Editorial

Fatigue following head and neck cancer radiotherapy: an unrecognized side effect of modern radiotherapy techniques?

Rosie Twomey[1], S. Nicole Culos-Reed[1,2,3], Guillaume Y. Millet[1], Harold Lau[3]

[1]Faculty of Kinesiology, University of Calgary, Calgary, Canada; [2]Department of Psychosocial Resources, Tom Baker Cancer Centre, Alberta Health Services, Calgary, Canada; [3]Department of Oncology, Cumming School of Medicine, University of Calgary & Tom Baker Cancer Centre, Calgary, Canada

Correspondence to: Dr. S. Nicole Culos-Reed. Faculty of Kinesiology, University of Calgary, KNB240, 2500 University Dr NW, Calgary, Alberta T2N 1N4, Canada. Email: nculosre@ucalgary.ca.

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Radiotherapy (RT) is an integral part of the treatment of squamous cell carcinoma of the head and neck, and is delivered post-operatively or in the intact setting, often with concurrent chemotherapy. Specifically, intensity modulated radiotherapy (IMRT) is an advanced method of delivering three-dimensional conformal radiotherapy (3D-CRT) using multiple intensity levels across each radiation beam. The purpose is to maximise the intended dose to the target while constraining unwanted irradiation to local tissues. As such, IMRT has become the standard of care in head and neck cancer (HNC). Substantial symptom burden remains with IMRT (1), but the phase 3 PARSPORT trial demonstrated that parotid-sparing IMRT reduces xerostomia, a highly prevalent and debilitating late toxicity (2), and improves health-related quality of life (HRQL) *vs.* conventional 3D-CRT (3). However, analysis of adverse events showed that compared to 3D-CRT, IMRT actually increases the incidence of fatigue graded as at least moderate severity during and up to 8 weeks after RT (3). Alongside other critical organs, central nervous system (CNS) structures lie adjacent or in close proximity to the tumor in HNC, and can receive low to moderate radiation doses during IMRT, i.e., higher than delivered with 3D-CRT. In their recent contribution to the field (4), Ferris and colleagues expand on a dosimetry analysis of the PARSORT trial (5) and further implicate irradiation of non-target delineated CNS structures during IMRT, and acute fatigue in HNC (where acute refers to during and in the weeks after treatment).

In this, the first prospective study on the topic, the major finding is an association between maximum dose to the medulla and brainstem (a union of the medulla, pons and midbrain structures) and patient-reported fatigue (4). HNC patients with mixed primary tumor sites and stages (n=124) were treated with highly-conformal IMRT as part of a definitive treatment plan. Fatigue was measured using the Multidimensional Fatigue Inventory (MFI-20) (6) before commencement of RT, in the sixth week of RT and at 1 month following RT completion. Maximum dose to both structures had a median value of ~30 Gy, and was associated with total MFI-20 score at both week 6 and 1-month post RT. In exploratory follow up analysis, scores for general fatigue and physical fatigue dimensions of the MFI-20 were associated with maximal dose at these times points, and reduced activity at 1 month only. In relation to pre- to post-RT treatment impact, the increase in fatigue from baseline can be considered clinically important for all MFI-20 subscales (7). The authors suggest that in some cases, a lower dose to the brainstem [where the whole brainstem can be treated with 54 Gy using conventional RT with limited risk of severe or permanent neurological damage (8)] could be considered during the treatment planning process. However, treatment should be modified judiciously as dose to other critical organs may be inadvertently affected.

Fatigue is a perceptual construct that can be recognized as pathological when it is not reversible by rest, and typical daily activities are limited or associated with undue effort. Fatigue has recently been defined from a physiological standpoint as 'a percept arising primarily from alterations

within the activation systems informing voluntary action' (9). Specifically in relation to cancer or cancer treatment, the experience of fatigue has been described as a distressing, persistent sense of physical, emotional, and/or cognitive tiredness or exhaustion that is not proportional to recent activity and interferes with usual functioning (10). From this perspective, cancer related fatigue (CRF) is a subjective and self-reported symptom, and it should therefore be intuitive that CRF is most meaningfully evaluated using a patient-reported metric. Unsurprisingly, there is empirical evidence that practitioners grossly underestimate the symptom burden of HNC treatment for symptoms that cannot be evaluated in a physical examination (11), such as fatigue.

The cause of CRF is likely to be multifactorial and in HNC, fatigue may be: (I) a direct result of the malignancy; (II) a direct result of cancer treatment; (III) secondary to a side-effect of cancer treatment (e.g., secondary to malnutrition and loss of body mass due to dysphagia caused by RT); (IV) a side effect of a comorbidity, such as anemia or hypothyroidism; and/or (V) related to psychological, social and/or behavioural factors such as fatigue expectations, lack of support, or sleep quality and quantity. The studies including a dosimetry analysis have evaluated fatigue in the acute setting (4,5,12), where fatigue is typically highest (13). Fatigue may persist as a late toxicity of IMRT dose to the CNS, but long-term time-points have not been evaluated in randomised studies. However, there is some evidence from non-randomised studies that fatigue scores recover to pre-RT values 12 months after treatment with both IMRT and 3D-CRT [e.g., (14)].

Although fatigue is not typically recognised as a neurologic complication of RT, Ferris *et al.* have shown that irradiation of brain structures contributes to fatigue scores. Mechanistically, this points to radiation-induced damage to neural tissues, and a neurobiological contribution to fatigue which we will discuss later. In regards to the role of discrete CNS structures in this IMRT-induced fatigue, to our knowledge, the available data comes from three studies (4,5,12). A lack of statistical significance for individual delineated structures for the same dose metric across these studies does not imply that the sum of the evidence supports no effect, and P values below a pre-specified alpha level across these studies may have different observed associations (15). Test results will be sensitive to the different study protocols (e.g., primary tumor site, fatigue metrics, statistical models with multiple comparisons and notably, differences in IMRT dose to individual structures), and due caution in interpreting these findings is therefore required. Commentary on IMRT and individual brain structures is largely speculative at this time. Nevertheless, there are numerous brain regions, mechanisms and neural correlates that are implicated in chronic fatigue, and it is under investigation as a characteristic of numerous neurological conditions (9,16). Perhaps the structure most convincingly involved in pathological fatigue in diseases where it is affected is the basal ganglia (17). Furthermore, in post-stroke fatigue there is evidence that sub-cortical lesions (e.g., in the basal ganglia or brainstem) result in higher incidence of fatigue [reviewed in (18)]. However, the current consensus is that lesion location does not determine fatigue. It is interesting that thus far, no study has reported the association between total radiation dose to brain structures and fatigue in HNC. Insight can be gained from trials of adjuvant whole-brain radiotherapy (WBRT) for the treatment of brain metastases.

Even where brain metastases are newly diagnosed, the majority of patients cannot be cured and treatment is directed at prolonging progression-free survival and HRQL. As such, the improvement in intracerebral tumor control has been unfavourably assessed against a lack of benefit in terms of overall survival, plus acute negative side-effects (19). In a prospective study where patients were randomised to WBRT (30 Gy total) or observation with MRI (i.e., WBRT withheld), fatigue was more severe at ~8 weeks and 3 months after the start of local treatment (either surgery or ablative radiosurgery to the brain metastases) (20) despite the greater volume of tissue being irradiated in comparison to IMRT for HNC. The choice of adjuvant WBRT *vs.* observation in more advanced brain metastases (i.e., where no treatment would result in a survival of ~1 month) is perhaps clearer, since treatment is focussed on alleviating symptoms which compromise HRQL (such as headaches and seizures), and not on prolonging survival. In this case where prognosis is poor, the burden of receiving WBRT outweighs the benefit. For example, in a retrospective study where fatigue scores were obtained from patient-report questionnaires, fatigue severity increased following WBRT and was negatively correlated with HRQL (21). It seems clear that WBRT is associated with fatigue. The body of work on fatigue and the brain is extensive, and evidence for the involvement of individual brain structures could likely be presented to provide a rationale for considering any structure to be 'at risk' in relation to causing fatigue. With RT, it may be that structures are associated with fatigue where they receive high doses (4,5,12). Therefore, overall CNS dose parameters from a union of all structures in

proximity to the target tissue should be included in future dosimetry analyses.

In HNC where the prognosis is typically superior to brain metastases, this acute toxicity may be a relatively acceptable consequence of a treatment paradigm with clear efficacy. Modification to treatment planning that decreases the dose to the CNS should maintain the sparing of tissue to avoid salivary gland sequelae, such that the maintenance of swallowing is prioritised as originally intended. Given that under-dosing of target tissues in order to constrain the dose to CNS structures is likely unacceptable, interventions to mitigate fatigue in HNC deserve consideration. If fatigue can be managed during and after treatment, and recovered in the months following IMRT, it may be acceptable in comparison to other late toxicities and any negative impact on tumor control. Where fatigue does persist in the months after IMRT, this may actually suggest different mechanisms given that RT-induced fatigue has recovered but other sequelae may remain. For example, in neurological conditions where chronic fatigue is a burden, peripheral neuromuscular factors (e.g., muscle contractile properties) may be unaffected. However, HNC involves distinct side effects such as substantial reductions in lean body mass and cancer cachexia. In this case, it may be that there is a neuromuscular contribution to fatigue related to changes in voluntary force production (22).

Given that parotid-sparing IMRT does increase fatigue during a time when malnutrition and cancer cachexia are prominent in HNC patients, failure to intervene may lead to prolonged deconditioning and a delayed recovery. While there is no efficacious pharmacological treatment for the prevention or treatment of CRF, exercise helps manage CRF in adults (23) and is also safe, feasible and beneficial for HRQL in HNC patients specifically, both during and following treatment (24). Adherence to resistance training programmes is lower during *vs.* after treatment completion (25), but alternatives such as tai chi or yoga are currently being investigated following benefits in other tumor groups, and may also mitigate fatigue in HNC. Alongside exercise, behavioural interventions involving patient education, self-management, mindfulness training or cognitive behavioural therapy may be useful in the management of fatigue in HNC (24).

Returning to the possible neurobiological causes of radiation-induced fatigue, neuronal tissue injury may relate to fatigue via a number of mechanisms. For example, functional magnetic resonance imaging studies in nasopharyngeal cancer patients following RT show altered functional connectivity of cerebellar-cerebral networks (26) and between cerebellum, sensorimotor, and cingulo-opercular networks (27). Although primarily investigated in relation to RT-induced cognitive impairments, these networks are involved in broad functions including attentional processing (26), coupling of sensory and motor functions, and goal-directed behaviour (27), any one of which could reasonably be suggested to be involved in the pathological state of fatigue. There is also interest in the role of the immune system in chronic fatigue across multiple diseases, largely focussed on increased inflammation and its role in immune-to-brain signalling (28). In particular, pro-inflammatory cytokines (which are released by activated immune cells in response to, for example, tissue injury), are of interest in relation to the effects on the brain in chronic fatigue syndrome (29) and multiple sclerosis (30). In the first study to evaluate inflammation in HNC after IMRT, fatigue was associated with inflammatory markers (31), and this should be considered a priority for future research.

As suggested by the authors of this original article, a prospective randomised study in which dose to CNS structures are constrained would be a future direction of interest. We would encourage the pre-specification of both the minimal difference that would be considered clinically relevant, and the statistical analysis plan. Validated patient-reported outcomes should be selected, and a dose analysis should include a union of all delineated brain structures, with time points following out to 1 year. In recognition of fatigue as a complex phenomenon, neurophysiological, biological and/or behavioural variables of interest should be considered for inclusion. Finally, with the rapid and wide adoption of proton beam therapy, its clinical usefulness (in regards to providing similar target coverage with minimal radiation of CNS and other non-target structures) for some types of HNC may soon be demonstrated (32). Future prospective randomised trials of proton beam therapy *vs.* IMRT for HNC cancer should include patient-reported outcomes to assess fatigue and HRQOL. Alongside ongoing research on interventions such as exercise during and/or after treatment of HNC, this work would provide further insight into the possible mechanisms of fatigue following treatment for HNC.

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References

1. Rathod S, Gupta T, Ghosh-Laskar S, et al. Quality-of-life (QOL) outcomes in patients with head and neck squamous cell carcinoma (HNSCC) treated with intensity-modulated radiation therapy (IMRT) compared to three-dimensional conformal radiotherapy (3D-CRT): evidence from a prospective randomized study. Oral Oncology 2013;49:634-42.
2. Jensen SB, Pedersen AM, Vissink A, et al. A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: prevalence, severity and impact on quality of life. Support Care Cancer 2010;18:1039-60.
3. Nutting CM, Morden JP, Harrington KJ, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. Lancet Oncology 2011;12:127-36.
4. Ferris MJ, Zhong J, Switchenko JM, et al. Brainstem dose is associated with patient-reported acute fatigue in head and neck cancer radiation therapy. Radiother Oncol 2017. [Epub ahead of print].
5. Gulliford SL, Miah AB, Brennan S, et al. Dosimetric explanations of fatigue in head and neck radiotherapy: an analysis from the PARSPORT Phase III trial. Radiother Oncol 2012;104:205-12.
6. Smets EM, Garssen B, Bonke B, et al. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 1995;39:315-25.
7. Purcell A, Fleming J, Bennett S, et al. Determining the minimal clinically important difference criteria for the Multidimensional Fatigue Inventory in a radiotherapy population. Support Care Cancer 2010;18:307-15.
8. Mayo C, Yorke E, Merchant TE. Radiation associated brainstem injury. Int J Radiat Oncol Biol Phys 2010;76:S36-41.
9. Kuppuswamy A. The fatigue conundrum. Brain 2017;140:2240-5.
10. Berger AM, Mooney K, Alvarez-Perez A, et al. Cancer-Related Fatigue, Version 2.2015. J Natl Compr Canc Netw 2015;13:1012-39.
11. Falchook AD, Green R, Knowles ME, et al. Comparison of patient- and practitioner-reported toxic effects associated with chemoradiotherapy for head and neck cancer. JAMA Otolaryngol Head Neck Surg 2016;142:517-23.
12. Powell C, Schick U, Morden JP, et al. Fatigue during chemoradiotherapy for nasopharyngeal cancer and its relationship to radiation dose distribution in the brain. Radiother Oncol 2014;110:416-21.
13. Spratt DE, Sakae M, Riaz N, et al. Time course and predictors for cancer-related fatigue in a series of oropharyngeal cancer patients treated with chemoradiation therapy. Oncologist 2012;17:569-76.
14. Fang FM, Chien CY, Tsai WL, et al. Quality of life and survival outcome for patients with nasopharyngeal carcinoma receiving three-dimensional conformal radiotherapy vs. intensity-modulated radiotherapy-a longitudinal study. Int J Radiat Oncol Biol Phys 2008;72:356-64.
15. Greenland S, Senn SJ, Rothman KJ, et al. Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations. Eur J Epidemiol 2016;31:337-50.
16. Chaudhuri A, Behan PO. Fatigue in neurological disorders. Lancet 2004;363:978-88.
17. Chaudhuri A, Behan PO. Fatigue and basal ganglia. J Neurol Sci 2000;179:34-42.

18. De Doncker W, Dantzer R, Ormstad H, et al. Mechanisms of poststroke fatigue. J Neurol Neurosurg Psychiatry 2017. [Epub ahead of print].
19. Li J, Brown PD. The diminishing role of whole-brain radiation therapy in the treatment of brain metastases. JAMA Oncol 2017;3:1023-4.
20. Soffietti R, Kocher M, Abacioglu UM, et al. A European organisation for research and treatment of cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life. J Clin Oncol 2013;31:65-72.
21. Pulenzas N, Khan L, Tsao M, et al. Fatigue scores in patients with brain metastases receiving whole brain radiotherapy. Support Care Cancer 2014;22:1757-63.
22. Twomey R, Aboodarda SJ, Kruger R, et al. Neuromuscular fatigue during exercise: methodological considerations, etiology and potential role in chronic fatigue. Neurophysiol Clin 2017;47:95-110.
23. Cramp F, Byron-Daniel J. Exercise for the management of cancer-related fatigue in adults. Cochrane Database Syst Rev 2012;11:CD006145.
24. Capozzi LC, Nishimura KC, McNeely ML, et al. The impact of physical activity on health-related fitness and quality of life for patients with head and neck cancer: a systematic review. Br J Sports Med 2016;50:325-38.
25. Capozzi LC, McNeely ML, Lau HY, et al. Patient-reported outcomes, body composition, and nutrition status in patients with head and neck cancer: Results from an exploratory randomized controlled exercise trial. Cancer 2016;122:1185-200.
26. Ma Q, Zeng LL, Qin J, et al. Radiation-induced cerebellar–cerebral functional connectivity alterations in nasopharyngeal carcinoma patients. NeuroReport 2017;28:705-11.
27. Ma Q, Wu D, Zeng LL, et al. Radiation-induced functional connectivity alterations in nasopharyngeal carcinoma patients with radiotherapy. Medicine (Baltimore) 2016;95:e4275.
28. Capuron L, Miller AH. Immune system to brain signaling: neuropsychopharmacological implications. Pharmacol Ther 2011;130:226-38.
29. Montoya JG, Holmes TH, Anderson JN, et al. Cytokine signature associated with disease severity in chronic fatigue syndrome patients. Proc Natl Acad Sci U S A 2017;114:E7150-8.
30. Hanken K, Eling P, Hildebrandt H. The representation of inflammatory signals in the brain: a model for subjective fatigue in multiple sclerosis. Front Neurol 2014;5:264.
31. Xiao C, Beitler JJ, Higgins KA, et al. Fatigue is associated with inflammation in patients with head and neck cancer before and after intensity-modulated radiation therapy. Brain Behav Immun 2016;52:145-52.
32. Leeman JE, Romesser PB, Zhou Y, et al. Proton therapy for head and neck cancer: expanding the therapeutic window. Lancet Oncol 2017;18:e254-65.

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