imputed MDADI scores were similar and our study results are valid.

TABLES

Journal Article 3

Table 1: Sensitivity Analysis Comparing Imputed Versus Non-Imputed MDADI Scores

	IMPUTED MDADI SCORES		NON-IMPUTED MDADI SCORES	
MDADI SCORE	Multivariate Analysis Coefficient (95%CI)	P Value	Multivariate Analysis Coefficient (95%CI)	P Value
Composite	- 6.7 (-12.0 to -1.3)	0.015	-4.8 (-11.3 to 1.6)	0.142
Global	-9.1 (-17.0 to -1.3)	0.023	-10.6 (-18.9 to -2.4)	0.012
Emotional	-5.9 (-11.4 to -0.3)	0.038	-5.6 (-11.7 to 0.6)	0.077
Physical	-7.7 (-14.0 to -1.3)	0.018	-7.8 (-15.0 to -0.6)	0.033
Functional	-6.0 (-11.4 to -0.6)	0.028	-5.3 (-11.1 to 0.5)	0.073

Abbreviations: MDADI, MD Anderson Dysphagia Inventory (MDADI)

Comment: Other than Composite scores all effect estimates are not very different.

Table 2: Sensitivity Analysis Comparing Final Model with and without RT Dose

	Final Model with RT Dose		Final Model without RT Dose	
MDADI SCORE	Multivariate Coefficient for late LCNP (95% CI)	P Value	Multivariate Coefficient for late LCNP (95% CI)	P Value
Composite	-6.6 (-12.0 to -1.2)	0.016	- 6.7 (-12.0 to -1.3)	0.015
Global	-9.1 (-17.0 to -1.3)	0.022	-9.1 (-17.0 to -1.3)	0.023
Emotional	-5.8 (-11.3 to -0.3)	0.039	-5.9 (-11.4 to -0.3)	0.038
Physical	-7.6 (-13.9 to -1.2)	0.019	-7.7 (114.0 to -1.3)	0.018
Functional	-6.0 (-11.4 to -0.6)	0.029	-6.0 (-11.4 to -0.6)	0.028

Abbreviations: MDADI, MD Anderson Dysphagia Inventory (MDADI); RT Dose (Radiation Dose)

Comment: Effect estimates for all MDADI scores for LCNP are similar.

Table 3: Sensitivity Analysis Comparing Final Model with and without HPV

	Final Model with HPV status		Final Model without HPV status	
MDADI SCORE	Multivariate Coefficient for late LCNP (95% CI)	P Value	Multivariate Coefficient for late LCNP (95% CI)	P Value
Composite	-6.7 (-12.1 to -1.3)	0.015	- 6.7 (-12.0 to -1.3)	0.015
Global	-9.2 (-17.0 to -1.4)	0.022	-9.1 (-17.0 to -1.3)	0.023
Emotional	-5.9 (-11.4 to -0.4)	0.037	-5.9 (-11.4 to -0.3)	0.038
Physical	-7.7 (-14.0 to -1.4)	0.017	-7.7 (114.0 to -1.3)	0.018
Functional	-6.0 (-11.4 to -0.7)	0.028	-6.0 (-11.4 to -0.6)	0.028

Abbreviations: MDADI, MD Anderson Dysphagia Inventory (MDADI); HPV (Human Papilloma Virus)

Comment: Effect estimates for all MDADI scores for LCNP are similar.

APPENDIX 2: Functional Status Metrics Survey Questions

Current Feeding Tube Status

1) Do you currently have a **feeding tube**?
□□Yes
□□No

Normalcy of Diet

2) What **kinds of foods** you are able to eat? (Mark one)
Please mark the item that represents the highest level of foods or liquids you eat. If you have a feeding tube, but also eat by mouth, please mark the highest level of foods you eat in addition to your tube feedings.
7. I eat **whatever I would like** (full diet no restriction).
6. I eat **whatever I would like, but require more liquids than usual with meals** (full diet with liquid assist).
5. I eat **solid food but avoid some hard to eat foods** (like meats, raw vegetables/ fruits).
4. I eat **soft chewable foods** (like pasta, cooked vegetables, fish, dry foods).
3. I eat **non-chewable or pureed foods**.
2. I drink **warm and cold liquids**.
1. I do **not eat or drink anything by mouth**; I only use a feeding tube.

Public Eating

3) Select the statement that best reflects if and how you **eat in public**:
□□I eat out at **any opportunity with no restriction of place, food, or companion**.
□□I eat out with **no restriction of place, but I restrict my diet when in public**.
□□I eat only in the presence of **selected person in selected places**.
□□I only eat **at home with selected persons**.
□□I always eat **alone**.

Understandability of Speech

4) How well are you understood when **speaking to other people?**
□□My speech is **always understandable**.
□□My speech is **understandable most of the time**, I am occasionally asked to repeat myself.
□□My speech is **usually understandable**, but face-to-face contact is necessary.
□□My speech is **difficult to understand**.
□□My speech is **never understandable**.

Aspiration Pneumonia

5) Since your cancer treatment, has a **doctor or other health professional told you** that you have:

	Yes	No	Don't Know
Pneumonia?	○	○	○

Tracheostomy

6) Do you currently have a **tracheostomy tube (or breathing tube)?**
□□Yes
□□No

7) Since your cancer treatment, has a **doctor or other health professional told you** that you have:

	Yes	No	Don't Know
Stricture of the throat or esophagus? (Stricture is a narrowing or tightness of the food tube that may cause sticking or obstruction of food.)	○	○	○

But we did not use this variable we abstracted EGD/Dilation Variable from the Charts.

Current Height and Weight

8) What are your current **height** and **weight**?
a) Height: _____ ft. _____in.
b) Weight: _____lbs.

JAMA Otolaryngology–Head & Neck Surgery | Original Investigation | FROM THE AMERICAN HEAD AND NECK SOCIETY

Symptom Burden Associated With Late Lower Cranial Neuropathy in Long-term Oropharyngeal Cancer Survivors

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Author Audio Interview

Supplemental content

IMPORTANCE Lower cranial neuropathy (LCNP) is a rare but potentially disabling result of radiotherapy and other head and neck cancer therapies. Survivors who develop late LCNP may experience profound functional impairment, with deficits in swallowing, speech, and voice.

OBJECTIVE To investigate the association of late LCNP with severity of cancer treatment-related symptoms and subsequent general functional impairment among oropharyngeal cancer (OPC) survivors.

DESIGN, SETTING, AND PARTICIPANTS This cross-sectional survey study analyzed 889 OPC survivors nested within a retrospective cohort of OPC survivors treated at MD Anderson Cancer Center from January 1, 2000, to December 31, 2013. Eligible survey participants were disease free and completed OPC treatment 1 year or more before the survey. Data analysis was performed from October 10, 2017, to March 15, 2018.

EXPOSURES Late LCNP defined by onset 3 months or more after cancer therapy.

MAIN OUTCOMES AND MEASURES The primary outcome variable was the mean of the top 5 most severely scored symptoms of all 22 core and head and neck cancer–specific symptoms from the MD Anderson Symptom Inventory Head and Neck Cancer Module (MDASI-HN). Secondary outcomes included mean MDASI-HN interference scores and single-item scores of the most severe symptoms. Multivariate models regressed MDASI-HN scores on late LCNP status, adjusting for clinical covariates.

RESULTS Overall, 36 of 889 OPC survivors (4.0%) (753 [84.7%] male; 821 [92.4%] white; median [range] age, 56 [32-84] years; median [range] survival time, 7 [1-16] years) developed late LCNP. Late LCNP was significantly associated with worse mean top 5 MDASI-HN symptom scores (coefficient, 1.54; 95% CI, 0.82-2.26), adjusting for age, survival time, sex, therapeutic modality, T stage, subsite, type of radiotherapy, smoking, and normal diet before treatment. Late LCNP was also significantly associated with single-item scores for difficulty swallowing or chewing (coefficient, 2.25; 95% CI, 1.33-3.18), mucus (coefficient, 1.97; 95% CI, 1.03-2.91), fatigue (coefficient, 1.35; 95% CI, 0.40-2.21), choking (coefficient, 1.53; 95% CI, 0.65-2.41), and voice or speech symptoms (coefficient, 2.30; 95% CI, 1.60-3.03) in multivariable models. Late LCNP was not significantly associated with mean interference scores after correction for multiple comparisons (mean interference coefficient, 0.72; 95% CI, 0.09-1.35).

CONCLUSIONS AND RELEVANCE In this large survey study, OPC survivors with late LCNP reported worse cancer treatment-related symptoms, a finding suggesting an association between late LCNP and symptom burden. This research may inform the development and implementation of strategies for LCNP surveillance and management.

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The incidence of oropharyngeal cancer (OPC) is increasing by 5% annually in the United States.[1] It is projected that, by 2030, half of head and neck cancers (HNCs) will be OPC.[1] This projection is attributable to the epidemic of human papillomavirus-associated OPC, which is usually diagnosed in middle age.[1-4] Human papillomavirus disease is biologically favorable, with excellent prognosis for long-term survival despite advanced-stage cancer.[2-4] Despite excellent prognosis, survivors may experience severe adverse consequences of cancer treatment, such as speech, breathing, and swallowing difficulties.

Late lower cranial neuropathies (LCNPs) are a rare but potentially severe late consequence of damage caused by radiotherapy (RT) and other cancer therapies. Lower cranial nerves include glossopharyngeal (cranial nerve IX), vagus (cranial nerve X), accessory (cranial nerve XI), and hypoglossal (cranial nerve XII) nerves, which are critical to the oropharyngeal phases of swallowing, shoulder function, and speech, respectively.[5-9] Fibrosis of nerve tracts or adjacent soft tissues can lead to delayed, typically progressive, neurovascular damage and eventually neuropathy, which over time causes profound functional impairments.[5] According to a recent single institution report,[6] the incidence of delayed LCNP among 59 OPC survivors was 5% at 5.7 years. Although late LCNP is rare, case reports suggest profound functional impairments and overall low quality of life (QOL) among patients with LCNP.[5-8]

Symptom burden is defined as severity of symptoms experienced by patients and the bearing of those symptoms on day-to-day life.[10] Patients may experience symptoms attributable to disease, recurrence, or treatment-related toxic effects.[10] Late toxic effects, such as late LCNP, conventionally persist or occur 3 months or later after treatment completion but may develop even years later.[11]

General functional impairment (GFI) is defined as a diminished ability to take care of oneself, manage the household, work, and indulge in activities for relaxation.[12] Thus, GFI can impede the daily lives of survivors.[12] Treatment-related symptoms may have a detrimental bearing on GFI marked by symptom interference scores. For some patients, the impairment is temporary, and with time, these patients return to normal activity and function. However, a substantial number of OPC survivors continue to experience limitations and disability and may be unable to return to normal activities, including work, leading to a long-term economic consequence.[12,13]

Previous studies[7,8] on late RT-associated LCNP have been case reports or small case series or included cohorts of predominantly nasopharyngeal cancer survivors. In OPC, severe symptoms have been described among patients with LCNP, but the association between late LCNP and symptoms, as well as GFI, has yet to be quantified.

For the increasing numbers of OPC survivors at risk for experiencing LCNP, it is critical to quantify the association between late LCNP and severity of cancer treatment-related symptoms and GFI to inform development and implementation of targeted strategies for late effect surveillance and management. The purpose of this analysis was to investigate the severity of cancer treatment-related symptoms (per the primary end point of the mean top 5 MD Anderson Symptom Inventory Head and Neck Cancer Module [MDASI-HN] symptom scores) and their subsequent association with GFI (per the secondary end point of mean MDASI-HN interference score) by late LCNP status among OPC survivors. The association of late LCNP and overall mean symptom burden of single-item scores among the most severe symptoms and categorical ratings of the top 5 symptoms was also assessed to explore the association with diverse symptom metrics. We hypothesized that late LCNP status would be associated with worse symptom scores and GFI.

Key Points

Question What is the association between late lower cranial neuropathy and severity of cancer treatment-related symptoms and general functional impairment among long-term oropharyngeal cancer survivors?

Findings In this cross-sectional survey study of 889 oropharyngeal cancer survivors, those with late lower cranial neuropathy reported significantly worse cancer treatment-related symptoms compared with those without late lower cranial neuropathy.

Meaning Further efforts may be necessary to lessen symptom burden associated with late lower cranial neuropathy experienced by oropharyngeal cancer survivors.

Methods

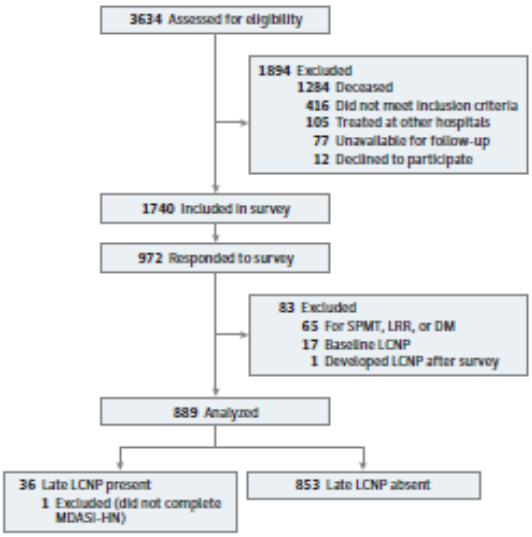
Patient Eligibility

A cross-sectional, patient-reported outcome survey was conducted among survivors of a retrospective cohort of patients with OPC treated at MD Anderson Cancer Center from January 1, 2000, to December 31, 2013. Eligible participants were 18 years or older at diagnosis, completed OPC treatment 1 year or more before survey administration, and consented to future research participation at new patient registration within the institution. Deceased patients, those who had a secondary primary malignant tumor or recurrent malignant tumor of the head and neck before survey, and those whose primary language was not English were excluded. Patients with LCNP of any cause at the time of cancer diagnosis or with clinical signs of LCNP before starting cancer treatment were also excluded. **Figure 1** shows participant recruitment and eligibility criteria for the study. Data analysis was performed from October 10, 2017, to March 15, 2018. Details of survey administration and response have been published previously.[14] The MD Anderson Cancer Center institutional review board approved this study with use of a consent statement on the survey cover letter for informed consent of survey responders.

OPC Treatment

Institutional practices regarding OPC treatment during the period of this study have been previously described.[15] Standard of care treatment during the current study period was definitive RT for patients with stage I/II OPC and definitive chemoradiotherapy for patients with locally advanced OPC (stage

Figure 1. Flowchart Showing Study Participant Recruitment and Eligibility Criteria



DM indicates distant metastasis; LCNP, lower cranial neuropathy; LRR, locoregional recurrence; MDASI-HN, MD Anderson Symptom Inventory Head and Neck Cancer Module; and SPMT, second primary malignant tumor.

III/IV).[15-17] During 2000 to 2006, intensity-modulated radiation therapy (IMRT) and 3-dimensional conformal RT technique were routinely used, but after 2006, IMRT became the primary modality of treatment.[15] The recommended radiation dose was 66 Gy for small-volume primary tumors and 70 to 72 Gy for more advanced tumors.[15] For treatment of primary tumors and nodes in the upper neck region, the IMRT approach was predominantly used, whereas for nodes in the lower neck anterior beam, a technique with laryngeal and/or full midline block was used. Furthermore, for treatment of primary tumors and the neck region when split-field IMRT was not possible, the whole-field IMRT technique was used. Individual extent of primary disease and preexisting comorbidities were taken into account to decide whether patients would receive systemic therapy. Definitive surgery with transoral resection to the primary site was rare, but after 2009, a small number of patients were treated with transoral robotic surgery with adjuvant therapy based on pathologic features.[15-17]

Demographic and Clinical Variables

Age at diagnosis, sex, race/ethnicity, educational level, smoking history, and human papillomavirus and p16 status were abstracted from electronic medical records. Clinical and treatment data abstracted included subsite of primary OPC tumor, tumor and nodal stage (American Joint Committee on Cancer version VII), treatment modality, RT dose, modality and fractionation, surgery, chemotherapeutic regimen, and ability to eat solid food at baseline (surrogate for baseline dysphagia). Survival time was calculated as the difference between age at diagnosis and age at time of survey administration.

Survey Items

The MDASI-HN is a 28-item, validated, patient-reported outcome instrument that evaluates symptom severity and interference in patients with HNC. The MDASI-HN includes 13 questions to assess core symptoms common across all cancers and 9 questions to assess HNC-specific symptoms. The MDASI-HN symptom severity item scores range from 0, indicating not present, to 10, indicating as bad as you can imagine. The MDASI-HN also includes 6 interference questions to assess the bearing of symptoms on daily function with respect to general activity, walking, work, mood, relationships with other people, and enjoyment of life. These item scores range from 0, indicating do not interfere, to 10, indicating interfere completely, such that higher scores indicate more limitations and lower QOL.[14-21] Symptom and interference scores are commonly classified as follows: 0, no symptom; 1 to 3, mild; 4 to 6, moderate; and 7 to 10, severe symptoms.[22] Mean subscale scores are internally consistent (Cronbach α = 0.72-0.92).[14-21]

Primary Exposure

Late LCNP was assessed during surveillance and rehabilitation visits by clinical examination of cranial nerves by head and neck surgeons, radiation oncologists, and speech pathologists and recorded in medical records. Late LCNP was defined as onset of swallowing-associated neuropathy of at least 1 of the glossopharyngeal (cranial nerve IX), vagus (cranial nerve X), and hypoglossal (cranial nerve XII) nerves, with minimum onset 3 months or more after the end of cancer treatment. Three months is considered the start of the late toxic effect interval according to the National Cancer Institute's *Common Toxicity Criteria Manual*: "Late radiation effects are defined as effects that occur 90 days and onwards after initiation of RT treatment."[31(p24)] For this reason, we elected to code any onset of LNCP after 3 months and up until the survey response as a late LCNP. Polyneuropathy was present in some patients with LCNP, but there was no standard method to document degree of neuropathy in medical records. Medical records were reviewed to identify LCNP cases. Physical examination reports were reviewed in detail. Objective methods, such as endoscopy and radiographic swallow studies, were not universally available for such a large study sample but were reviewed in detail when available. Computed tomography and magnetic resonance imaging were used to verify LCNP, but they were not a requirement for case status assessment. Case status was verified through independent review by a head and neck surgeon (R.P.G.) with review of surveillance computed tomography and magnetic resonance imaging to rule out malignant tumors or other sources of neuropathy. Electromyography was not routinely used.

Primary Outcome

The primary outcome variable for this study was the mean of the top 5 most severely scored symptoms of all 22 core and HNC-specific symptoms. This method, reported in the MDASI

user guide and previous symptom research studies,[23-26] serves as an estimate of the severity of the most meaningful and prevalent symptoms reported by this population.

Secondary Outcome

Results of the MDASI-HN can be summarized in various ways. Therefore, 4 secondary outcomes of the MDASI-HN were evaluated to fully explore the association of late LCNP with symptom burden. Secondary outcomes included (1) overall mean of 22 symptom items, (2) mean interference, (3) single-item scores of the top 5 most severe symptoms, and (4) categorical ratings of the top 5 symptoms.

Overall mean symptom scores summarize all 22 items of core and HNC-specific symptoms to reflect overall symptom severity. Mean interference serves as a marker of GFI with subdomains of activity-related interference (using item scores related to general activity, work, and walking) and psychosocial-related interference (using item scores related to mood, relationships with other people, and enjoyment of life). Single-item scores of the top 5 most severe symptoms, although extant in our primary end point (mean of the top 5 symptoms), were evaluated separately to reflect the association of LCNP with individual symptoms. Single-item scores were considered to provide insight on particular functional domains with the greatest negative association with LCNP, which might help to focus supportive care efforts for this population. Finally, categorical ratings were examined to allow ease of clinical interpretation to identify proportions of patients with LCNP experiencing high-grade symptoms.[22]

Statistical Analysis

Descriptive and univariate analyses were performed. For the primary outcome (mean top 5 MDASI-HN symptom scores), multiple linear regression was used to investigate associations between LCNP status and MDASI-HN scores, controlling for age, sex, race/ethnicity, T stage, subsite, RT dose, fractionation and modality, chemotherapy, surgery, eating solid food at baseline, survival time, and smoking, which according to previous literature are cofactors associated with toxic effects and symptom burden.[27,28]

Model building followed the purposeful variable selection method of Hosmer and Lemeshow.[29] Candidate predictive factors with $P < .25$ on the univariate Wald test were entered into multivariable models and removed stepwise ($P > .20$). Age, T stage, subsite, treatment modality, and smoking were a priori retained as clinically important covariates and included in all models. Coefficients (unadjusted and adjusted) and corresponding 95% CIs were estimated. The association of late LCNP and secondary outcomes was evaluated using multiple regression methods adjusting for the same variables as the primary outcome analysis. All data were analyzed without imputation for missing information. Given our consideration of multiple MDASI-HN scores as symptom burden outcomes, analysis of all 12 primary and secondary outcomes, including mean top 5 symptom scores, overall 22-item mean score, mean interference (including activity-related and psychosocial domains) score, individual scores for the top 5 symptoms, and voice and categorical ratings, was corrected for multiple comparisons. After Bonferroni correction ($\alpha = 0.05/12$), statistical significance was conferred at $P < .004$. Statistical analysis was conducted using Stata software, version 14.0 (StataCorp).

Results

Sample Characteristics

A total of 889 eligible survivors (753 [84.7%] male; 821 [92.4%] white; median [range] age, 56 [32-84] years) were included in the final analytic sample, with a median survival duration at time of survey of 7.0 years (range, 1-16 years). Of the 889 survivors, 881 were treated with RT (99.1%), and 24 were treated with definitive surgery (2.7%).

Late LCNP

Overall, 36 OPC survivors (4.0%) were diagnosed with late LCNP, and these individuals had longer survival (median, 10.5 years; range, 2-16 years). The median time to onset among patients with LCNP in our study was 5.25 years (range, 0.25-12.30 years) after RT. Among the 36 patients with late LCNP, 22 (58.3%) had T1 to T2 tumors, 15 (41.7%) received accelerated RT, 9 (25.0%) were treated with 3-dimensional conformal RT, 23 (63.9%) received split-field IMRT, and 35 (97.2%) could functionally eat a normal diet before treatment.

Median RT dose among respondents with LCNP was slightly higher (70 Gy; range, 60-72 Gy) compared with that among those without late LCNP (69.3 Gy; range, 40-72.6 Gy). Of the 889 respondents, 605 (68.1%) received chemotherapy, and the rate of LCNP was slightly higher among respondents who received chemotherapy (risk difference, 0.26; 95% CI, −2.60 to 3.00) compared with those who did not.

Treatment-Related Symptom Burden (Mean Top 5 Symptom Scores)

The mean (SD) of the top 5 most severe symptoms reported by OPC survivors are summarized in **Table 1** and included the following symptoms in descending order: 3.9 (2.9) for dry mouth, 2.6 (2.8) for swallowing and chewing, 2.3 (2.4) for mucus, 2.0 (2.5) for fatigue, and 2.0 (2.6) for choking. Overall treatment-related symptom burden among all survivors was low (mean, 2.6; median, 2.0; range, 0-10). Patients with late LCNP reported significantly worse mean treatment-related symptom scores compared with those without LCNP (4.5 for patients with LCNP vs 2.5 for patients without LCNP; mean difference, −2.0; 95% CI, −2.7 to −1.3).

Unadjusted univariate analyses found that survival time, T stage, therapeutic modality, chemotherapy, RT dose, fractionation and modality, and smoking had significant associations with mean scores. Multiple linear regression identified that late LCNP was significantly associated with worse mean top 5 MDASI-HN symptom scores (coefficient, 1.54; 95% CI, 0.82-2.26; adjusted $R^2 = 0.08$), adjusting for age, survival time, sex, therapeutic modality, T stage, subsite, RT modality, smoking, and normal diet before treatment. **Table 2** summarizes the univariate and multivariate regression for LCNP with mean of the top 5 MDASI-HN scores.

Table 1. Patient Characteristics and the Top 5 MDASI-HN Symptoms Score[a]

Variable	No. (%) of Patients (N = 889)		Top 5 MDASI-HN Symptoms Score, Mean (SD) (N = 889)
	Total Patients	Patients With LCNP	
Sex			
Male	753 (84.7)	31 (4.1)	2.57 (2.1)
Female	136 (15.3)	5 (3.7)	2.81 (2.3)
Educational level			
High school or less	168 (18.9)	8 (4.8)	2.95 (2.4)
More than high school	637 (71.7)	27 (4.2)	2.49 (2.1)
Missing	84 (9.4)	1 (1.2)	2.86 (2.3)
Race/ethnicity			
Others	59 (6.6)	3 (5.0)	2.79 (2.7)
White	821 (92.4)	32 (3.9)	2.60 (2.1)
Missing	9 (1.0)	1 (11.1)	2.44 (1.7)
Primary site			
Tonsil	438 (49.3)	17 (3.8)	2.58 (2.2)
Base of tongue	451 (50.7)	19 (4.2)	2.64 (2.2)
T stage			
1	334 (37.6)	8 (2.4)	2.37 (2.1)
2	345 (38.8)	13 (3.8)	2.52 (2.1)
3	131 (14.7)	8 (6.1)	2.89 (2.3)
4	79 (8.9)	7 (8.9)	3.56 (2.5)
N stage			
0	81 (9.1)	3 (3.7)	2.58 (2.3)
1 + 2a	236 (26.5)	7 (2.9)	2.48 (2.2)
2b + 3	429 (48.3)	19 (4.4)	2.50 (2.0)
2c	143 (16.1)	7 (4.9)	3.16 (2.4)
HPV status			
Negative	56 (6.3)	2 (3.6)	2.37 (1.9)
Positive	429 (48.3)	9 (2.1)	2.46 (2.1)
Unknown	404 (45.4)	25 (6.2)	2.80 (2.3)
Smoking			
Never	409 (46.0)	16 (3.9)	2.49 (2.1)
Former	422 (47.5)	17 (4.0)	2.64 (2.1)
Current	58 (6.5)	3 (5.2)	3.22 (2.5)
Solid food before treatment			
Yes	879 (98.9)	35 (4.0)	2.56 (1.8)
No	10 (1.1)	1 (10.0)	2.61 (2.2)
Treatment group			
Single modality	278 (31.3)	11 (4.0)	2.34 (2.1)
Multimodality	611 (68.7)	25 (4.1)	2.73 (2.2)
Treatment group			
RT alone	270 (30.4)	11 (4.1)	2.38 (2.1)
Surgery alone	8 (0.9)	0	0.80 (0.7)
RT plus systemic treatment	596 (67.0)	23 (3.9)	2.73 (2.2)
Surgery plus adjuvant treatment	15 (1.7)	2 (13.3)	2.64 (2.3)
RT			
No	8 (0.9)	0	0.80 (0.8)
Yes	881 (99.1)	36 (4.1)	2.62 (2.2)
Chemotherapy			
No	284 (31.9)	11 (3.9)	2.34 (2.1)
Yes	605 (68.1)	25 (4.1)	2.73 (2.2)

(continued)

Table 1. Patient Characteristics and the Top 5 MDASI-HN Symptoms Score* (continued)

Variable	No. (%) of Patients (N = 889)		Top 5 MDASI-HN Symptoms Score, Mean (SD) (N = 889)
	Total Patients	Patients With LCNP	
Surgery			
No	865 (97.3)	34 (3.9)	2.63 (2.2)
Yes	24 (2.7)	2 (8.3)	1.91 (2.0)
Neck dissection			
No	665 (74.8)	27 (4.1)	2.64 (2.2)
Yes	224 (25.2)	9 (4.0)	2.52 (2.2)
RT schedule			
Standard fractionation	778 (88.3)	21 (2.7)	2.54 (2.1)
Accelerated	95 (10.8)	15 (15.8)	3.40 (2.4)
Missing	8 (0.9)	0	1.76 (1.9)
RT type			
3-Dimensional conformal	50 (5.7)	9 (18.0)	4.34 (2.6)
IMRT-SF	675 (76.6)	23 (3.4)	2.63 (2.1)
IMRT-WF	33 (3.8)	1 (3.0)	2.72 (2.3)
Proton	23 (2.6)	1 (4.4)	2.14 (1.6)
IMRT ipsilateral	100 (11.3)	2 (2.0)	1.8 (1.6)

Abbreviations: HPV, human papillomavirus; IMRT-SF, split-field intensity-modulated radiation therapy; IMRT-WF, whole-field intensity-modulated radiation therapy; LCNP, lower cranial neuropathy; MDASI-HN, MD Anderson Symptom Inventory Head and Neck Cancer Module; RT, radiotherapy.

* The median age at diagnosis was 56 years (range, 32-84 years), median survival was 7 years (range, 1-16 years), and median radiation dose was 70 Gy (range, 40-73 Gy).

Overall Mean (22-Item) MDASI-HN Scores

Patients with LCNP reported significantly worse overall 22-item mean scores compared with those without LCNP (2.4 for patients with LCNP vs 1.4 for patients without LCNP; mean difference, −1.0; 95% CI, −1.5 to −0.5). **Figure 2** summarizes the crude difference in individual MDASI-HN symptoms by LCNP status. Late LCNP remained significantly associated with worse overall 22-item mean scores (coefficient, 0.75; 95% CI, 0.2-1.2) after multivariable adjustment.

GFI and Mean Interference

Late LCNP was not significantly associated with worse mean interference scores (coefficient, 0.72; 95% CI, 0.09-1.35) after multivariable adjustment and correction for multiple testing. Association of late LCNP with individual domains of interference scores categorized as activity related (coefficient, 0.90; 95% CI, 0.25-1.54) and psychosocial related (coefficient, 0.56; 95% CI, −0.08 to 1.21) was also not statistically significant after correction for multiple comparison.

Individual Top 5 Symptoms and Voice and Speech Symptoms

Individual symptoms that were most severe among patients with late LCNP, in rank order of means, included difficulty swallowing and chewing (5.5 in patients with LCNP vs 2.5 in patients without LCNP; mean difference, −2.9; 95% CI, −3.9 to −2.0), dry mouth (4.9 in patients with LNCP vs 3.8 in patients without LCNP; mean difference, −1.0; 95% CI, −2.0 to −0.4), mucus (4.7 in patients with LCNP vs 2.3 in patients without LNCP, mean difference, −2.5; 95% CI, −3.4 to −1.5), voice and speech (4.4 in patients with LCNP vs 1.3 in patients without LCNP; mean difference, −3.1; 95% CI, −3.9 to −2.3), and choking (4.1 in patients with LCNP vs 1.9 in patients without LCNP; mean difference, −2.1; 95% CI, −3.0 to −1.3).

Late LCNP was significantly associated with worse mean swallowing and chewing scores (coefficient, 2.25; 95% CI, 1.33-3.18; adjusted R^2 = 0.10), mucus problems (coefficient, 1.97; 95% CI, 1.03-2.91; adjusted R^2 = 0.07), fatigue (coefficient, 1.35; 95% CI, 0.40-2.21; adjusted R^2 = 0.03), and choking and coughing (coefficient, 1.53; 95% CI, 0.65-2.41; adjusted R^2 = 0.07), adjusting for the same variables as the primary outcome analysis. However, late LCNP was not significantly associated with worse dry mouth after multivariable adjustment (coefficient, 0.63; 95% CI, −0.36 to 1.62). Because late LCNP can include vocal cord paralysis and/or lingual paralysis (with an association with voice and speech production), the association of late LCNP with voice and speech was assessed in exploratory post hoc analysis despite its exclusion from the top 5 items in the overall sample. Late LCNP was independently associated with worse mean MDASI-HN voice scores (coefficient, 2.30; 95% CI, 1.60-3.03; adjusted R^2 = 0.17) after multivariable adjustment. **Figure 3** summarizes multivariate adjusted coefficients for late LCNP and MDASI-HN scores.

Among patients with LCNP, a higher proportion reported severe (20.0% in patients with LCNP vs 5.8% in patients without LCNP) and moderate (40.0% in patients with LCNP vs 15.6% in patients without LCNP) symptoms. In addition, among patients with LCNP, severe scores (≥7) were reported by 15 of 35 (42.9%) for swallowing and chewing symptoms and 13 of 35 (37.1%) for voice and speech problems. Among 35 patients with late LCNP, 6 patients rated difficulty swallowing, 4 rated voice and speech problems, 4 rated choking, and 3 rated mucus as 10 of 10 severity, the worst possible score on the MDASI-HN (eFigure in the Supplement).

Discussion

This large, cross-sectional survivorship survey yielded a comprehensive, quantitative assessment of the association between late LCNP and cancer treatment-related symptoms and subsequent

Table 2. Top 5 MD Anderson Symptom Inventory Head and Neck Cancer Module Univariate and Multivariate Regression

Variable	Analysis Coefficient (95% CI)	
	Univariate	Multivariate
Late LCNP		
No	1 [Reference]	1 [Reference]
Yes	2.00 (1.28 to 2.72)[a]	1.54 (0.82 to 2.26)[a]
Age at diagnosis	0.001 (−0.02 to 0.02)	0.007 (−0.01 to 0.02)
Survival time	0.06 (0.02 to 0.09)[b]	0.02 (−0.03 to 0.06)
Radiation dose	0.10 (0.04 to 0.15)[b]	NA
Sex		
Male	−0.24 (−0.64 to 0.16)	−0.32 (−0.71 to 0.08)
Female	1 [Reference]	1 [Reference]
Education		
High school or less	1 [Reference]	1 [Reference]
More than high school	−0.46 (−0.83 to 0.09)[b]	NA
Missing	−0.09 (−0.66 to 0.48)	NA
Race/ethnicity		
Others	1 [Reference]	1 [Reference]
White	−0.20 (−0.78 to 0.39)	NA
Missing	−0.35 (−1.87 to 1.18)	NA
Primary site		
Tonsil	1 [Reference]	1 [Reference]
Base of tongue	0.07 (−0.22 to 0.36)	−0.08 (−0.38 to 0.23)
T stage		
1	1 [Reference]	1 [Reference]
2	0.15 (−0.17 to 0.48)	0.007 (−0.33 to 0.35)
3	0.52 (0.08 to 0.96)[b]	0.06 (−0.42 to 0.54)
4	1.19 (0.65 to 1.73)[a]	0.73 (0.16 to 1.30)[c]
Smoking		
Never	1 [Reference]	1 [Reference]
Former	0.14 (−0.15 to 0.44)	0.12 (−0.18 to 0.41)
Current	0.73 (0.12 to 1.33)[b]	0.62 (0.03 to 1.22)[c]
Solid food before treatment		
Yes	1 [Reference]	1 [Reference]
No	0.06 (−1.29 to 1.42)	0.60 (−0.64 to 1.85)
Treatment group		
Single-modality treatment	1 [Reference]	1 [Reference]
Multimodality treatment	0.40 (0.09 to 0.71)[b]	0.17 (−0.20 to 0.53)
RT		
No	1 [Reference]	NA
Yes	1.83 (0.32 to 3.33)[b]	NA
Chemotherapy		
No	1 [Reference]	1 [Reference]
Yes	0.40 (0.09 to 0.70)[b]	NA
Surgery		
No	1 [Reference]	1 [Reference]
Yes	−0.72 (−1.61 to 0.18)	NA
Neck dissection		
No	1 [Reference]	1 [Reference]
Yes	−0.11 (−0.46 to 0.22)	NA
RT schedule		

(continued)

Table 2. Top 5 MD Anderson Symptom Inventory Head and Neck Cancer Module Univariate and Multivariate Regression (continued)

Variable	Analysis Coefficient (95% CI)	
	Univariate	Multivariate
Standard fractionation	1 [Reference]	1 [Reference]
Accelerated	0.85 (0.39 to 1.32)[a]	NA
Missing	−0.77 (−2.27 to 0.74)	NA
RT type		
3-Dimensional conformal	1 [Reference]	1 [Reference]
IMRT-SF	−1.71 (−2.33 to −1.10)[a]	−1.34 (−2.02 to −0.66)[a]
IMRT-WF	−1.62 (−2.55 to −0.68)[b]	−1.33 (−2.29 to −0.38)[c]
Proton	−2.20 (−3.25 to 1.15)[a]	−1.76 (−2.89 to −0.63)[c]
IMRT Ipsilateral	−2.54 (−3.27 to −1.81)[a]	−2.06 (−2.89 to −1.23)[a]

Abbreviations: IMRT-SF, split-field intensity-modulated radiation therapy; IMRT-WF, whole-field intensity-modulated radiation therapy; LCNP, lower cranial neuropathy; NA, not applicable; RT, radiotherapy.

[a] $P < .001$.

[b] $P < .25$ during univariate analysis.

[c] $P < .05$ after multivariate analysis.

GFI among OPC survivors. Survey results for 889 OPC survivors treated from 2000 to 2013 indicated that, although overall cancer treatment-related symptom burden among all survivors was low, the small subgroup of patients with late LCNP (4.0%) reported significantly worse cancer treatment-related symptom severity. Although the burden of late LCNP is clinically recognized, prior studies, to our knowledge, have yet to quantitatively estimate the burden of this late effect.

Our results suggest that the mean top 5 MDASI-HN symptom score is 1.54 points worse among survivors with LCNP compared with those without LCNP after adjusting for age, survival time, sex, therapeutic modality, T stage, subsite, RT modality, smoking, and normal diet before treatment. This finding reflects a moderate effect size of LCNP on most prevalent symptoms in this survivor population. The adjusted R^2 of the model suggests that late LCNP explained 8% of the variation in the mean top 5 MDASI-HN symptom scores after accounting for the effects of other covariates. This modest to moderate adjusted R^2 for a single exposure may reflect the variability of nerve paresis associated with symptoms among survivors because of the cross-sectional sampling along the continuum of nerve paresis (partial through complete denervation) because progressive deterioration over time is characteristic of late LCNP.[30] That is, patients with LCNP responded to the survey from 2 to 16 years after treatment, a timeframe during which the clinical course of LCNP was likely to vary. This observation is consistent with previous case reports that suggest that functional status of cases approximated the trajectories of their neuropathies.[7] That is, as late LCNP remained clinically stable, physiologic impairment remained steady, and as late LCNP progressed, coincident severe decline in function and body weight occurred.[7]

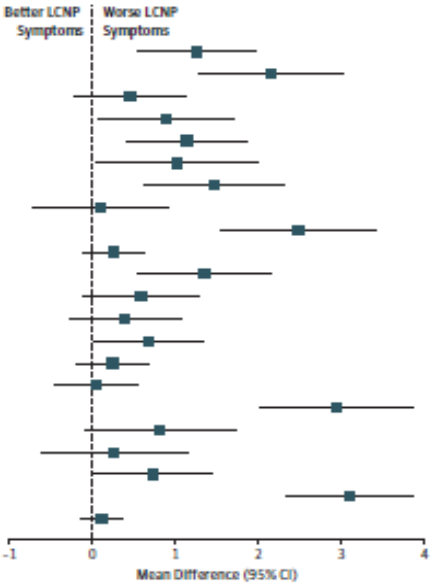
Treatment of OPC may lead to multiple local symptoms, including dry mouth, dysphagia, mucositis, choking, speech problems, and lack of taste, among others, which can contribute to excessive distress and lower QOL.[27,31] The mean top 5 symptoms

reported by our study population predominantly featured similar local head and neck-specific adverse effects (4 of 5, except fatigue). Given the central role of these symptoms in daily functioning, it is not surprising that patients with late LCNP also reported higher levels of GFI, which was correlated with symptom severity; however, this association was not statistically significant after multiple comparison correction. Of interest, among individual components of the interference domain, late LCNP was more strongly associated with activity-related interference but not psychosocial-related scores, but this association was also not statistically significant. These findings might suggest a more lasting burden of LCNP on activity as opposed to emotional distress. The association between psychosocial distress and late symptoms may attenuate over time as patients learn to cope with the emotional distress associated with physical impairment. Similarly, a previous study[32] that investigated QOL among patients with oral cancer according to the Functional Assessment of Cancer Therapy-Head and Neck found significantly improved emotional scores in the same time that functional scores decreased between 1 month and 6 months after treatment. The authors attributed this finding to a response shift, which they described as emotional adaptation to decline in physical functioning and improved coping with the new normal level of functioning.[32] These trends are also consistent with results of a study among patients with HNC that used the MD Anderson Dysphagia Inventory (MDADI) and reported better scores for the emotional vs functional component.[33]

Overall, late LCNP was most strongly associated with worse swallowing and chewing as well as speech and voice symp-

Figure 2. Unadjusted Difference in Means of Individual MD Anderson Symptom Inventory Head and Neck Cancer Module (MDASI-HN) Symptom Severity by Late Lower Cranial Neuropathy (LCNP) Status

MDASI-HN Core and Head and Neck Symptom	Crude Difference (95% CI)
Appetite[a]	1.26 (0.50 to 1.90)
Choking and coughing[a]	2.15 (1.30 to 3.00)
Constipation	0.45 (−0.20 to 1.10)
Disturbed sleep[a]	0.89 (0.10 to 1.70)
Drowsy[a]	1.14 (0.40 to 1.90)
Dry mouth[a]	1.02 (0.04 to 2.00)
Fatigue[a]	1.47 (0.60 to 2.30)
Memory	0.09 (−0.70 to 0.90)
Mucus[a]	2.48 (1.60 to 3.40)
Nausea	0.25 (−0.10 to 0.60)
Numbness[a]	1.35 (0.50 to 2.20)
Pain	0.58 (−0.10 to 1.30)
Sad	0.39 (−0.30 to 1.10)
Shortness of breath[a]	0.68 (0.02 to 1.30)
Skin	0.24 (−0.20 to 0.70)
Sores	0.04 (−0.50 to 0.50)
Swallowing and chewing[a]	2.94 (2.00 to 3.90)
Taste	0.80 (−0.10 to 1.70)
Teeth	0.26 (−0.60 to 1.10)
Upset	0.70 (0.02 to 1.40)
Voice and speech[a]	3.10 (2.30 to 3.90)
Vomiting[a]	0.10 (−0.10 to 0.40)

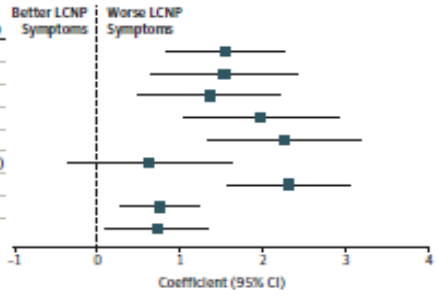


Squares represent estimate of difference in means; error bars, 95% CIs; vertical line, no difference in means.

[a] Statistical significance conferred if the 95% CI for the estimate did not include the null value.

Figure 3. Multivariate Adjusted Coefficients for Late Lower Cranial Neuropathy (LCNP) and MD Anderson Symptom Inventory Head and Neck Cancer Module (MDASI-HN) Scores

Mean MDASI-HN Score	Coefficient (95% CI)
Top 5 symptom mean[a]	1.54 (0.82 to 2.26)
Choking/coughing[a]	1.53 (0.65 to 2.41)
Fatigue[a]	1.35 (0.40 to 2.21)
Mucus[a]	1.97 (1.03 to 2.91)
Swallowing/chewing[a]	2.25 (1.33 to 3.18)
Dry mouth	0.63 (−0.36 to 1.62)
Voice and speech[a]	2.30 (1.60 to 3.03)
Mean MDASI-HN (22-item) symptom[a]	0.75 (0.20 to 1.20)
Mean interference score[b]	0.72 (0.09 to 1.35)



All regression models adjusted for age, survival time, sex, therapeutic modality, T stage, subsite, radiotherapy modality, smoking, and normal diet before treatment.

[a] Statistically significant in multivariate model after multiple comparison correction.

[b] Statistically significant in multivariate model before multiple comparison correction.

toms, with LCNP being associated with 10% of the variation in swallowing and chewing scores and 17% of the variation in speech and voice symptoms scores. These findings agree with those reported by a longitudinal study[6] among 57 OPC survivors, wherein 3 patients with LCNP experienced a severe decline in swallowing function over time according to patient-reported MDADI scores, practitioner-rated radiographic dysphagia grades, and standard diet scales. Late LCNP was also associated with worse mucus and choking scores in the present survey, which may reflect symptoms associated with swallowing effects of LCNP. Inefficient swallows described previously in patients with LCNP affect the ability to clear food and liquids through the oropharynx, including mucus.[7] Mucus accumulation can lead to unpleasant symptoms of gagging and choking, which may also reflect aspiration of food and liquids during swallowing, as previously reported in 100% of cases of neuropathy-mediated, late RT-associated dysphagia largely occurring in long-term OPC survivors at more than 5 years after treatment.[34]

Lower cranial nerves are critical to the oropharyngeal phase of swallowing as well as voice and speech production.[5-9] Cranial nerve IX palsy may lead to swallowing problems by way of loss of function of the stylopharyngeus muscle and loss of pharyngeal sensation, whereas cranial nerve X injury can cause paralysis of the pharyngeal constrictors and/or vocal cords (depending on the branch) and thereby contribute to dysphagia and voice impairment. Neuropathy of cranial nerve XII results in tongue paresis, atrophy, and fibrillations, with implications also for swallowing and speech precision.[5-9] Therefore, the specific patterns of symptom burden detected in this survey align with the clinical findings of specific LCNPs among patients with OPC.

Fatigue is widely prevalent in HNC survivors but was also reported with greater severity among patients with LCNP, possibly because of late LCNP-associated mucus problems that could exacerbate sleep disturbance.[35] In addition, LCNP-associated swallowing dysfunction can contribute to long-term micronutrient deficiency and complications, such as anorexia, malnutrition, anemia, and cachexia. Cachexia especially has been linked in a past study[36] to functional limitations and fatigue. Furthermore, lack of association between late LCNP and dry mouth is expected given that dry mouth is not a consequence of lower cranial nerve injury and is instead caused by RT-induced hypofunction of salivary glands.[37]

Symptom burden can be reflected by many measures of the MDASI-HN. Each of the MDASI-HN outcomes that we reported in this analysis is described in the MDASI user guide as an option to report findings from the instrument. It is important to acknowledge, however, that the mean top 5 MDASI-HN metric has not been evaluated for validity in a dedicated publication. The metric is, however, supported by both the MDASI user manual and the expected performance relative to clinical and demographic classifiers in this report and other publications.[23-26] Evaluation of individual items as a secondary end point also suggests that late LCNP had the greatest negative association with difficulty swallowing, speech, mucus problems, choking, and fatigue symptoms among OPC survivors. For this reason, the functional translation of late LCNP may lead to placement of feeding tubes, tracheostomy tubes, aspiration, and pneumonia, as has been described in smaller series with more objective metrics.[6-8] Smaller series, however, failed to include non-LCNP controls such that effect sizes from these more objective metrics are not available in the current literature. It is our hope that these survey-based quantifications offer initial progress toward quantifying the burden of this rare but devastating late consequence of treatment.

This research can inform development of supportive care interventions among OPC survivors to target these symptom domains through personalized speech and swallowing therapy and nutritional consultations, and such implications need to be assessed in future studies. Given the high degree of symptom burden, integration of interdisciplinary supportive care should be given early to potentially attenuate or slow the functional burden of LCNP. Diverse symptoms likely merit involvement of speech pathologists, oral oncologists, physiatrists, physical therapists, nutritionists, and oncology nurses, among others, to optimize outcomes. Targeted and individualized treatments must take into consideration patient perspectives, and routine symptom screening using validated patient-reported outcomes, such as the MDASI-HN, in patients with LCNP may also be of value to prioritize areas for intervention.

Limitations

With 889 OPC survivors, this study is the first, to our knowledge, to quantitatively estimate the association between late LCNP and cancer treatment-related severity of symptoms. There are, however, limitations to acknowledge. Cross-sectional survey administration led to respondents with varying survival time and survival bias. Given the long latency period for late LCNP development, risk is highest among responders with greater survival time. For this reason, survival time was accounted for in all regression models. The small number of events is a limitation inherent to studies of LCNP because it is known to be a rare late occurrence. Nonetheless, consistently robust estimates on study outcomes were identified that reflect expected outcomes from clinical observations. This study was conducted in a tertiary care cancer center, making it subject to referral bias that can limit generalizability of results to other hospitals and communities, but sample characteristics are common of modern OPC in the United States; therefore, this issue is expected to be negligible. The largest threat to validity is the possibility of misclassification. Late LCNP ascertainment may be incomplete because of loss to follow-up, missing medical record details, or differential follow-up among patients with mild cranial neuropathy symptoms insufficient to merit return to the clinic for late LCNP. Therefore, exposure misclassification in this study would most likely lead to underreporting of LCNP and consequently to underestimation of the association of LCNP with symptom burden. Thus, if misclassification was substantial, actual coefficients for LCNP and symptom burden may be higher than reported in this study. Because this was a cross-sectional survey, the degree or time course of LCNP was not standard in all cases. There was, for instance, no standard method to document degree of neuropathy in medical records. Likewise, the association between LCNP and diet and other functional variables was not assessed

and will be investigated in future publications. We also did not obtain detailed, validated measures of anxiety and depression; therefore, the association of late LCNP with these domains needs to be investigated in future studies using other, more robust measures.

Conclusions

In this large survey study, patients with late LCNP reported significantly worse cancer treatment-related symptoms and worse symptoms associated with motor functions of the upper aerodigestive tract (swallowing, voice), revealing the relevance of late LCNP to both symptom severity and QOL. Among patients with LCNP, a higher proportion reported severe and moderate symptoms. The study findings suggest the need for long-term surveillance of late LCNP among patients with HNC and OPC, particularly in light of epidemiologic trends that suggest increasing numbers of OPC survivors at risk of late symptoms in the immediate years ahead.[6-8] Furthermore, efforts may be necessary to lessen symptom burden associated with this disabling late burden among OPC survivors.

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ORIGINAL ARTICLE

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Swallowing-related outcomes associated with late lower cranial neuropathy in long-term oropharyngeal cancer survivors: cross-sectional survey analysis

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Abstract

Background: The purpose of this study was to quantify the association of late lower cranial neuropathy (late LCNP) with swallowing-related quality of life (QOL) and functional status among long-term oropharyngeal cancer (OPC) survivors.

Methods: Eight hundred eighty-nine OPC survivors (median survival time: 7 years) who received primary treatment at a single institution between January 2000 and December 2013 completed a cross-sectional survey (56% response rate) that included the MD Anderson Dysphagia Inventory (MDADI) and self-report of functional status. Late LCNP events ≥3 months after cancer therapy were abstracted from medical records. Multivariate models regressed MDADI scores on late LCNP status adjusting for clinical covariates.

Results: Overall, 4.0% (n = 36) of respondents developed late LCNP with median time to onset of 5.25 years post-treatment. LCNP cases reported significantly worse mean composite MDADI (LCNP: 68.0 vs no LCNP: 80.2; $P < .001$). Late LCNP independently associated with worse mean composite MDADI ($\beta = -6.7$, $P = .02$; 95% confidence interval [CI], −12.0 to −1.3) as well as all MDADI domains after multivariate adjustment. LCNP cases were more likely to have a feeding tube at time of survey (odds ratio [OR] = 20.5; 95% CI, 8.6-48.9), history of aspiration pneumonia (OR = 23.5; 95% CI, 9.6-57.6), and tracheostomy (OR = 26.9; 95% CI, 6.0-121.7).

Conclusions: In this large survey study, OPC survivors with late LCNP reported significantly poorer swallowing-related QOL and had significantly higher likelihood of poor functional status. Further efforts are necessary to optimize swallowing outcomes to improve QOL in this subgroup of survivors.

KEYWORDS
dysphagia, lower cranial neuropathy, oropharyngeal cancer, radiotherapy, survivorship

1 | INTRODUCTION

Swallowing is a complex and multifaceted neuromuscular process that involves five cranial nerves (CN) and almost 30 muscles in the upper aerodigestive tract. Patients with oropharyngeal cancer (OPC) receive local treatments, radiotherapy (RT), and/or surgery, to this functionally critical region that can cause chronic dysphagia with adverse impact on swallowing-related quality of life (QOL).[1-6] Dysphagia is one of the most impactful and prevalent functional toxicities reported in approximately 30%-50% of survivors.[7-10] Prior analysis of this OPC survivorship found that, among 22 symptoms queried, the severity of dysphagia symptoms most strongly associated with decisional regret about cancer treatment.[11] The rising incidence of highly curable human papillomavirus (HPV)-associated OPC leads to greater numbers of OPC survivors at risk of dysphagia with great impetus to understand factors that associate with poor swallowing outcomes and adversely impact QOL in this growing population. Dysphagia also leads to excessive morbidity, negatively impacting functional status, and health of OPC survivors. Impaired airway protection can lead to aspiration pneumonia, and inefficient bolus clearance may result in low food intake, extended gastrostomy tube dependence, weight loss, and malnutrition.[12] Patients with dysphagia often modify their diet, need extended meal times, feel self-conscious to eat in social settings, and thereby experience social isolation and diminished QOL.[12]

Radiation-associated dysphagia (RAD) is typically linked with soft tissue injuries including inflammation, edema, fibrosis, and stricture.[13] Acute tissue injury results from cell depletion and inflammation that contribute to edema, erythema, and mucositis of the oropharyngeal region.[13,14] Late RT injury is defined classically as 3 months or more after cancer treatment and may represent persistence of early injury (ie, "consequential late effects") or new damage linked to excessive collagen accumulation, microvascular damage, and overproduction of pro-fibrotic growth factors β (TGF-β1) resulting in fibrosis and atrophy.[14,15] The superior pharyngeal constrictor (SPC) region comprises minor nerve tracts and the constrictor and longitudinal pharyngeal muscles, which are important for pharyngeal shortening and constriction during swallowing for safe and efficient bolus propulsion into the esophagus.[16] Irradiation to this region, specifically the mean SPC region dose, has been reported in numerous studies to be associated with chronic and late RAD.[16-18] Thereby, dysphagia may occur as a consequence of reduced base of tongue retraction and elevation of larynx, inadequate retroflexion of epiglottis, pharyngeal transit delay, and inadequate swallowing muscle action.[14]

Surgical treatment for OPC including tongue resection involving geniohyoid or mylohyoid muscles, mandibulotomy-related genioglossus injury and loss of occlusion, lateral soft palate resection may also cause muscle and nerve injury and contribute to dysphagia.[13] Site and extent of tumor resection thereby contribute to severity of dysphagia.[13] Reports also suggest that patients with head and neck (HNC) cancer treated with surgery followed by postoperative RT may experience cumulative effects and more accelerated effects of RT.[6,13,19] This may contribute to additional decline in swallowing function due to diminished oropharyngeal swallow efficiency.[6,13,19]

Lower cranial neuropathies (LCNP) are a rare but permanent late effect of HNC treatment that injures the glossopharyngeal (IX), vagus, (X), accessory (XI), and/or hypoglossal (XII) nerves.[1,20-23] These nerves (except XI) play a pivotal role in the oropharyngeal swallowing mechanism and thereby their damage can contribute to profound functional impairment in terms of dysphagia often with coexisting problems in speech and voice and shoulder impairment.[1,16,20-24] A previous study among 59 OPC survivors treated with intensity modulated radiotherapy (IMRT) reported a 5% incidence rate of late LCNP at median follow-up of 5.7 years (range, 4.6-7.6 years).[1] Among LCNP cases, onset of neuropathy preceded quantifiable, clinically significant decline in both patient-reported (per MD Anderson Dysphagia Inventory; MDADI) and clinician-rated (per Modified Barium Swallow Study; MBS) swallowing function.[1] Likewise, the investigators recently published a large survey of 889 long-term OPC survivors in which LCNP was significantly associated with excess symptom burden and had the greatest impact on swallowing/ chewing and voice/speech symptoms among the 22 symptom items rated using the MD Anderson Symptom Inventory Head and Neck Cancer Module (MDASI-HN), a validated multi-symptom survey instrument.[25]

Previous literature also specifically implicates LCNP as a major contributor to late radiation associated dysphagia (late-RAD).[20,21] Patients with late RAD often have clinically detectable LCNP with unilateral paralysis, muscle wasting leading to atrophy of lingual and pharyngeal musculature with clinical series supporting a prominent role of nerve injury in the functional decline experienced by these patients.[24] A series of 29 survivors of HNC with late-RAD reported that 48% of cases had clinically detectable cranial neuropathies, and CN XII and X palsies were most common.[24] Several small published series and case reports consistently describe severe problems in swallowing, eating, and extreme functional impairment in pharyngeal phase of swallowing among survivors with late LCNP, with associated swallowing inefficiency, pharyngeal residue, and silent aspiration.[1,16,20-24] Consequently, about 85% of OPC survivors with late-RAD develop pneumonia, and more than 60% require long-term gastrostomy tube placement highlighting

the possible extreme functional relevance of late LCNP if it indeed is a driver of late dysphagia.[16,21]

The previous literature and prior analysis of symptom burden suggests a strong association between late LCNP and the severity of dysphagia; however, the nature of this association has not been comprehensively evaluated or quantified in a large population of survivors. Few studies have addressed late LCNP among OPC survivors, as most of the published literature on LCNP has comprised case reports or studies primarily conducted among nasopharyngeal cancer survivors.[26,27] Studies suggest that the risk of CN damage increases over time,[1,21,27] and as survival probabilities improve for OPC, there is an ever-growing pool of OPC survivors who have received surgery and/or curative doses of RT sufficient to induce LCNP. Therefore, there is urgent need to understand to our fullest ability the functional impact of this disabling late effect of therapy. Thus, the purpose of this analysis was to quantify the association of late LCNP with swallowing-related QOL using the MDADI and functional status metrics. We hypothesized that late LCNP among OPC survivors would be associated with significantly worse swallowing-related QOL (per MDADI survey scores) and LCNP status would relate to differences in functional status metrics.

2 | MATERIALS AND METHODS

2.1 | Study Design, Eligibility, and Consent

This cross-sectional survey was conducted in 2015 among a cohort of OPC survivors who received primary cancer treatment at MD Anderson Cancer Center between January 2000 and December 2013. An institutional review board-approved patient-reported outcome (PRO) survey was administered to eligible OPC survivors in the cohort who were 18 years or older at diagnosis, completed their treatment at least 1 year before survey administration, and consented to the study. Exclusion criteria were patients who were deceased, those with second primary malignancy or recurrent HNC tumors preceding survey, and those whose primary spoken language was not English. For this analysis, patients diagnosed with LCNP or with clinical signs of LCNP before initiation of OPC treatment were excluded. The survey items included in this analysis were the MDADI, a patient-reported adaptation of the Performance Status Scale for Head and Neck cancer (PSS-HN) with questions on normalcy of diet and public eating, as well as a self-report of aspiration pneumonia, current feeding tube status, and current weight. A previous publication provides details of survey administration and response.[7]

2.2 | MD Anderson Dysphagia Inventory

The MDADI is a 20-item validated PRO instrument that quantifies perceived limitations in swallowing ability and their impact on day-to-day activities.[28] MDADI provides subscale scores which comprised emotional (6 questions), physical (8 questions), and functional components (5 questions). It also estimates a global summary score (based on one question—"My swallowing limits my day to day activities") and a composite score (based on 19 questions excluding the global item).[12,28-30]

Scoring of MDADI: The questions related to swallowing function are Likert scaled with the options of "strongly agree," "agree," "no opinion," "disagree," or "strongly disagree," scored on a scale of 1-5, respectively, with the exception of two questions (E7 and F2) for which reverse scoring is calculated. After summation of response scores, the mean value is estimated and multiplied by 20 to estimate the total score.[31] Total scores range from 20 to 100 with higher scores reflecting higher perceived swallowing-related QOL.[12,28,30,31] MDADI scores can be analyzed as continuous or categorical variables with scores classified in the following categories: ≥80 as optimal, 60-79 as adequate and <60 as poor.[10] MDADI was validated among patients with HNC and has internal consistency scored by Cronbach's alpha of 0.96 and was documented to have test-rest reliability correlations ranging from 0.69 to 0.88.[28]

2.3 | PSS-HN adaptation

An adapted version of the PSS-HN, a validated, clinician-rated interview-based measure of performance status among patients with HNC was included in the survey instrument.[1] The scale was adapted for patient-reported administration and consisted of questions pertaining to the survivor's diet level and public eating experience.[1] Normalcy of diet options included the following: full diet no restriction, full diet with liquid assist, solid food but avoid some hard to eat foods, soft chewable foods, non-chewable or pureed foods, drink warm and cold liquids only, or nothing orally only use a feeding tube. Public eating was coded as the following: no restriction of place, food, or companion; no restriction of place; restrict diet in public; eat only in the presence of selected person in selected places; only eat at home with selected persons; or always eat alone.

2.4 | Primary and secondary outcomes

The primary outcome for this study was mean composite MDADI score that serves as an estimate of overall swallowing-related QOL.[12,28-31] The secondary outcomes for analysis included the emotional, physical, and functional subscale and the global MDADI scores as well as self-

reported functional status metrics including current feeding tube status, normalcy of diet, public eating, history of aspiration pneumonia, current weight, understandability of speech, and current tracheostomy. Chart abstracted functional data included baseline weight to calculate percent change in weight between weight at the time of survey and pretreatment weight, and history of dilations due to the presence of stricture. Current feeding tube status, aspiration pneumonia history, and current tracheostomy were coded as binary variables. Change in weight was calculated as baseline weight minus current weight, and percent change in weight was calculated as change in weight divided by baseline weight. Survey questions on functional status metrics have been listed in Appendix S2.

2.5 | Primary exposure

Late LCNP was the primary exposure for this analysis. Late LCNP case status was ascertained by a detailed review of medical records of survivors as previously described.[25] For this study, late LCNP was defined as a clinical evidence of neuropathy of at least one of the glossopharyngeal (IX), vagus (X), and hypoglossal (XII) nerves ≥3 months after the end of cancer treatment.[25] The time period was defined considering the NCI-Common Toxicity Manual's definition of late radiation effects as occurring 90 days and onwards after RT therapy initiation.[32]

2.6 | Clinical and demographic variables

Demographic variables including age at diagnosis, sex, race, and education, and clinical variables including primary tumor subsite, tumor and nodal staging (American Joint Committee on Cancer, version VII), treatment modality, chemotherapy, surgery, neck dissection, RT dose, fractionation, and modality were abstracted from the electronic medical records. Pretreatment diet (ability to eat solid foods) was also collected as a surrogate variable for the presence of baseline dysphagia. Survival time for this population was estimated as the difference between the age of diagnosis and the age at the time of the survey. History of pharyngoesophageal dilation was used as a surrogate variable for stricture, which can contribute to dysphagia and act as a confounder in our analysis.

2.7 | Statistical analysis

Demographic, clinical, and treatment variables and distribution of MDADI scores by these variables were summarized using descriptive statistics and univariate analysis. With a rare event leading to small case numbers for our primary exposure (LCNP), imputation of MDADI scores was conducted to minimize the loss of statistical power due to skipped or missing MDADI items. Imputation used the mean of responses to MDADI items among those patients who responded to that specific item (mean score among nonmissing on that item).[33] Post hoc sensitivity analysis was conducted to assess the impact of imputed, missing MDADI responses on study results.

Multiple linear regression was used to investigate the association between late LCNP and MDADI scores controlling for confounders following model building strategies using the purposeful variable selection method.[34] Age, subsite, T-stage, treatment modality, and smoking based on previous literature were defined a priori as clinically important variables and retained for adjustment in all models. Variance inflation factor was used to assess collinearity among variables. Biologically plausible interaction terms were also assessed using the likelihood ratio tests and were considered statistically significant when P-values were $<.05$. Adequacy and fit of model were assessed using R squares, adjusted R squares, and chi-square goodness of fit tests. Coefficients (univariate and multivariate adjusted) for impact of late LCNP on MDADI scores and their 95% confidence intervals (CI) were estimated. As secondary analyses, the relationships between late LCNP and functional status metrics were assessed according to their distributions using the Fisher's exact test, Wilcoxon rank-sum test, and Kruskal-Wallis test. All reported P-values are two-sided and considered statistically significant at P-value of $\leq.05$. Statistical analysis was conducted using the STATA software, version 14.0 (StataCorp LP, College Station, Texas).

3 | RESULTS

3.1 | Sample characteristics

A total of 889 eligible OPC survivors with a median survival time 7.0 (range, 1-16) years were included in the analysis. Table 1 displays the distribution of demographic, tumor, and treatment-related characteristics in the study population. The patient characteristics of this study population have been described fully in an earlier publication.[18] Briefly, 84.7% were male, 92.4% were white, 71.7% were educated beyond high school, 76.4% had been treated for T1-T2 tumors, 98.9% could eat a normal solid food diet before treatment, 99.1% were treated with RT of which 76.6% were treated with intensity-modulated radiotherapy split-field technique (IMRT-SF), and median radiation dose was 70 Gy (range, 40-73 Gy). Definitive surgery was rare (2.7%).

TABLE 1 Patient characteristics, late LCNP rate, and mean composite MDADI scores

Variables	All patients (n = 889)	Patients with LCNP (n = 36)	Composite MDADI score ± standard deviation: All patients (n = 889)	P-value
Continuous variables				
Age at diagnosis, median (range)	56 (32-84)	57 (42-72)	rho = −0.034	.31[a]
Survival time, median (range)	7 (1–16)	10.5 (2-16)	rho = −0.076	.02[a]
Radiation dose, median (range), Gy	70 (40–73)	70 (60-72)	rho = −0.201	<.001[a]
Categorical variables	**All patients, n (%)**	**Patients with LCNP, n (%)**	**All patients (n = 889)**	**P-value**
Sex				.44[b]
Female	136 (15.3)	5 (3.7)	78.3 ± 17.5	
Male	753 (84.7)	31 (4.1)	79.9 ± 16.3	
Education				<.001[b]
≤High school	168 (18.9)	8 (4.8)	75.6 ± 16.7	
>High school	637 (71.7)	27 (4.2)	80.9 ± 15.9	
Missing	84 (9.4)	1 (1.2)	78.6 ± 18.9	
Race				.98[b]
Others	59 (6.6)	3 (5.0)	78.5 ± 20.0	
White	821 (92.4)	32 (3.9)	79.8 ± 16.2	
Missing	9 (1.0)	1 (11.1)	78.4 ± 19.3	
Primary site				.20[b]
Tonsil	438 (49.3)	17 (3.8)	80.3 ± 16.4	
Base of Tongue	451 (50.7)	19 (4.2)	79.1 ± 16.6	
T classification				<.001[b]
1	334 (37.6)	8 (2.4)	82.6 ± 15.2	
2	345 (38.8)	13 (3.8)	80.8 ± 15.7	
3	131 (14.7)	8 (6.1)	75.8 ± 17.0	
4	79 (8.9)	7 (8.9)	68.7 ± 18.9	
N classification				.007[b]
N0	81 (9.1)	3 (3.7)	79.9 ± 16.1	
N1 + 2a	236 (26.5)	7 (2.9)	81.8 ± 14.7	
2b + 3	429 (48.3)	19 (4.4)	80.1 ± 16.4	
2c	143 (16.1)	7 (4.9)	74.7 ± 18.9	
HPV status				.03[b]
Negative	56 (6.3)	2 (3.6)	80.9 ± 16.8	
Positive	429 (48.3)	9 (2.1)	81.0 ± 15.9	
Unknown	404 (45.4)	25 (6.2)	78.1 ± 17.0	
Smoking				<.001[b]
Never	409 (46.0)	16 (3.9)	81.4 ± 16.2	
Former	422 (47.5)	17 (4.0)	79.0 ± 16.3	
Current	58 (6.5)	3 (5.2)	72.5 ± 17.9	
Solid food pre-Tx				.85[b]
Yes	879 (98.9)	35 (4.0)	79.9 ± 14.0	
No	10 (1.1)	1 (10.0)	79.7 ± 16.5	

(Continues)

TABLE 1 (Continued)

Variables	All patients (n = 889)	Patients with LCNP (n = 36)	Composite MDADI score ± standard deviation	
			All patients (n = 889)	*P*-value
Treatment group				<.001[b]
Single modality	278 (31.3)	11 (4.0)	83.2 ± 14.3	
Multimodality	611 (68.7)	25 (4.1)	78.1 ± 17.2	
Treatment group				.001[b]
RT alone	270 (30.4)	11 (4.1)	83.0 ± 14.4	
Surgery alone	8 (0.9)	0	89.9 ± 9.4	
RT plus systemic	596 (67.0)	23 (3.9)	78.1 ± 17.3	
Surgery plus adjuvant	15 (1.7)	2 (13.3)	78.4 ± 14.2	
Radiotherapy				.07[b]
No	8 (0.9)	0	89.9 ± 9.4	
Yes	881 (99.1)	36 (4.1)	79.6 ± 16.5	
Chemotherapy				<.001[b]
No	284 (32.0)	11 (3.9)	83.0 ± 14.3	
Yes	605 (68.0)	25 (4.1)	78.1 ± 17.2	
Surgery				.40[b]
No	865 (97.3)	34 (3.9)	79.6 ± 16.6	
Yes	24 (2.7)	2 (8.3)	83.0 ± 13.8	
Neck dissection				.43[b]
No	665 (74.8)	27 (4.1)	79.9 ± 16.5	
Yes	224 (25.2)	9 (4.0)	79.0 ± 16.5	
RT schedule				.002[b]
Standard fractionation	778 (88.3)	21 (2.7)	80.3 ± 16.1	
Accelerated	95 (10.8)	15 (15.8)	73.5 ± 18.3	
Other	8 (0.9)	0	78.3 ± 24.3	
RT type				<.001[b]
3D conformal	50 (5.7)	9 (18.0)	67.8 ± 20.4	
IMRT-SF	675 (76.6)	23 (3.4)	79.6 ± 16.1	
IMRT-WF	33 (3.8)	1 (3.0)	74.7 ± 17.8	
Proton	23 (2.6)	1 (4.4)	87.5 ± 11.3	
IMRT ipsilateral	100 (11.3)	2 (2.0)	84.9 ± 14.3	
Dilation/stricture				<.001[b]
No	873 (98.2)	31 (3.6)	80.0 ± 16.3	
Yes	16 (1.8)	5 (31.3)	61.0 ± 14.6	

Abbreviations: 3D Conformal, three-dimensional (3D) conformal radiation therapy; IMRT-SF, intensity-modulated radiation therapy with split field technique; IMRT-WF, intensity-modulated radiation therapy with whole field technique; LCNP, lower cranial neuropathy; MDADI, MD Anderson Dysphagia Inventory; pre-Tx, pretreatment; rho, Spearman rho; RT, radiotherapy; T, tumor.

[a]*P*-value for continuous variables and composite scores calculated using Spearman test.

[b]*P*-value for categorical variables and composite scores calculated using Kruskal-Wallis test.

3.2 | Late lower cranial neuropathy

Overall, 36 (4.0%) OPC survivors were diagnosed with late LCNP with median time to LCNP onset after treatment of 5.3 (range, 0.3-12.3) years. Among them, 21 (58.3%) of LCNP cases had been treated for T1-T2 tumors, 35 (97.2%) reported eating a normal solid food diet before treatment, all 36 of them received RT, 23 (63.9%) were treated with RT in

TABLE 2 Univariate and multivariate regression: composite MDADI[a] (n = 889)

Variables	Univariate analysis coefficient (95% CI)	*P*-value	Multivariate analysis coefficient (95% CI)	*P*-value
Late LCNP				
No	Reference		Reference	
Yes	−12.2 (−17.6 to −6.7)	**<.001**	−6.6 (−12.0 to −1.3)	**.02**
Age at diagnosis	−0.1 (−0.2 to 0.1)	.33	−0.1 (−0.2 to 0.1)	.28
Survival time	−0.4 (−0.7 to −0.1)	**.009**	−0.2 (−0.6 to 0.1)	.15
Radiation dose	−1.1 (−1.5 to −0.7)	**<.001**		
Sex				
Female	Reference		Reference	
Male	1.6 (−1.4 to 4.6)	.30	2.3 (−0.6 to 5.2)	.12
Education				
≤High school	Reference		Reference	
>High school	5.3 (2.5 to 8.1)	**<.001**	4.2 (1.5 to 6.9)	**.002**
Missing	3.0 (−1.3 to 7.3)	.17	2.8 (−1.4 to 7.0)	.20
Race				
Others	Reference			
White	1.3 (−3.1 to 5.7)	.56		
Missing	−0.1 (−11.7 to 11.5)	.99		
Primary site				
Tonsil, soft palate, and pharyngeal wall	Reference		Reference	
Base of tongue and GPS	−1.2(−3.4 to 1.0)	.28	−1.1 (−3.4 to 1.2)	.33
T classification				
1	Reference		Reference	
2	−1.8 (−4.2 to 0.6)	.14	−1.1 (−3.6 to 1.5)	.41
3	−6.9 (−10.1 to −3.6)	**<.001**	−3.3 (−6.8 to 0.3)	.07
4	−14.0 (−17.9 to −10.0)	**<.001**	−9.9 (−14.1 to −5.8)	**<.001**
Smoking				
Never	Reference		Reference	
Former	−2.4 (−4.6 to −0.1)	**.04**	−1.6 (−3.8 to 0.5)	.14
Current	−8.9 (−13.4 to −4.3)	**<.001**	−7.0 (−11.4 to −2.7)	**.001**
Solid food pre-Tx				
Yes	Reference		Reference	
No	−0.2 (−10.5 to 10.1)	.96	−2.1 (−12.0 to 7.8)	.68
Treatment group				
Single modality Tx.	Reference		Reference	
Multimodality Tx.	−5.1 (−7.4 to −2.8)	**<.001**	−2.7 (−5.4 to −0.1)	**.05**
Radiotherapy				
No	Reference			
Yes	−10.4 (−21.9 to 1.1)	**.08**		
Chemotherapy				
No	Reference			
Yes	−4.9 (−7.2 to −2.6)	**<.001**		

(Continues)

TABLE 2 (Continued)

Variables	Univariate analysis coefficient (95% CI)	*P*-value	Multivariate analysis coefficient (95% CI)	*P*-value
Surgery				
No	Reference			
Yes	3.5 (−3.2 to 10.1)	.31		
Neck dissection				
No	Reference			
Yes	−0.9 (−3.4 to 1.6)	.50		
RT schedule				
Standard fractionation	Reference			
Accelerated	−6.9 (−10.4 to −3.4)	**<.001**		
Missing	−2.0 (−13.5 to 9.4)	.73		
RT type				
3D conformal	Reference		Reference	
IMRT-SF	11.8 (7.2 to 16.4)	**<.001**	8.1 (3.1 to 13.1)	**.002**
IMRT-WF	6.9 (−0.2 to 14.0)	**.06**	5.9 (−1.3 to 13.0)	.11
Proton	19.7 (11.7 to 27.7)	**<.001**	14.4 (6.0 to 22.9)	**.001**
IMRT-ipsilateral	17.1 (11.6 to 22.5)	***<.001***	9.9 (3.8 to 16.0)	**.002**
Stricture/dilation				
No	Reference			
Yes	−19.0 (−27.1 to −10.9)	**<.001**	−13.1 (−21.1 to −5.2)	**.001**

Notes: Reported *P* values in bold are values which are statistically significant in uni-variate analysis ($P < .25$) and multivariate analysis ($P < .05$) respectively. Statistical significance: *P*-value <.25 after univariate analysis; *P*-value <.05 after multivariate analysis.

Abbreviations: 3D conformal, three-dimensional (3D) conformal radiation therapy; CI, confidence interval; IMRT-SF, intensity-modulated radiation therapy with split field technique; IMRT-WF, intensity-modulated radiation therapy with whole field technique; LCNP, lower cranial neuropathy; MDADI, MD Anderson Dysphagia Inventory; pre-Tx, pretreatment; rho, Spearman rho; RT, radiotherapy; T, tumor.

[a]Missing values imputed.

combination with systemic treatment, 2 (5.6%) had surgery to the primary OPC tumor, 9 (25.0%) had neck dissection, and 23 (63.9%) were treated with IMRT-SF. Median time from LCNP onset to survey completion was 2.7 (range, 0.1-14.0) years.

Among patients without LCNP, composite MDADI scores had a mean of 80.1 ± 16.3 and median of 83.2, (range, 26.3-100), whereas LCNP cases had a mean of 68.0 ± 17.4 and median of 67.4 (range, 36.8-97.9). Also, among LCNP cases, CN XII palsy was most common and present in 86.1% (31/36). Isolated IX nerve palsy was difficult to ascertain, rather those with pharyngeal paresis were included as CN IX/X nerve palsy and 50% (18/36) of LCNP cases had CN IX or/and CN X neuropathy. Polyneuropathy was also present among 36.1% (13/36) of LCNP cases.

3.3 | MDADI composite scores

The MDADI composite scores reported by OPC survivors are summarized in Table 1. Lowest (worse) scores were reported by patients with T4 tumors (68.7 ± 18.9) and those treated with three-dimensional conformal RT technique (67.8 ± 20.4), whereas the highest (better) scores were reported by patients who did not receive RT (89.9 ± 9.4) and those treated with proton therapy (87.5 ± 11.3). Unadjusted univariate analyses demonstrated that survival time, education, T-classification, smoking, therapeutic modality, chemotherapy, RT dose, fractionation, and modality, and stricture had significant associations ($P < .25$) with composite MDADI scores. Composite MDADI scores were also significantly different based on patient-reported diet levels at the time of survey ($P < .001$).

Late LCNP cases reported significantly worse composite MDADI scores compared to those without LCNP (LCNP: 68.0 ± 17.4, 95% CI, 62.1-73.9 vs no LCNP: 80.2 ± 16.3, 95% CI, 79.1-81.3; $P < .001$). Multiple linear regression identified that late LCNP was significantly associated with lower (worse) composite MDADI scores (coefficient, −6.7; 95% CI, −12.0 to −1.3; *P*-value = .02; adjusted R^2, 0.13) after adjusting for age, survival time, sex, education, subsite,

T-stage, smoking, therapeutic modality, RT modality, solid food diet before treatment, and stricture. These results have been summarized in Table 2. When MDADI composite scores were categorized, 38.9% (14/36) of LCNP cases had poor swallowing scores (MDADI<60) in comparison to 12.9% (110/853) of patients without LCNP (odds ratio [OR] = 4.3; 95% CI, 2.2-8.6).

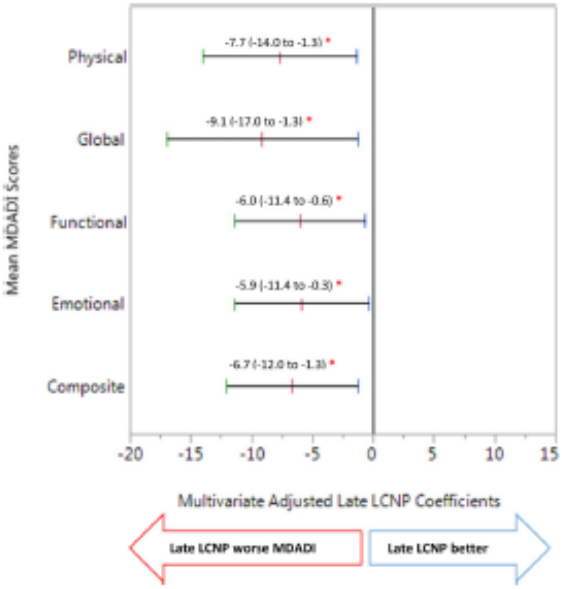

FIGURE 1 Multivariate adjusted coefficients for late LCNP and MDADI scores. Multiple linear regression models adjusted for age, survival time, sex, education, subsite, T-stage, smoking, therapeutic modality, RT modality, solid food diet prior to treatment, and stricture. The regression model for global scores adjusted for an additional variable, neck dissection. LCNP, lower cranial neuropathy; MDADI, MD Anderson Dysphagia Inventory [Color figure can be viewed at wileyonlinelibrary.com]

3.4 | MDADI subscale scores

Late LCNP cases reported significantly lower (worse) scores on all MDADI subscales and on global MDADI scores. The associations remained significant in multiple linear regression models after adjusting for significant covariates (Figure 1). These results are summarized in Table 3. Additionally, global MDADI scores were also highly correlated with composite MDADI scores (Spearman's rho = 0.8, $P < .001$).

We also compared composite MDADI scores among patients without LCNP, LCNP IX/X only, LCNP XII only,

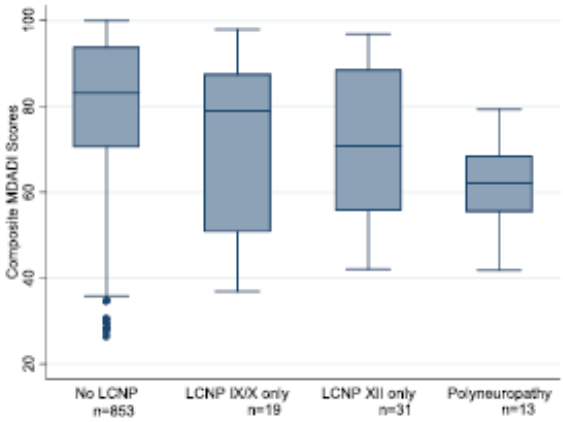

FIGURE 2 Composite MDADI scores by Type of LCNP. Composite MDADI scores among patients without LCNP, LCNP IX/X only, LCNP XII only, and polyneuropathy. Polyneuropathy included LCNP cases with both CN XII and CN IX/X palsy. Patients without LCNP had higher (better) scores than LCNP cases, but lowest (worst) mean scores and least variability of scores were reported by LCNP cases with polyneuropathy. IX/X, glossopharyngeal or vagus nerve; XII, hypoglossal nerve; LCNP, lower cranial neuropathy; MDADI, MD Anderson Dysphagia Inventory [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 MDADI scores by late LCNP status (n = 889)

	Mean ± SD (95% CI)			Analysis coefficient (95% CI)		
MDADI scores[a]	Patients with LCNP (n = 36)	Patients without LCNP (n = 853)	*P*-value	Univariate (95% CI)	Multivariate (95% CI)	*P*-value
Composite	68.0 ± 17.4 (62.1 to 73.9)	80.2 ± 16.3 (79.1 to 81.3)	<.001	−12.2 (−17.6 to −6.7)	- 6.7 (−12.0 to −1.3)	.02
Global	65.1 ± 28.9 (55.3 to 74.8)	81.3 ± 23.2 (79.8 to 82.9)	<.001	−16.3 (−24.1 to −8.4)	−9.1 (−17.0 to −1.3)	.02
Emotional	70.1 ± 19.2 (63.6 to 76.5)	81.0 ± 16.4 (79.9 to 82.1)	<.001	−10.9 (−16.5 to −5.4)	−5.9 (−11.4 to −0.3)	.04
Physical	62.5 ± 18.0 (56.4 to 68.6)	75.9 ± 19.0 (74.6 to 77.2)	<.001	−13.5 (−19.8 to −7.1)	−7.7 (−14.0 to −1.3)	.02
Functional	74.4 ± 20.7 (67.4 to 81.4)	86.0 ± 16.1 (84.9 to 87.1)	<.001	−11.6 (−17.1 to −6.1)	−6.0 (−11.4 to −0.6)	.03

Multiple linear regression models adjusted covariates including, age, survival time, sex, education, subsite, T-stage, smoking, therapeutic modality, RT modality, solid food diet prior to treatment, and stricture. The regression model for global scores adjusted for an additional variable, neck dissection.

Abbreviations: CI, confidence interval; LCNP, lower cranial neuropathy; MDADI, MD Anderson Dysphagia Inventory.

[a]Missing values imputed.

TABLE 4 Functional status metrics by late LCNP status (n = 889)

Variables	Patients with LCNP, n (%)	Patients without LCNP, n (%)	*P*-value	Crude OR (95% CI)
Current feeding tube			<.001	
No	25 (71.4)	819 (98.1)		Reference
Yes	10 (28.6)	16 (1.9)		20.5 (8.6 to 48.9)
Normalcy diet			<.001	
Full Diet no restrictions	6 (18.2)	357 (43.7)		Reference
Full Diet with liquid assist	8 (24.2)	315 (38.5)		3.5 (1.5 to 8.3)
Solid food but avoid some hard to eat foods	10 (30.3)	96 (11.7)		
Soft chewable foods	2 (6.1)	33 (4.0)		
Non-chewable or pureed foods	1 (3.0)	3 (0.4)		
Warm and cold liquids	2 (6.1)	10 (1.2)		
Not eat or drink anything by mouth	4 (12.1)	4 (0.5)		
Public eating			<.001	
No restriction of place/food/companion	8 (25.8)	582 (70.3)		Reference
No restriction of place, but restrict diet in public	14 (45.2)	191 (23.1)		6.8 (3.1 to 15.1)
In the presence of selected person in selected places	7 (22.6)	36 (4.3)		
Only eat at home with selected persons	1 (3.2)	14 (1.7)		
Always eat alone	1 (3.2)	5 (0.6)		
Aspiration pneumonia			<.001	
No	21 (67.7)	741 (98.0)		Reference
Yes	10 (32.3)	15 (2.0)		23.5 (9.6 to 57.6)
Weight loss			.05	
No	4 (11.4)	202 (24.4)		Reference
Yes	31 (88.6)	626 (75.6)		2.5 (0.9 to 6.9)
Change in weight: mean, median (range)[a]	22.9, 16.8(14.2,87.8)	13.3, 9.4(103.1164.6)	.005	
%change in weight: mean ± SD, median (range)[b]	11.7 ± 10.4, 9.9 (−7.9,33.4)	6.0 ± 10.7, 5.1(−96.4, 43.4)	.002	
Understandability of speech			<.001	
Always understandable	6 (17.6)	528 (63.3)		Reference
Understandable most of the time	16 (47.1)	269 (32.3)		8.1 (3.4 to 19.2)
Usually understandable	3 (8.8)	19 (2.3)		
Difficult to understand	8 (23.5)	17 (2.0)		
Never understandable	1 (2.9)	1 (0.1)		
Tracheostomy			.001	
No	31 (91.2)	834 (99.6)		Reference
Yes	3 (8.8)	3 (0.4)		26.9(6.0 to 121.7)
Dilation/stricture			<.001	
No	31 (86.11)	842 (98.71)		Reference
Yes	5 (13.89)	11 (1.29)		12.3 (4.2 to 36.3)

P-values estimated by Fishers Exact Test. [a, b] *P*-values estimated by Wilcoxon Rank-Sum Test. Odds ratio for normalcy of diet calculated with full diet no restrictions as reference category and all other categories collapsed. Odds ratio for public eating calculated with no restriction of place/food/companion as reference category and all other categories collapsed. Odds ratio for understandability of speech calculated with always understandable as reference category and all other categories collapsed. Abbreviations: CI, confidence interval; LCNP, lower cranial neuropathy; OR, odds ratio.

and polyneuropathy, which are illustrated in Figure 2. Lowest (worst) mean scores and least variability of scores were reported by LCNP cases with polyneuropathy, which might suggest worsening of swallowing function with more CN injury indicating a dose-response relationship. Of great concern was that LCNP cases with polyneuropathy reported a drop of 18.2 in mean scores in comparison to patients without late LCNP with about half of them reporting poor composite scores indicating a clinically meaningful reduction in MDADI scores, but this was not statistically significant likely due to small numbers in subgroup analyses by particular nerves.

Sensitivity analysis was also conducted including RT dose and HPV status in final models for all MDADI scores, and as the effect estimates for late LCNP remained unchanged, these variables were excluded in favor of a more parsimonious model. Results are presented in Tables S2 and S3.

3.5 | Functional status metrics

LCNP status was also significantly associated with ($P \leq .001$) worse functional outcomes and health metrics reported by the patient or chart abstracted at the time of survey as detailed in Table 4. LCNP cases were more likely to have a current feeding tube (OR = 20.5; 95% CI, 8.6-48.9), history of aspiration pneumonia (OR = 23.5; 95% CI, 9.6-57.6), tracheostomy (OR = 26.9; 95% CI, 6.0-121.7), and were more likely to have undergone dilation for stricture (OR = 12.3; 95% CI, 4.2-36.3) than patients without LCNP. LCNP cases were also more likely to report restricted oral diets at the time of survey (LCNP: OR = 3.5; 95% CI, 1.5-8.3). Mean percentage of reported weight loss from baseline weight to weight at the time of survey was also significantly higher among patients with LCNP than patients without LCNP (LCNP: mean 11.7% vs no LCNP: 6.0%, $P = .002$).

4 | DISCUSSION

Late LCNP is rare with reports of incidence ranging from 3.7% to 25.6%. However, another cohort study reported 14% incidence of LCNP in 10-year survivors of HNC, suggesting that risk increases over time.[35] Our previous report confirmed high symptom burden among OPC survivors who developed LCNP, with largest effect sizes (coefficient, 2.3 of 10) on swallowing-related symptoms.[25] This phenomenon is also clinically recognized, but previous work has failed to quantify the impact of LCNP on individual swallowing domains and functional metrics. This large single-center cross-sectional survivorship survey study among OPC survivors provides a comprehensive evaluation and found significant associations with moderate effect size between late LCNP and overall swallowing-related QOL, domain-specific swallowing function, as well as functional status metrics related to swallowing.

Overall, swallowing-related QOL among all 889 OPC respondents suggested most survivors perceived acceptable levels of functioning (as per composite MDADI means of 79.7 ± 16 and 55.2% of survivors reported composite scores ≥80), but the small group of survivors (n = 36) with late LCNP reported a clinically meaningful reduction of >10 points difference relative to survivors without LCNP in univariate analyses.[36] This meaningful reduction was observed for all summary and domain-specific MDADI scores. After multivariate adjustment for clinical covariates, on an average, composite MDADI scores were 6.7 points lower (worse) among late LCNP cases vs those without late LCNP. The adjusted R^2 demonstrated that late LCNP explained 13% of the variation in composite MDADI scores after accounting for the effect of other covariates, which according to Cohen's criteria is a moderate effect.[37] This moderate effect size is consistent with effect estimate for the impact of LCNP on patient-reported MDASI-HN swallowing/chewing symptoms (coefficient, 2.3 of 10) reported in an earlier study and may in part reflect the subjective nature of PROs that likely vary with individuals' overall contentment and satisfaction with life and functional abilities.[12,13,38]

Late LCNP was also significantly associated with all domain-specific MDADI subscale scores. Late LCNP cases experienced the greatest deterioration of physical subscale scores that represent patient perception of swallowing ability; LCNP explained 10% of the variation in this domain controlling for important confounders. Previous studies have also reported lowest MDADI scores on the physical subscale among patients with HNC.[10,36] Furthermore, among late LCNP cases, the least impact of nerve injury was on the emotional subscale scores. Emotional subscale scores reflect psychological response to diminished swallowing ability, and functional subscale scores reflect the impact of swallowing impairment on daily functioning and activities.[30] Previous studies among patients with HNC have reported the highest subscale scores in the functional domain and substantial recovery of emotional MDADI scores over time.[10,38] This may be indicative of adjustment and adaptation to a decline in swallowing function overtime.[38]

It is generally believed that PRO instruments may underestimate the prevalence of dysphagia.[39,40] For this reason, we also explored the relationship between LCNP with other functional status measures of swallowing ability. As expected, late LCNP status was also significantly associated with worse functional status metrics including current feeding tube status, normalcy of diet, public eating, self-reported

history of aspiration pneumonia, weight loss since diagnosis, understandability of speech, tracheostomy, and esophageal dilations due to the presence of stricture. Thereby, late LCNP was consistently associated with substantial functional morbidity among OPC survivors. These results are not surprising given the degree of swallowing dysfunction previously reported among long-term OPC survivors in earlier case reports, which suggested that treatment-related LCNP may play a major role in late RAD and precipitate delayed but extreme oropharyngeal impairment as recorded by MBS studies.[1,20,21] These observations also align to numerous reports of significant swallowing dysfunction caused by lower CN deficits among populations (in the absence of head and neck RT) due to traumatic injury, vascular causes, and infection, documented primarily in case reports.[41-45]

Approximately one-third (28.6%) of patients with late LCNP in our study reported having a feeding tube at the time of survey. High rates of gastrostomy dependence among LCNP cases again support a high prevalence of dysphagia in this population. In an earlier study among patients with OPC with advanced stage treated with concurrent RT and chemotherapy, feeding tube use had the maximum impact on QOL (−30 points compared to controls) evaluated by SF36 and HNQOL.[46] Late LCNP cases also had significantly higher rates of aspiration pneumonia (32.3% LCNP vs 2.0% no LCNP), which support association with high dysphagia-related morbidity. Similarly, a study using SEER data among patients with HNC treated with chemoradiation reported 23.8% 5-year rates of aspiration pneumonia.[47] Additionally, as late LCNP occurs many years after treatment with a tendency for silent aspiration, symptoms of LCNP may be missed due to lack of adequate surveillance among OPC survivors. This may further enhance the risk of aspiration pneumonia and contribute to debilitating functional morbidity with increased feeding tube dependence, hospitalization, weight loss, and life-threatening complications.

Overall, late LCNP with accompanying dysphagia is a clinical condition of great concern as it does not typically respond well to treatment. With progressive long-term functional decline with aspiration and recurring aspiration-pneumonia, long-standing feeding tube dependence and elective laryngectomy may be required.[1,16,20,21,48] Therefore, risk reduction and management of late effects like LCNP, late-RAD, and associated functional toxicities need to be prioritized in contemporary OPC treatment and management. That is, providers should be alerted that survivors found to have a new IX, X, or XII nerve palsy in routine surveillance likely merit return to the speech pathologist for instrumental swallowing evaluation, counseling, and therapy as well as interdisciplinary consideration of risk reduction strategies for aspiration that preserve oral intake but diminish pneumonia risk. This research may also help to provide benchmarks for novel interventions and surveillance efforts. Routine PRO administration coupled with instrumental examination using fiberoptic endoscopic evaluation of swallowing and MBS may also help identify patients in need of more intense, targeted therapy.[48] Multidisciplinary supportive treatment including routine swallowing and speech assessment, risk-based treatment planning, swallowing and nutritional therapy, counseling to improve coping skills, and guidance in effective meal preparation may help to attenuate the impact of late LCNP-associated swallowing impairment, diminish life-threatening complications, and enhance swallowing-related QOL.[48]

This study is the first to quantify the association between late LCNP and swallowing-related QOL in a study population of almost 900 OPC survivors finding the hypothesized significant associations. However, there are limitations to acknowledge. Complete case analysis was not feasible as 126 of 889 (14.2%) respondents returned surveys with skipped or missing MDADI items. Thus, complete case analysis would have contributed to attrition of approximately one-third of LCNP cases that would have substantially diminished power in our study that focused on a rare event like LCNP. Therefore, we imputed missing MDADI scores for 27% (10/36) of the patients with late LCNP. The validity of our imputed results is supported by sensitivity analyses finding similar effect size estimates using imputed vs non-imputed data (Table S1). Imputed composite MDADI scores and nonimputed composite MDADI scores by LCNP status have also been presented as Figure S1, and their distribution is more or less similar with less variation among LCNP cases which was expected given imputation was conducted using scores from missing items only. Post-imputation, unadjusted means and accompanying standard deviations of composite, global, emotional, physical, and functional scores were similar to estimates of means and standard deviations of an earlier study among patients with HNC.[36] Furthermore, consistency of results with previous literature was demonstrated as survivors in our study treated with multimodality treatment vs single modality, those who did not receive chemotherapy vs those who did, those treated with accelerated RT vs standard fractionation, those who received conventional 3D conformal RT vs IMRT/proton therapy and current smokers vs never smokers reported significantly worse composite scores, and those with early stage vs more advanced stages reported significant positive trend for better swallowing scores[5,8-10,31,48] These results indicate that our primary outcome variable, composite MDADI, consistently performed well and showed expected variation across clinical and tumor-related factors. Large and statistically significant differences in functional metrics by LCNP status also support our findings of high functional morbidity among

LCNP cases. Our study results also support a previous survey analysis in this study population, which used complete case analysis of MDASI-HN, with low attrition of cases due to missing data and demonstrated a strong impact of LCNP on swallowing, choking, mucus, fatigue, and voice symptoms.[25]

Our study may also be subject to limitations inherent to cross-sectional PRO survey collection including survival bias, which we tried control by including survival time in all our multivariate models. MDADI and PSS-HN scores prior to late LCNP diagnosis were not available to fully control for subtle differences in baseline function. Rather, oral diet at baseline was included as a covariate in analysis; among LCNP cases, all but one could eat a solid food diet pretreatment suggesting functional baseline swallow in the vast majority of LCNP cases. Furthermore, chart abstraction of the LCNP case status precluded the ability to identify sensory deficits associated with LCNP as clinical documentation typically focused on motor deficits. We suspect that inclusion of sensory deficits of late LCNP might have led to higher number of late LCNP cases detected. Several factors may limit generalizability of these results. Given that few patients in our study received definitive surgery, our study results may have less application to patients with OPC treated with primary surgery. Our study population was treated at a single tertiary cancer care institution, and thus demographic characteristics may limit generalizability to other more varied populations. However, the study population demographics are similar to those expected among patients with OPC across the United States. Finally, it was beyond the scope of this work to identify predictors of late LCNP as would be necessary avoid this severe late functional toxicity. However, a recent cohort study among 10-year survivors identified an association between primary tumor site, RT dose, chemotherapy, and post-RT neck dissection as clinical predictors of cranial neuropathy on univariate analysis.[35] Predictors of LCNP will be addressed in future work by the authors, as well.

5 | CONCLUSIONS

In this large cross-sectional analysis, OPC survivors with late LCNP had significantly lower (worse) swallow-related QOL as per MDADI scores with significantly higher likelihood of adverse functional status metrics like dietary restrictions, nutritional impairment, weight-loss, and decline in public food consumption with possible consequences of social isolation, aspiration pneumonia, long-term feeding tube dependence, and tracheostomy. These data support and quantify the detrimental relationship of late LCNP with swallowing-related measures.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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