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Incidence and outcomes of radiation-induced late cranial neuropathy in 10-year survivors of head and neck cancer

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ABSTRACT

Objectives: To characterize the late cranial neuropathy among 10-year survivors of head and neck cancer treatment.

Materials and methods: We retrospectively evaluated patients treated with curative-intent radiation for HNC between 1990 and 2005 at a single institution with systematic multidisciplinary follow-up ≥ 10 years. New findings of CNP were considered radiation-induced when examination, imaging and/or biopsy did not demonstrate a structural or malignant cause. Cox proportional hazards modeling was used for univariable analysis (UVA) and multivariable analysis (MVA) for time to CNP after completion of radiation.

Results: We identified 112 patients with no evidence of disease and follow-up ≥ 10 years (median 12.2). Sixteen (14%) patients developed at least one CNP. The median time to CNP was 7.7 years (range 0.6–10.6 years). Most common was CN XII deficit in eight patients (7%), followed by CN X deficit in seven patients (6%). Others included CN V deficit in three, and CN XI deficit in two. Eight of the thirteen patients with a CN X and/or CN XII deficit required a permanent gastrostomy tube.

On UVA, site of primary disease, post-radiation neck dissection, chemotherapy, and radiation dose were significantly associated with increased risk of CNP.

Conclusion: Iatrogenic CNP may develop years after head and neck cancer treatment and often leads to swallowing dysfunction. Long-term follow up is essential for these patients receiving head and neck radiation.

Introduction

Cranial nerves are generally considered radio-resistant. [1] However, radiation-induced cranial nerve palsy (CNP) has been reported as early as the 1960 s-1970 s. [2–5] Since then, many small cohort studies and case reports have been published on radiation-induced CNP in patients with head and neck cancer (HNC); most focus on patients with nasopharyngeal cancer [6–9]. The literature on radiation-induced CNP in patients treated for non-nasopharyngeal cancer is growing, but limited [10].

Radiation-induced CNP can significantly affect the quality of life of HNC survivors. Patients with lower CNP involving CN IX, X, XI, and XII can be devastating because these nerves are involved in the execution of crucial physiological functions including tasting, swallowing, and speech [11]. Once, HNC was a disease of the elderly associated with tobacco/ethanol abuse and comorbidity [12]. Due to changing demographics with increasing human papillomavirus (HPV)-associated oropharyngeal cancer [13–15], patients with HNC are generally younger and living longer after treatment than they once did. Because the latency of radiation-induced CNP in patients treated for HNC can be many years [2,7,8,16,17], it is most likely to afflict patients with a high likelihood of long term cure. Hence, it is important to characterize this "late" toxicity in long term survivors of HNC after radiation therapy.

Our tertiary care center practices systematic multidisciplinary (head and neck surgical oncology and radiation oncology) follow-up for all HNC survivors treated with radiation, regardless of whether an operation was performed. Patients are never discharged – follow-up is scheduled in perpetuity. This retrospective study aims to characterize

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the late toxicity of CNP in 10-year HNC survivors.

Materials and methods

We queried our institutional cancer registry for HNC patients treated with external beam radiation (EBRT) from 1990 to 2005 with systematic multidisciplinary follow up for at least 10 years. Those developing recurrence and/or second primary head and neck cancers were excluded as were patients with connective tissue disorders. HPV and/or p16 testing was not performed at our institution for the time period 1990–2005. At our institution most oral cavity cancers were managed with surgery followed by adjuvant therapy according to accepted indications for post-operative therapy. [18,19] Most oropharyngeal cancers were managed with primary (chemo)radiation. Laryngeal and hypopharyngeal tumors were managed with surgery and/or (chemo)radiation based upon multidisciplinary tumor board discussions and protocol criteria. Salivary gland and paranasal sinus tumors were treated with surgery followed by adjuvant (chemo)radiation.

After completion of (chemo)radiation, all well patients were recommended a standardized institutional alternating follow-up schedule with a head and neck surgeon and a radiation oncologist: every 2 months for the first year, every 3 months for years 2–3, every 4 months for years 4–5, and biannually thereafter (one visit with each provider separated by 6 months).

The medical records, clinic notes, referral records and subsequent evaluations were reviewed retrospectively for each included patient. Radiation-induced CNP was diagnosed by exclusion. Patients with new CNP of any nerve appreciated on clinical examination were addressed with imaging and further measures (e.g. biopsy) as necessary. When evaluation did not identify a structural or malignant cause of a new CNP that developed after the acute toxicity of treatment had resolved (generally 3 months after the completion of radiation), it was considered radiation-induced. Neurology consultation and/or electromyography (EMG) confirmation of nerve injury were not regularly undertaken. CNPs diagnosed both prior to or beyond 10 years of follow-up were considered events.

Multiple pre-treatment and treatment-related factors held potentially to predispose patients to radiation-induced CNP were included in statistical analysis. These included site of primary disease (pharynx/larynx vs others), 7th ed T-category (T3-T4 vs T1-T2), 7th ed N-category (N2-N3 vs N0-N1), primary surgery before radiation (yes vs no), post-radiation neck dissection as these neck dissections are typically more comprehensive and may cause more fibrosis [20] (yes vs no), chemotherapy (yes vs no), and radiation dose (continuous variable). Documented cranial neuropathy prior to treatment (either malignant or unrelated to index cancer) was not considered an event, although subsequent development of a cranial nerve injury (appreciated after treatment) in such a patient was considered a radiation-induced late CNP in absence of a different identifiable etiology. Cox proportional hazards modeling was used for univariable analysis (UVA) for time to CNP after completion of radiation. All hypothesis tests were 2-sided with a type 1 error of 5%. Given the small number of events and high correlation among statistically significant predictors of CNP on univariable analysis a multivariable analysis was not performed. In view of the low event rate and heterogeneous patient population certain variables of interest were dichotomized.

Results

We identified 1100 consecutive HNC patients treated with EBRT as a part of curative-intent regimen at our institution from 1990 to 2005. One-hundred-twelve patients met inclusion criteria (CONSORT diagram Fig. 1) with a median follow-up of 12.2 years (10.0–22.8 years). The primary tumor sites were pharynx (n = 47, 42%), oral cavity (n = 38, 34%), larynx (n = 15, 13%), and other (n = 12, 11%). Consistent with practice patterns, almost half of the patients received radiation after an operation (n = 49, 44%) and almost half of those managed with definitive radiation underwent a post-treatment neck dissection according to contemporary practice patterns (n = 27, 42% of those managed with primary RT). Almost half of the patients (n = 53, 47%) received chemotherapy. Among those treated with chemotherapy, the overwhelming majority (n = 45) received concurrent chemotherapy with radiation, most commonly cisplatin as a single agent (n = 30) or in combination with paclitaxel or 5FU (n = 11). Nearly all patients (96%) were treated with 2D radiation planning with a median prescribed RT dose of 70 Gy (50–75 Gy) to the isocenter. Eight (7%) patients were treated with an accelerated regimen, of which 1 developed a CNP. A majority of patients (n = 75, 67%) had a history of smoking cigarettes, with a median of 30 (range 0–150) pack-years. Of the smokers, 67 (89%) quit smoking either before starting RT or within six months of its completion (Table 1).

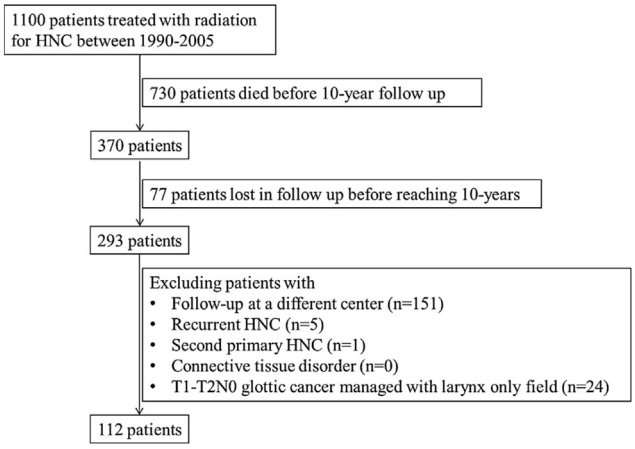

Fig. 1. Patient selection for this retrospective study.

Sixteen (14%) patients were found to have at least one radiation-induced CNP, including five with two separate CNPs, and two with three separate CNPs (Table 2). The median time to first documented radiation-induced CNP was 7.7 years (range 0.6–10.6 years); the majority occurred between five and 11 years (Fig. 2). The most common CNP was a CN XII deficit in eight patients (7%) at a median time of 8.4 years after completion of radiotherapy, appreciated as a flaccid, atrophied hemi-tongue with ipsilateral deviation on protrusion. A cranial nerve X deficit was appreciated in a similar frequency of patients (n = 7, 6%) at a median 8.5 years after completion of radiotherapy, most commonly presenting as vocal cord paralysis. Three patients were diagnosed with a cranial nerve injury in significantly less time than the median – patients 1, 2, and 16. Two of these patients had post-radiation neck dissections that specifically documented manipulation but preservation of the cranial nerve that soon thereafter exhibited dysfunction (patients 1 and 16). The third patient had a maxillectomy and soon thereafter exhibited V2/V3 numbness out of proportion to what would be expected from the operation. All documented cranial neuropathy was appreciated in CN V, CNX, CNXI, and CNXII.

Among the 13 patients who developed radiation-induced CNP of CN X and/or XII, seven required a permanent (life-long) gastrostomy tube and two have expired from aspiration pneumonia.

In UVA, site of primary tumor (pharynx/larynx vs others) with hazard ratio (HR) = 6.2 (95% CI 1.4–27.3) and p = 0.02, post-RT neck dissection with HR = 2.9 (95% CI 1.1–7.8) and p = 0.04, chemotherapy with HR = 5.4 (95% CI 1.5–18.9) and p = 0.01, RT dose with HR 1.2 (95% 1.0–1.3) and p = 0.02 showed significant association with increased risk of radiation-induced CNP. (Table 3, Kaplan Meier curves in supplementary Figs. 1A–C).

Table 1
Baseline patient characteristics.

	All	LCNP	Pharynx				Larynx	Oral Cavity	Other
			All	Oropharynx	Nasopharynx	Hypopharynx			
	(n = 112)	(n, %)	(n = 47)	(n = 39)	(n = 6)	(n = 2)	(n = 15)	(n = 38)	(n = 12)
Age (median, range)	54 (18–83)	9 (16%)*	54 (19–83)	54 (41–76)	54 (19–61)	71.7 (60–83)	56 (46–69)	53 (32–83)	55 (18–76)
Follow-up (yr) (median, range)	12.2 (10.0–22.8)	11.5 (10.1–22.8)	11.8 (10.0–21.0)	11.5 (10.0–17.0)	13.9 (10.6–21.0)	11 (10–12.1)	14.5 (10.3–18.7)	13.7 (10.2–22.8)	11.2 (10.2–19.3)
LCNP (n, %)	16 (14%)		10 (21%)	9 (23%)	1 (17%)	0 (0%)	4 (27%)	2 (5%)	0 (0%)
Smokers (%)	80 (71%)	12 (15%)	29 (62%)	29 (74%)	4 (67%)	1 (50%)	15 (100%)	26 (68%)	5 (42%)
Pack-Year [PY] (median, range)	30 (0–150)	8 (14%)^	20 (0–80)	20 (0–80)	20 (0–45)	30 (0–60)	45 (20–150)	30 (0–100)	0 (0–50)
T3-T4 disease	57 (51%)	9 (16%)	15 (32%)	12 (31%)	2 (33%)	1 (50%)	11 (73%)	24 (63%)	7 (58%)
N2-N3 disease	52 (46%)	10 (19%)	31 (66%)	25 (64%)	5 (83%)	1 (50%)	8 (53%)	9 (24%)	4 (33%)
Stage IV disease	69 (62%)	11 (16%)	30 (64%)	25 (64%)	5 (83%)	2 (100%)	8 (53%)	26 (68%)	5 (42%)
Surgery before RT (n, %)	49 (44%)	4 (8%)	5 (11%)	4 (10%)	0 (0%)	1 (50%)	1 (7%)	32 (84%)	11 (92%)
Post-RT neck dissection (n, %)	27 (24%)	7 (27%)	17 (36%)	15 (38%)	0 (0%)	1 (50%)	6 (40%)	4 (11%)	0 (0%)
Chemotherapy	53 (47%)	13 (25%)	35 (74%)	27 (69%)	6 (100%)	2 (100%)	11 (73%)	5 (13%)	2 (17%)
Concurrent	45 (85%)	11 (25%)	32 (91%)	24 (89%)	6 (100%)	2 (100%)	6 (55%)	5 (100%)	2 (100%)
Sequential	8 (15%)	2 (25%)	3 (9%)	3 (11%)	0 (0%)	0 (0%)	5 (45%)	0	0 (0%)
RT dose, median (range)	70 (50–75)	70 (60–72)	70 (60–75)	70 (60–74)	70 (68–70)	70 (N/A)	70 (60–74)	60 (50–70)	60 (60–70)

Abbreviation: RT: radiation, LCNP: late cranial neuropathy

* Number and percentage reports LCNP rate for patients with age greater than the median.

^ Number and percentage reports LCNP rate for patients with smoking PY greater than the median.

Discussion

Radiation-induced cranial nerve palsy among head and neck cancer survivors has been sporadically reported for decades. Lower cranial nerve palsy (CN IX, X, XI, XII) can particularly affect patient's quality of life because these nerves are involved in critical physiological functions including tasting, swallowing, breathing and speaking [11] and dysfunction can result in fatal complications [21]. In the United States patients are increasingly receiving a head and neck cancer diagnosis at a younger age and living longer [13,15], so better understanding of this late toxicity is needed for appropriate management of long-term HNC patient survivorship.

In this study, the most commonly observed radiation-induced CNP was CN XII, followed by CN X, consistent with other recent studies [6,8,9]. On univariable analysis treatment intensification with concurrent chemotherapy and/or increased radiation dose and/or the manipulation of CN X, XI, and XII in a post-radiation neck dissection increased the incidence of LCNP as did a pharyngeal/laryngeal primary tumor site. While post-radiation neck dissections are less common in 2019 than 1990–2005 [22,23] our series was not able to conclusively demonstrate if concurrent chemotherapy, increased radiation dose, or pharyngeal/laryngeal primary sites are independent risk factors for the phenomenon given that following more than 1000 patients in systematic fashion provided only 112 10-year survivors who met criteria for inclusion in the analysis. Although a prior study of radiation-induced CNP in patients with nasopharyngeal cancer by Luk and coworkers identified CNP at presentation as an independent prognostic factor for the development of radiation induced CNP in multivariable analysis, the fact that the CNP was present prior to radiation strongly suggests that radiation is not source of the condition. Otherwise, prior analyses similarly failed to identify factors (T category, N category, gender, age, radiotherapy technique and the use of chemotherapy) believed suggestive of LCNP [6]. Better understanding of what factors predict LCNP is needed.

The actual rate of radiation-induced CNP among HNC survivors is not clear. This is perhaps due to the rarity of durable follow-up with attention to CN dysfunction and the heterogeneity of subjects and treatment technique included in the limited studies available. Three studies of some 7000 patients treated with a variety of fraction sizes and total doses with median follow-up of less than 10 years showed rates of CNP ranging from one to five percent [6,24,25]. In contrast a recent study reported an astonishingly high rate of CNP in 20.7% of 323 patients with nasopharyngeal cancer after a first course of radiation therapy between 1994 and 2006 using megavolt therapy using a linear accelerator and standard fractionation [9]. Unfortunately it is uncertain how many of these patients had cranial neuropathy at diagnosis. Nasopharynx cancer patients largely comprised these analyses of CNP, probably due a large population of patients with cured locally advanced disease and also to a belief that CNP was only common in survivors treated with high dose volumes to the skull base.

In the current study radiation-induced CNP developed in 14% of patients, which is higher than the rate of 1–5% in the limited prior literature. The rate of late CNP appreciated here may be due in part to the long median follow-up of 12.2 years and minimum follow up of at least 10 years and our inclusion of cases where LCNP was seemingly influenced by surgical manipulation. With the median time to develop a late CNP of 7.7 years other reports with shorter [6,25] or unreported [26] assessment would underestimate the frequency of the problem, or conversely our analysis could overstate the frequency by exclusively reporting the outcomes of patients with extremely long follow-up. It is noteworthy that the majority of patients in this series have oropharyngeal cancers, a disease that is increasing in incidence with high rates of survivorship. All cases of LCNP without a clear surgical contribution appeared more than 5 years after the completion of radiation – in our experience it is common for many providers to discharge patients from care at 5 years of survivorship. Our data suggests that policy is not advantageous for patients.

The development of radiation-induced CNP can create a great burden on the patient's quality of life and can be fatal. Among our 16 patients with radiation-induced CNP, half required the placement of permanent gastrostomy tube. For those 7 patients with a CN X deficit, a nerve which innervates the majority of the muscles of the larynx and pharynx [21], 5 (71%) required permanent gastrostomy tube. The timing of permanent gastrostomy tube placement varied with respect to the first documentation of CNP although two patients continued with oral nutrition for years prior to the placement of permanent

Table 2
Cases of patients with late toxicity of CNP.

Patient	Site	Stage and subsite	Treatment	CNP	Latency of CNP (Years)	Outcome
1	OPX	T3N3 Base of Tongue	70 Gy + cisplatin + bilateral post chemoRT neck dissection	Ipsilateral CN XI Contralateral CN XI	1 1	G-tube placed following mandibulectomy for ORN 8 years post RT
2	Oral cavity	T4N0 maxillary alveolus	Resection + post-op RT	Ipsilateral CN V	1.7	–
3	OPX	T3N1 Tonsil	70 Gy + cisplatin + post chemoRT neck dissection	Ipsilateral CN XII	5.9	–
4	Larynx	T3N0 glottic larynx	70 Gy + cisplatin	Ipsilateral CN X	6.3	G-tube placed 14 years after LCNP diagnosis
5	OPX	T2N2b Tonsil	Transoral resection + neck dissection + PORT to 66 Gy	Ipsilateral CN XII Contralateral CN XII Ipsilateral CN X	6.4 8.5 10.6	G-tube placed during adjuvant radiation and never removed
6	Larynx	T3N2b Suparglottic larynx	70 Gy + cisplatin + post chemoRT neck dissection	Ipsilateral CN X	6.5	–
7	OPX	T1N2b tonsil	70 Gy + cisplatin	Ipsilateral CN XII	7.4	–
8	OPX	T1N2b tonsil	Transoral resection + neck dissection + adjuvant chemoRT to 70 Gy	Ipsilateral CN XII	8.1	No G-tube but known aspirator. Currently tolerates nectar thick
9	Nasopharynx	T3N3 Nasopharynx	70 Gy + cisplatin + post chemoRT chemotherapy	Ipsilateral CN XII Contralateral CN XII Ipsilateral CN X	8.1 8.1 9.1	Deceased - aspiration pneumonia
10	Larynx	T3N2b Glottic larynx	Sequential chemotherapy → radiation to 70 Gy + post chemoRT neck dissection	Ipsilateral CN X Contralateral CN X	8.5 8.5	G-tube placed at time of bilateral CN X injury diagnosis
11	OPX	T1N1 tonsil	70 Gy + cisplatin	Ipsilateral CN XII	9	–
12	OPX	T1N2b Base of Tongue	70 Gy + cisplatin + post chemoRT neck dissection	Ipsilateral CN XII Ipsilateral CN XI	9.4 10.4	Deceased - aspiration pneumonia
13	OPX	T3N1 Tonsil	72 Gy + cisplatin	Ipsilateral CN X Contralateral CN X	10.3 10.3	G-tube placed 1.4 years prior to LCNP diagnosis
14	Oral cavity	T2N2b oral tongue	Resection + post-op RT to 60 Gy + cisplatin	Ipsilateral CN XII	9.5	–
15	OPX	T1N1 tonsil	Transoral resection + excisional biopsy + 70 Gy	Ipsilateral CN V	10.6	–
16	Larynx	T3N2b Glottic larynx	Sequential chemotherapy → radiation to 70 Gy + post chemoRT neck dissection	Ipsilateral CN X Contralateral CN XII	0.6 12.6	G-tube placed 9.9 years after X and 2.1 years before XII

Abbreviations: OPX, oropharynx; Gy, Gray; chemoRT, chemoradiation; RT , radiation; CN, cranial nerve; G-tube, gastrostomy tube.

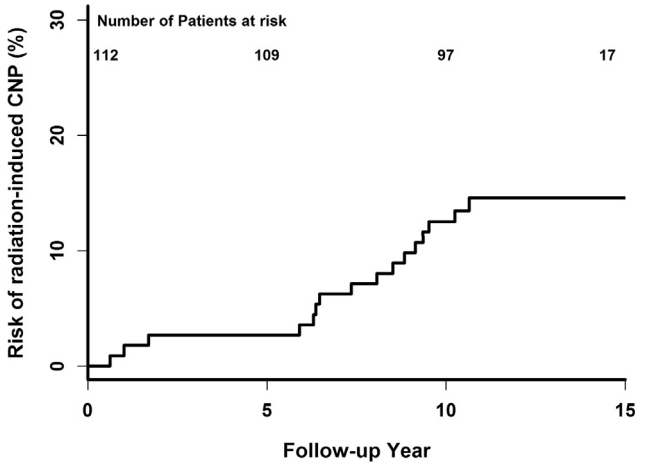

Fig. 2. Risk of radiation-induced CNP (patients censored at time of diagnosis of CNP).

Table 3
Univariate analyses for time to CNP after completion of radiation.

Variables	UVA		
	HR	95% CI	p
Pharynx/larynx vs other sites	6.2	1.4–27.3	0.02
Post-RT neck dissection (yes vs no)	2.9	1.1–7.8	0.04
Chemo (yes vs no)	5.4	1.5–18.9	0.01
RT dose (continuous)	1.2	1.0–1.3	0.02
T3-T4 vs T1-T2	1.3	0.5–3.6	0.57
N2-N3 vs N0-N1	2	0.7–5.6	0.17
Surgery before RT (yes vs no)	0.4	0.1–1.3	0.12

gastrostomy tube. Therefore, identifying patients with clinically silent radiation-induced CNP is important to prepare for future management. At our center patients with newly appreciated late cranial neuropathy are referred to speech language pathology (SLP) and physical therapy (PT). Our rehabilitation approach includes a thorough assessment in order to objectively define dysfunction(s), impairment(s), and goals of therapy. Due to the risk for "silent" dysphagia and aspiration in HNC survivors, and irrespective of the patient's perception of his or her swallowing function, an instrumental evaluation of swallowing is always a component of the assessment (i.e. Videofluoroscopic Swallowing Study or Flexible Endoscopic Evaluation of Swallowing). If there is CNP without significant functional impairment we will provide education and re-assess at a 6 month interval, or sooner if the patient becomes impaired. For patients with functional impairment, typical goals of therapy are to facilitate participation in activities of daily living, as defined by the patient, and to minimize lung injury associated with oral intake of food/liquids for as long as possible. Interventions tend to be supportive (e.g. compensatory strategies, behavioral modifications) and include significant education and counseling. Restorative approaches (e.g. therapeutic exercises, neuromuscular re-education) are also applied when optimizing unaffected muscle groups has the potential to improve functional capacity. Unfortunately, there is no proven method to reverse radiation-induced CNP, although a case was reported where a patient with chronic bilateral CN XII palsy secondary to chemoradiation therapy for nasopharyngeal cancer had significant improvement in swallowing and speech after high doses of intravenous methylprednisolone infusions [27].

This analysis is limited to patients treated between 1990 and 2005, an era when HNC management differed considerably from current approaches. Almost all patients in this series were treated with 2D radiotherapy based upon bony landmarks. Thus, the dose distribution of patients reported in this series was relatively homogenous. Most node positive patients received skull base irradiation to ensure adequate coverage of primary and nodal targets. With modern treatment planning and better understanding of the dose-volume relationships that predict acute and late toxicity [28], one might assume that the rate of late toxicity of CNP reported in the present series is greater than what may be anticipated in ten years for patients seen in the clinic today. However, the courses of CN X, XI, and CNXII in particular lie in areas often requiring high radiation doses because of nodal involvement in immediate proximity to the nerves themselves and these structures are not readily seen on imaging (and thus cannot be easily contoured and avoided). Hence while treatment planning has advanced in the past 25 years, it is prudent to assume that patients treated today may experience late CNP similar to that caused by large-field radiation 25 years ago. In fact, a recent study reported three of 59 oropharyngeal cancer survivors treated with modern intensity modulated radiation therapy developed lower CNP with a median follow-up of 5.7 years [29]. The correspondence between the findings of these two reports is striking. Hence, the results defined in this report warrant attention in the current era. In view of the courses of the cranial nerves and their inclusion in typical target volumes, it may be that the best way to limit late CNP would be through overall dose reduction in favorable patients [30].

The strengths of this study include the relatively large number of patients, remarkably long follow-up, and inclusion of different HNC primary sites (most of the relatively recent studies on this subject focus on nasopharyngeal cancer) [6–9]. The weaknesses of this study includes the inherent limitation of retrospective review which may lead to underreporting of LCNP, the heterogeneity of treatment regimens among patients, the preponderance of 2D conformal RT that is no longer widely utilized, and the decision to exclude patients with less than 10 years of follow-up.

Conclusion

Radiation-induced CNP can emerge many years after completion of radiation therapy for HNC, and can significantly affect patients' quality of life. Long-term follow up is essential to enhance their survivorship.

Key points

Question: What is the rate of late cranial neuropathy among 10-year survivors of head and neck cancer treatment and what are the predictors and consequences of this phenomenon?

Findings: The median time to develop late cranial neuropathy is 7.7 years and all cases of CN X and CN XII potentially leading to aspiration were diagnosed > 5 years after the completion of treatment. In total 2/16 patients with late cranial neuropathy have expired from aspiration pneumonia. Factor(s) independently predictive of late cranial neuropathy are unclear.

Meaning: Iatrogenic injury to peripheral cranial nerves can occur many years after the completion of head and neck cancer treatment with devastating consequences. Although predictors were unable to be identified in this analysis, better understanding of the risks of late cranial neuropathy will hopefully help improve survivorship.

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Declaration of Competing Interest

None declared

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.05.014.

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