

INTRODUCTION

- Primary nasopharynx (NPC) tumors** are the most common subsite associated with “frightening”, **irreversible late onset cranial neuropathy** (1,2); morbidity increases with concurrent chemotherapy (3)
- Surprisingly little detail** is known of the **survivorship course** of this rare, unfortunate subgroup of irradiated head and neck cancer (HNC) patients who also demonstrate **late onset progressive swallowing and speech toxicity**
- Functional impairments, such as **dysphagia, dysarthria, and trismus** in NPC, are particularly destructive to **quality of life (QoL)** (4)
- Large N, cross-sectional studies** of late toxicity (2,4) document wide-ranging symptoms, but **omit “trajectory traces”** characterising **evolving impairment**. Long intervals prior to symptom onset make prospective studies unrealistic. Thus, **features at onset, temporal evolution, and later sequelae** are all ill-defined (5)
- Discharge from active oncologic surveillance** after a defined period of disease-free survival, but prior to symptom onset, may **limit patient access to informed management** of late dysphagia (6)
- Natural history studies** of **degenerative processes** permit **chronological scrutiny** within a limited **window of opportunity**, and provide a critical baseline for evaluation of potential treatments (7)

- A **natural history study** of **dysphagia progression** and related toxicities, may yield “**red flags**” promoting **earlier patient identification, proactive management, and more impactful survivorship care**.

METHOD

Purpose: To systematically illustrate the time-course of **locoregional functional deterioration**, identifying **manifestations** associated with progressive dysphagia/dysarthria in NPC, mapping out **features at onset, sequential and synchronous developments, and health context**.

Study Design: Case series

Subjects: **Four young, previously healthy individuals** treated for **NPC** with concurrent **chemoradiation (CCRT)** in a tertiary care centre; referred to SLP for functional evaluation after **late onset dysphagia/dysarthria** (Table 1).

Each case had an **unrestricted diet** Functional Oral Intake Scale scores (FOIS=7) at **6 months post-treatment** (8). At variable time-points in their trajectories, each case underwent **treatment(s) for late toxicity, and/or dysphagia**, including HBOT (9), oral-pharyngeal and swallow-strengthening exercise protocols (10,11), Pentoclo (12), IV and high-dose steroids (13). None had achieved sustained benefit.

Data Analysis: **Detailed chart review**, collating **case history, serial functional data** (PRO’s and instrumental findings), and **interdisciplinary evaluations**. These targeted anatomical, neurogenic, and parallel health perturbations.

Graphic Data Display: A simple time-line of “**milestone**” events (“**chronoplot**”) was charted for each case, thereby annotating the **deterioration trajectory**. **Sequential events** were plotted (y axis) against **time** (x axis), from symptom onset to most recent event.

CORRESPONDENCE: Marlene Carno Jacobson, PhD
Speech-Language Pathology, Oncology Program
marlene.jacobson@sunnybrook.ca

Table 1: Patient, Tumour, and Treatment Details

	Case 1	Case 2	Case 3	Case 4
Age/Gender	52y/M/ 2013	51/M/ 2006	47/M/ 2014	39y/M/ 2004
Diagnosis (year)				
NPC Stage	T4N2c	T1N3	T4N2	T2N2
Treatment	70Gy/33 CCRT(Cis) Carbo + 5FU (x2)	70Gy/33 CCRT(Cis)	70Gy/33 CCRT(Cis) Cis. + 5FU	70Gy/33 CCRT(Cis) Carbo +5FU (x2)
All Treatment Completed	Feb. – Aug., 2013	Sept. – Nov., 2006	July – Dec., 2014	Jan. – May, 2015
Comorbidities at diagnosis	GERD, Barrett’s, asthma, arthritis. Sleep apnea	Nil Former smoker	Nil Former smoker	Nil
Symptom Onset	3.5y	4.5 y	2.25y	1.5y
Total follow-up	8y	14.5y	6.5 y	14.5y

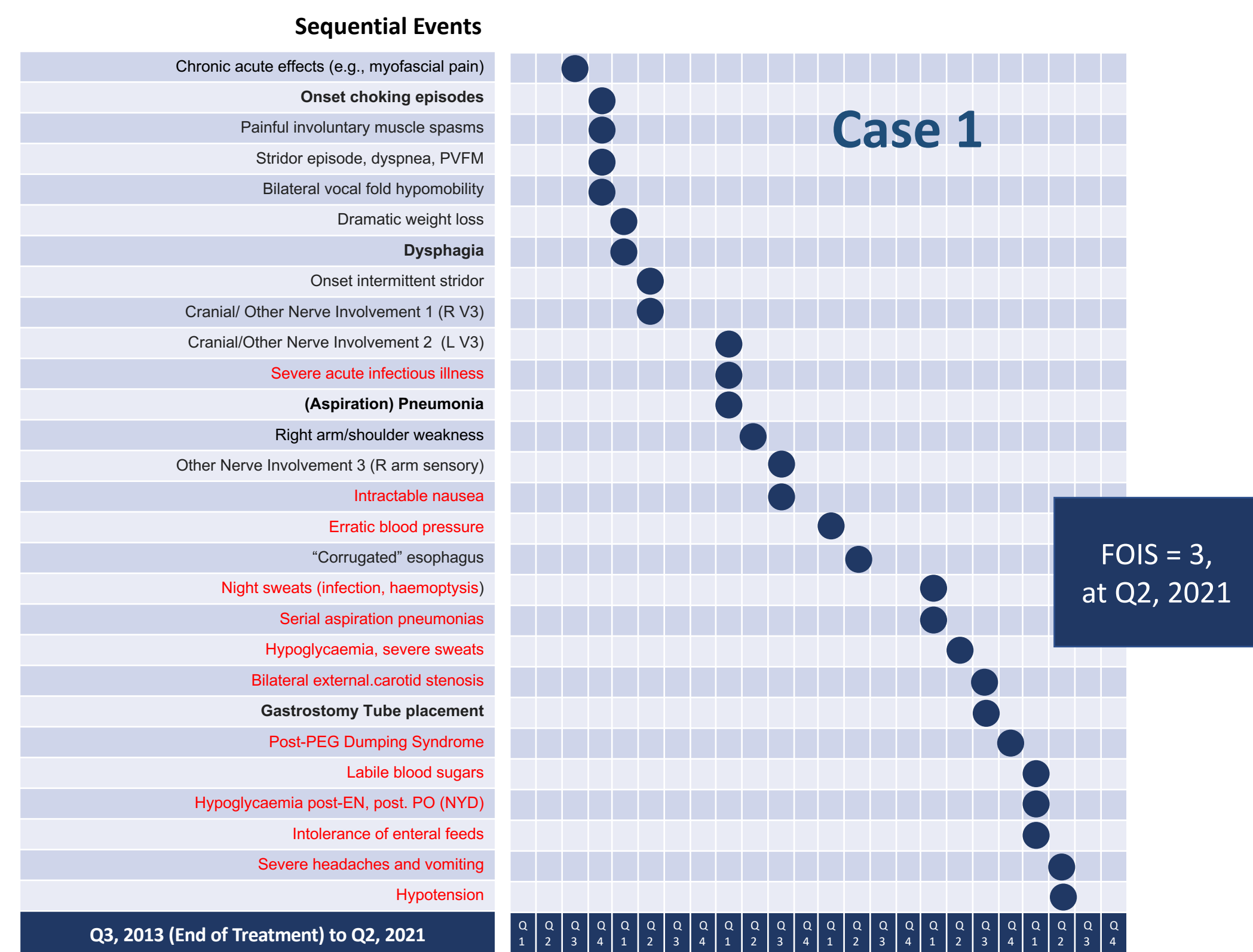


Fig. 1

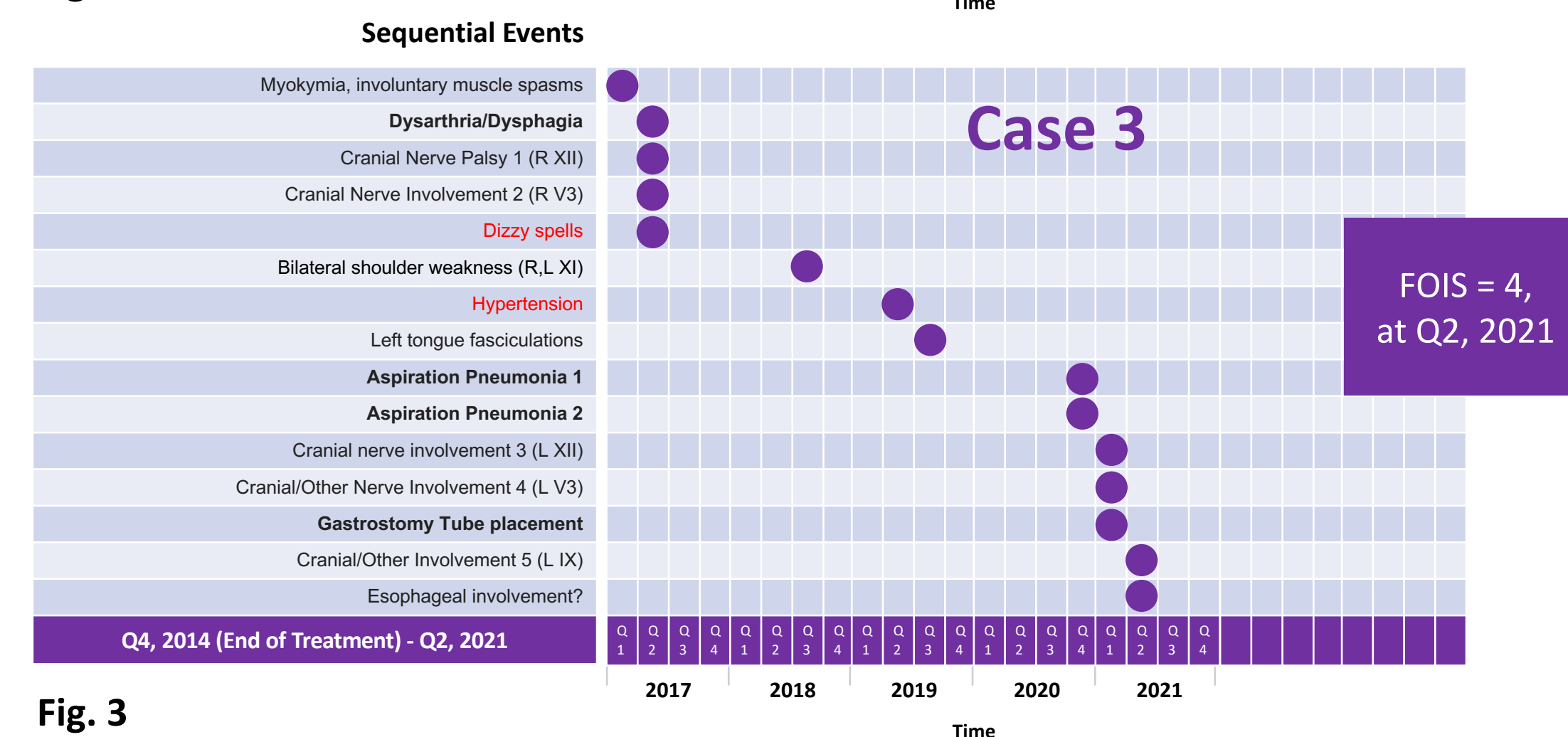


Fig. 3

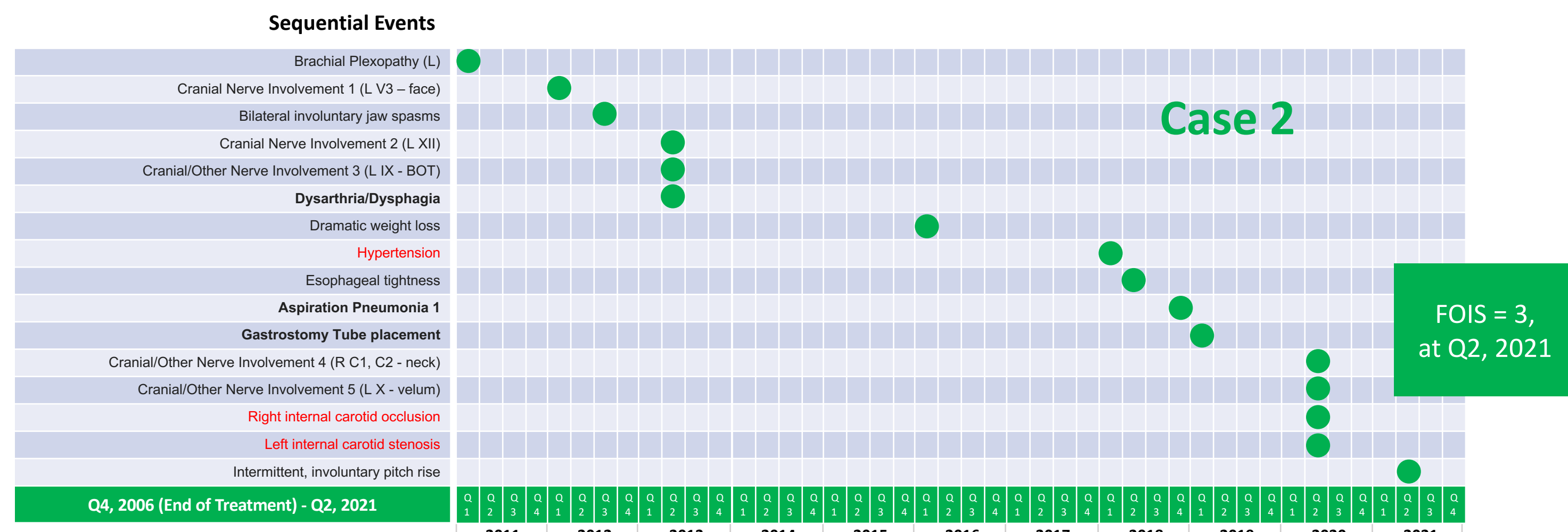


Fig. 2

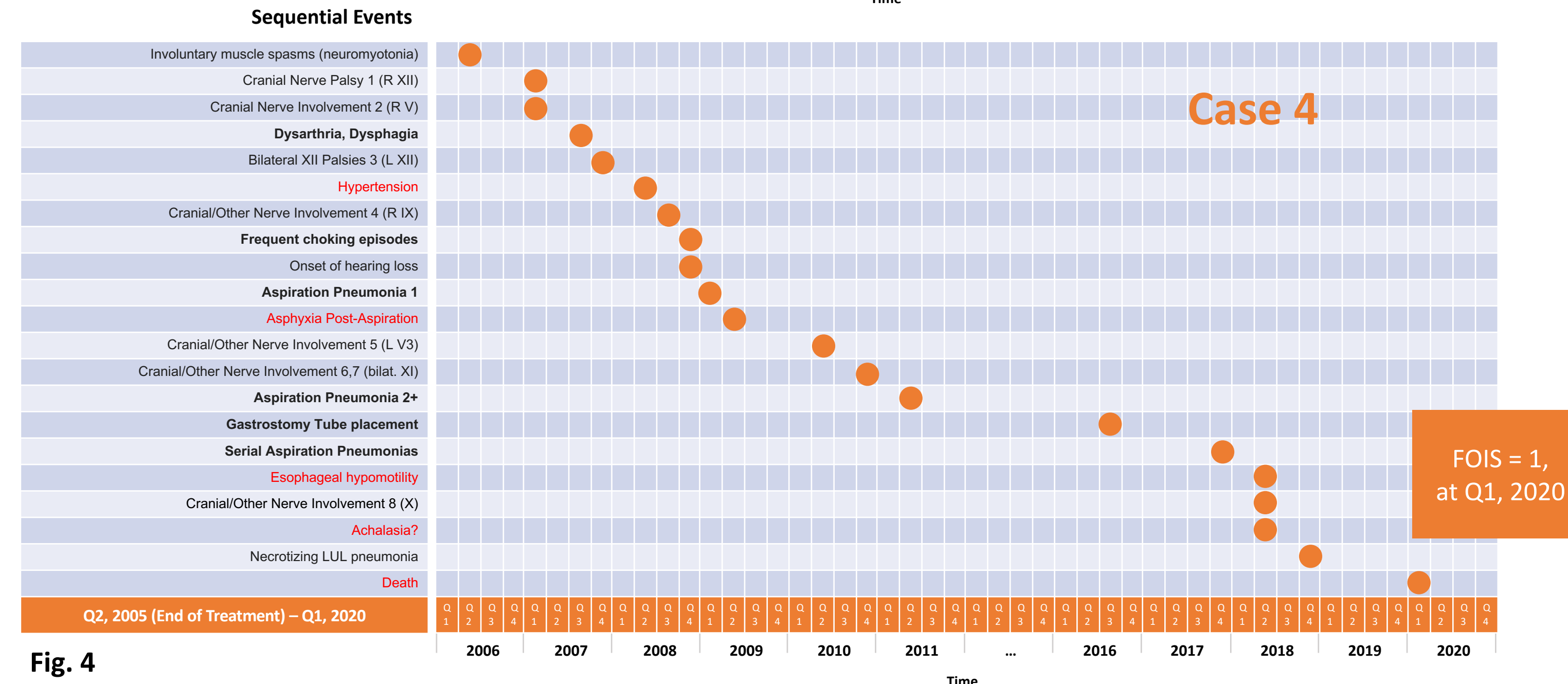


Fig. 4

Figures 1 - 4: “Chronoplots” for Cases 1, 2, 3 and 4, representing progressive late toxicity

RESULTS AND DISCUSSION

This study tracked temporal functional (d)evolution in 4 cases of NPC with post-CCRT progressive dysphagia onset from 2.25 - 6.5 years post-treatment (Figs. 1 – 4). Ultimately, each case manifested a combination of both **locoregional functional impairments**, e.g., dysphagia, evident early on, and wider **systemic sequelae**, later on.

To date, these **two components of disruption** have rarely been juxtaposed on the same individual’s trajectory, or explored within the same study. Their **combined consideration**, and **synchronous evolution** in some cases, begs further study of an underlying association, and suggests the **need to take heed of early symptoms**.

In each case, **onset of progressive dysphagia/ dysarthria**, was foreshadowed 3 to 15 months prior, by episodes of **involuntary jaw/cervical/lingual muscle spasms** (myokymia/ neuromyotonia) - reflecting hyperexcitability of the neuromuscular tissues (14), and/or **cranial neuropathy**, arising either simultaneously or up to 1.25y prior, thus identifying potential **harbingers of functional decline**.

Total cranial neuropathies per case ranged from 4 to 8, emerging steadily over periods of 1.25 – 8.25 years. Each case demonstrated (at least unilateral) **V3 sensory cranial neuropathy** (7 of 8 in total), followed by 5 of 8 **XII (hypoglossal) palsies** and/or **XI (accessory) nerve involvement**, 3 of 8 **IX (glossopharyngeal)**, 2 of X (vagal – palatopharyngeal), and 1 **brachial plexopathy**.

Early onset of **V3 (sensory) cranial neuropathy** in the trajectory of each of these cases was striking, flagging an **unexplored potential marker of the impending cranial neuropathy “cascade”**.

Each of 4 cases suffered **pneumonia** (1.0 – 5.5y post-dysphagia onset; 3.75 – 12y post-treatment) and subsequent or **serial aspiration pneumonias**, leading to death in Case 4. Incidence of late pneumonia in NPC is at least 5.5% (15), increasing over time. Each case also required associated **gastrostomy tube placement** (3.5 – 10.25y post-dysphagia onset; 4.25 – 12.25y post-treatment) for either reduced swallowing safety and/or inefficiency.

This was poorly tolerated in Cases 1 and 4. Final FOIS scores ranged from 1 (no oral intake) - 4 (total oral intake of a single consistency).

Each of 4 cases demonstrated **de novo blood pressure concerns**, viz., hypertension initially, hypotension later, and/or blood pressure instability (2.0 - 4.75 y post-dysphagia onset; 3 – 11.25y post- treatment). Definitive **carotid occlusion or stenosis** was identified in Cases 1 and 2. Post-radiotherapy **carotid vasculopathy** is well-documented for representing stroke risk (16,17); however, **concomitant cranial neuropathy and vasculopathy** in the same individuals has not been explicitly reported to date.

Unexpected findings included insidious late onset **esophageal hypomotility** at 12y post-dysphagia onset (Case 4), and **inexplicable precipitous multi-system health decline** (Case 2). Case 2 was referred for investigation of **hypopituitarism**, an under-recognised post-treatment sequela (18), after presenting with inexplicable hypoglycaemia, labile blood sugars, intolerance of both PO and enteral nutrition, severe headaches, episodic nausea and vomiting, sweats, and severe hypotensive episodes.

Based on present findings, a preliminary **severity-based trajectory of the degenerative process** is postulated comprising **three clinical phases: Phase 1** (incipient): onset of spasms or cranial neuropathy with imminent dysphagia onset; **Phase 2** (intermediate): onset of hypertension/ cardiovascular issues or pneumonia, and **Phase 3** (advanced): serial (aspiration) pneumonias and weight loss signalling compounding medical complexity. Additional neuropathies could appear through all three phases.

CONCLUSIONS AND IMPLICATIONS

Late radiation dysphagia and associated nutritional and pulmonary sequelae **dominate and drive QoL**, yet may comprise just one element of a potentially **complex multi-system degenerative condition**, which requires further research and definition. Suitable **evaluation procedures and clinical linkages** may be needed to manage its multifaceted nature.

NPC patients with late progressive dysphagia are a **small, high-risk clinical population** whose **surveillance needs potentially exceed** routine endoscopy and imaging, particularly when transitioning away from active surveillance. They warrant diligent, knowledgeable survivorship care by the **primary multidisciplinary HNC healthcare team**. Establishing access to the expertise of a diverse **informed, secondary layer of specialties** may be prudent. This could include internal medicine, gastroenterology, palliative care, endocrinology, neurology, respiratory, vascular surgery, and others.

Early identification and tracking of late toxicities in NPC afford the opportunity to **enhance quality of survivorship care and better meet patient needs**, to **mitigate clinician helplessness** in the face of functional decline, to **empower patients** through knowledge of possible connections with new onset systemic effects, and to **minimize patient sense of abandonment**.

REFERENCES

- Kong L, Lu JJ, Liss AL, Hu C, et al. (2011). Radiation-induced cranial nerve palsy: a cross-sectional study of nasopharyngeal cancer patients after definitive radiotherapy. *Int J Radiat Oncol Biol Phys* 79(5):1423-7.
- Tsai WJ, Huang TJ, Luo KC, et al. (2014). Impact of late toxicities on quality of life for survivors of nasopharyngeal carcinoma. *BMC Cancer* 14: 856.
- Du Cr, Ying HM, Kong FF, et al. (2015). Concurrent chemoradiotherapy was associated with a higher severe late toxicity rate in nasopharyngeal carcinoma patients compared with radiotherapy alone: A meta-analysis based on randomized controlled trials. *Radiat Oncol* 10: 70. <https://doi.org/10.1186/s13014-015-0377-9>
- McDowell L, Rock K, Xu W, et al. (2018). Long-term late toxicity, quality of life, and emotional distress in patients with nasopharyngeal carcinoma treated with intensity modulated radiation therapy. *Int J Radiation Oncol Biol Phys* 102(2): 340-352.
- Jacobson MC, Balogh J. (2009) Post-Radiotherapy Neuromyotonia, Bilateral Hypoglossal Palsies, and Progressive Dysphagia in Nasopharynx Cancer (Poster). *Seventeenth Annual Meeting of the Dysphagia Research Society*, New Orleans, Louisiana, March 5 – 7, 2009
- Hutchesson KA (2013). Late radiation-associated dysphagia (RAD) in head and neck cancer survivors. *Perspectives Swallowing Disorders (Dysphagia)* 22: 61- 72.
- Logemann JA (1997). Natural History Studies (Editorial). *Dysphagia* 12: 194-195
- Crany MA, Camaby Mann GD, Groher ME (2005). Initial psychometric assessment of a functional oral intake scale for dysphagia in stroke patients. *Arch Phys Med Rehabil* 86:1516-20. doi: 10.1016/j.apmr.2004.11.049
- Feldmeier JJ, Hampson NB. (2002) A systematic review of the literature reporting the application of hyperbaric oxygen prevention and treatment of delayed radiation injuries: an evidence-based approach. *Undersea Hyperb Med* 29(1):4-30.
- Krekelier, B.N., Rowe, L.M. & Connor, N. P. Dose in Exercise-Based Dysphagia Therapies: A Scoping Review. *Dysphagia* 36, 1–32 (2021). <https://doi.org/10.1007/s00455-020-10104-z>
- Kraaijenka SAC, et al. (2017) Efficacy of a novel swallowing exercise program for chronic dysphagia in long-term head and neck cancer survivors. *Head Neck* 39:1943-61.
- Delanian S, Lefaix J, Maisonneuve T, et al. (2008). Significant clinical improvement in radiation-induced lumbosacral polyradiculopathy by a treatment combining pentoxifylline, tocopherol, and clonidine (Pentoclo). *J Neurol Sci* 275: 164-6.
- McDowell L, Jacobson MC, Levin W (2017). High-dose intravenous steroid regimen for radiation-induced hypoglossal nerve palsy. *Head Neck* 39: E23-E28, 2017. doi:10.1002/hed.24600.
- Gutmann L, Gutmann I. (2004) Myokymia and neuromyotonia. *J Neurol* 251(2):138-42. doi: 10.1007/s00415-004-0331-5
- Yen Tt, Lin Ch, Jiang Rs, et al. (2015). Incidence of late onset pneumonia in patients after treatment with radiotherapy for nasopharyngeal carcinoma: A nationwide population-based study. *Head Neck* 37: 1756-176
- Carpenter DJ, Mowery YM, Broadwater G, et al. (2018). The risk of carotid stenosis in head and neck cancer patients after radiotherapy. *Oral Oncol* 80: 9-15
- Struder D, Hellwig S, Rennau et al. (2021) Screening for radiation vasculopathy by intima-media thickness sonography in head and neck cancer patients. *Eur Arch Oto-Rhino-Laryngol* 278:2017-2026
- Ratnasingham J, Karim N, Paramasivam SS, et al. (2015). Hypothalamic pituitary dysfunction amongst nasopharyngeal cancer survivors. *Pituitary* 18: 448-455. <https://doi.org/10.1007/s11102-014-0593-6>