BRAIN COMMUNICATIONS

Expanded neuromuscular morbidity in Hodgkin lymphoma after radiotherapy

Tatsuya Oishi,[1] Cory J. Kogelschatz,[1,2] Nathan P. Young,[1] Ernest M. Hoffmann,[1] Nathan P. Staff,[1] Sue L. Visscher,[3] Bijan J. Borah,[3] William E. Krauss,[4] Kogulavadanan Arumaithurai,[1] Shahar Shelly,[1] Stephen M. Ansell[5] and Christopher J. Klein[1,6]

Our study aims to quantitate neuromuscular morbidity from radiotherapy in Hodgkin lymphoma including: (i) frequency and (ii) time of onsets for neurological localizations; (iii) degree of disabilities and (iv) number of clinical visits compared to cardiopulmonary Hodgkin lymphoma-radiation complications. Medical records from Mayo Health systems were retrieved; identifying neuromuscular radiation treated Hodgkin lymphoma-complications from 1 January 1994 to 31 December 2016. Of an estimated 4100 post-radiotherapy Hodgkin lymphoma patients, 4.6% (189) were identified with complications. Mean latency to physician visit for symptoms was 23.7 years (range: 1–50). Most commonly identified complications included: head drop 10% (19) with or without myopathy, myopathy 39% (73), plexopathy 29% (54), myelopathy 27% (51) and polyradiculopathy 13% (24). Other findings included benign and malignant nerve sheath tumours 5% (9), phrenic and long thoracic mononeuropathies 7% (14) and compressive spinal meningioma 2% (4). Patients frequently had multiple coexisting complications (single = 76% [144], double- = 17% [33], triple = 4% [8], quadruple = 2% [4]). Cardiac 28% (53) and pulmonary 15% (29) complications were also seen in these patients. History of Hodgkin lymphoma was initially overlooked by neurologists (14.3%, 48/336 clinical notes). Hospital and outpatient visits for complications were frequent: neuromuscular 19% (77/411) versus cardiopulmonary 30% (125/411). Testing was largely exclusionary, except when imaging identified secondary malignancy. Modified Rankin score at diagnosis varied: 0–1 (55.8%), 2–3 (5.8%) and 4–5 (38.3%). Neuromuscular complications among post-radiation Hodgkin lymphoma are diverse, occurring in ~1 of 20 having markedly delayed onsets often eluding diagnosis. Frequent care visits and major morbidity are common. Survivorship recommendations should recognize the diverse neurological complications.

1 Department of Neurology, Mayo Clinic, Rochester, MN 55905, USA
2 Intermountain Neurosciences Institute, Murray, UT 84107, USA
3 Center of the Science of Health Care Delivery, Mayo Clinic, Rochester, MN 55905, USA
4 Department of Neurologic Surgery, Mayo Clinic, Rochester, MN 55905, USA
5 Division of Hematology, Mayo Clinic, Rochester, MN 55905, USA
6 Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN 55905, USA

Correspondence to: Christopher J. Klein, Department of Neurology, Mayo Clinic
200 First St. SW, Rochester, MN 55905, USA
E-mail: klein.christopher@mayo.edu

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Abbreviations: ADL = activities of daily living; e-MRS = estimated-Modified Rankin Score; HL = Hodgkin lymphoma

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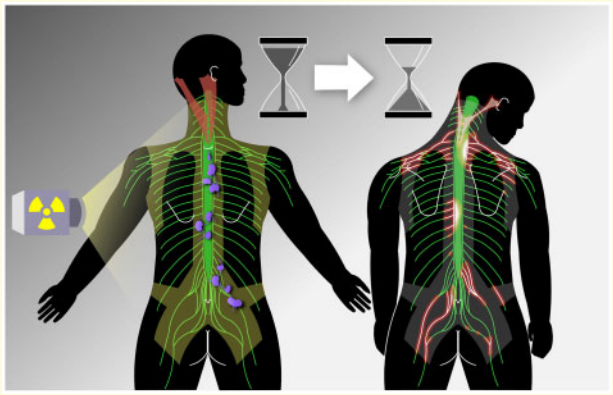
Graphical Abstract



Introduction

Hodgkin lymphoma (HL) arises from germinal and post-germinal centres of lymph nodes, most commonly affecting persons in the second and seventh decades of life (Townsend and Linch, 2012; Ansell, 2015, 2018). The incidence is 2.7–2.8 per 100 000 per year (Bray *et al.*, 2018; Siegel *et al.*, 2018). Up to 80% of patients will have a curable form utilizing a combination of radiation and chemotherapy (Ansell, 2018). Large field radiation (e.g. 'mantle', 'inverted-Y' or total nodal radiation) was the mainstay of therapy up until ~15–20 years ago, and this was used to broadly treat the thoracic and/or abdominal lymph nodes affected by the lymphoma. While the success of the therapy is celebrated as one of the great medical breakthroughs of the 20th century, the longitudinal study of long-term survivors also revealed the consequences of radiation treatment—namely secondary malignant neoplasms, cardiovascular disease, pulmonary fibrosis, gastrointestinal complications and axial myopathy from radiation fibrosis (Ng, 2014; Ansell, 2018). Subsequent evolution in radiotherapy technology led to more sophisticated approach, allowing for a dynamic and focused radiation field directed against PET-identified tumours (such as involved field radiation therapy), alongside the adjuvant chemotherapy (Engert *et al.*, 2003; Andre *et al.*, 2017).

HL survivorship guidelines have focused on myopathy as the sole neurological complication (Ng, 2014; Ansell, 2018), but individual case reports suggest radiation treated cancers including HL may affect the entire neuromuscular system inclusive of the spinal cord (Stubblefield, 2011; van Leeuwen-Segarceanu *et al.*, 2012; Ghosh and Milone, 2015; Rastogi *et al.*, 2017; Stubblefield, 2017). Nevertheless, a comprehensive large-scale single institution study of HL reviewing all neuromuscular morbidity has not been reported.

This study addresses the neuromuscular burden of radiation therapy of HL in our tertiary and primary care centre, characterizing (i) neurological localizations and the (ii) elapsed time between the radiation therapy and presentation, (iii) the degree of disability at time of diagnosis and (iv) frequency of clinical visits in the emergency department, inpatient and outpatient settings due to radiation complications of the neuromuscular compared to their cardiopulmonary involvements.

Materials and methods

The project was approved by the Mayo Clinic Institutional Review Board. An electronic medical records linkage system (averaging 1.2 million outpatient visits and 129 000 hospital admissions per year) was used to identify all patients who were seen within Mayo Clinic Health System, 1 January 1994 to 31 December 2016. Identified were all patients with history of HL who had undergone radiotherapy, and matching at least one keyword from a pre-defined set of known neuromuscular complications of radiation (e.g. myopathy, scapular winging, polyradiculopathy, plexopathy, nerve sheath tumour, myelopathy, dropped head and phrenic neuropathy); these keywords were derived from prior literature, past case reports and experiences from physicians. Charts were manually reviewed to exclude cases where the patient in fact had non-HL, or did not receive radiation. Patients were also excluded via manual chart review if a neuromuscular condition was explained by another cause or was absent (e.g. keyword query for 'plexopathy' resulting in: 'cervical spondylosis without evidence of plexopathy', keyword query 'myopathy' resulting in 'inflammatory myopathy'). Patients who had neuromuscular conditions before HL was diagnosed (and otherwise had no other subsequent complications) were excluded. Patients who declined to participate in research studies were also excluded. There were also HL patients who had established neuromuscular manifestations of some form (flagged positive on pre-defined keyword search), but the symptom onset was in the same year as the HL

diagnosis. These patients were analysed separately because their complication was not delayed, which has been felt typical of earlier reported cases.

Information of interest included patient's age at diagnosis of HL, type of radiation, the date when a clinician (neurologist or non-neurologist) entered the diagnosis of neuromuscular complication and patient-reported functional status with regards to activities of daily living. For analysis purposes, if the year of HL diagnosis was documented to the decade only (as noted in four of our patients), then the year of diagnosis was assumed to be the middle of that decade (e.g. patient who 'developed Hodgkin Lymphoma in the 1970s' was assumed to be diagnosed in 1975). The radiotherapy was always assumed to be on the same year as the HL diagnosis, since typically there is no reason to delay the HL treatment for over a year. The location and modality of the radiation was collected when available; due to diverse, sometimes vague description of the radiation field (such as 'radiation to chest and abdomen'), the field of radiation was grossly classified as exposure to 1) head/neck, 2) chest, 3) abdomen/pelvis, or 4) some combination of these regions. For example, para-aortic and inverted-Y radiations were both classified as abdomen/pelvis exposure, whereas mantle radiation was classified as exposure to both head/neck and chest (Fig. 1). In addition to the Mayo Clinic records linkage system, the clinic's EMG database was used to review all identified cases for accurate neuromuscular localizations.

For determination of disability we utilized the fact that as a part of the medical record, all patients complete a survey of their general health condition at each clinic visit; this includes a yes/no questionnaire on their ability to complete activities of daily livings, including related to walking, climbing stairs, bathing and feeding. Using this information, an estimated-Modified Rankin Score (e-MRS) could be determined within 2 years of initial neurology visit for their neuromuscular complaint. The e-MRS was designated a value of '0–1' when they denied any difficulty with bathing, dressing, self-feeding, housekeeping, toileting or walking. If the patient affirmed he/she had difficulty with these tasks but had no difficulty with bathing, eating, toileting or walking, then the e-MRS was designated a value of '2–3'. When they affirmed they had any difficulty with bathing, eating, toileting or walking, their e-MRS was assigned a value of 4–5.

In order to ascertain neurology doctor awareness of earlier radiation treatment for HL, the medical records system was utilized to perform a key word search of all notes from the identified cohort including: outpatient initial encounter notes; inpatient or outpatient consultation notes; and hospital admission notes. Specifically queried where 'Hodgkin', and or 'radiation'. Among the patients with neuromuscular complications and HL, the number of clinical visits in emergency, inpatient and outpatient settings was reviewed in the study period using billing encounters to identify points of contact for visits. The chief complaint for each clinical encounter was categorized to cardiopulmonary, neuromuscular or other aetiologies. Only visits for neuromuscular complaints felt to be relevant to the radiation history were included (e.g. admission for acute stroke or clinic visit for Parkinson's disease were not included).

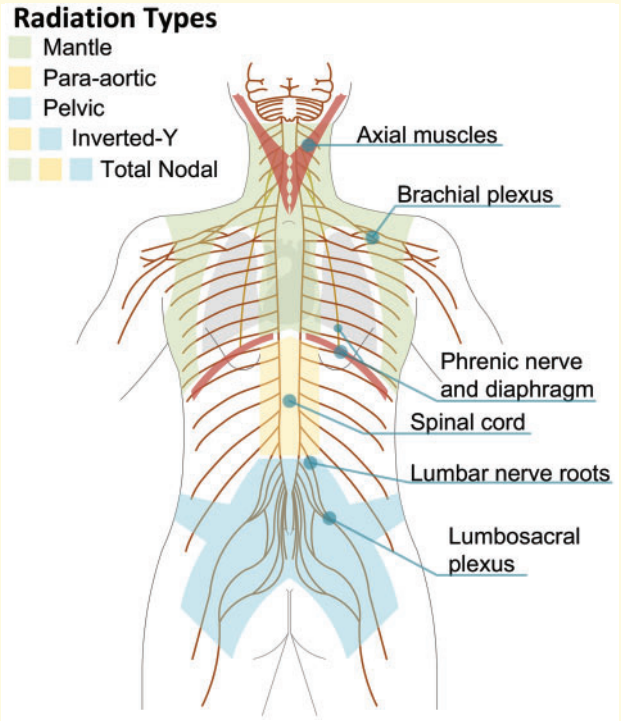


Figure 1 Radiation fields used to treat HL. Shown are the common radiation field modalities traditionally used to treat HL. Mantle radiation (green shading) is directed towards cervical, supraclavicular, axillary and mediastinal lymph nodes. Para-aortic radiation (yellow shading) is directed towards para-aortic lymph nodes, and pelvic radiation (blue shading) is directed towards subinguinal and iliac lymph nodes. Healthy tissue within the field including the spinal cord, peripheral nerves and muscles may be exposed.

Statistical analysis

The mean, median, percentage and range of data were calculated using Excel functions.

Data availability

The data used to generate the manuscript are available on reasonable request.

Results

Study population of patients with delayed complications

A total of 189 patients (101 male, 88 female) were identified as having HL post-radiotherapy neuromuscular complications diagnosed within at least 1 year after lymphoma diagnosis (Fig. 2). Only three patients (one plexopathy, two myelopathy) in the series were confirmed to have received modern radiation sculpted approaches (Filippi *et al.*, 2014; Specht *et al.*, 2014; Petersen *et al.*, 2015). These three patients had bulky cervical and thoracic lymph node tumour involvements. Mean age at time of HL diagnosis was 30.5 years (range: 11–79 years). Of these 189 patients, 144 patients had a single neurologic complication, 33 had double complication (e.g. proximal myopathy and myelopathy), 8 had triple complications and 4 had quadruple complications. Mean time from HL diagnosis to recognition of first delayed neuromuscular complication was 23.7 years (range: 1–50 years). Notably, the patients sought medical evaluation for their neuromuscular complications on average about 24 years after HL diagnosis, regardless of the complication (Fig. 3). During the study period 2838 patients were given a diagnosis code of HL. However, based on a key word search against the entire medical record including clinical notes for HL alone 4100 unique patients were estimated. This translates into 4.6% (189/4100) of HL patients having a post-radiation neuromuscular complication.

Delayed radiation complications

Head drop

A total of 19 cases had 'head drop' in their post-radiation diagnosis, with mean time to physician presentation of 24.9 years following HL diagnosis (range: 5–42 years).

EMG. Of these 19 cases, 15 patients underwent an EMG. Similar to earlier reports (Rowin *et al.*, 2006), the findings on EMG were not uniformly the same; proximal myopathy was noted in 10 patients, whereas severe cervical polyradiculopathy without myopathy were noted in 3 patients. One patient had both severe cervical polyradiculopathy and a superimposed axial myopathy.

Myopathy

Myopathy was the most frequent neuromuscular complication. A total of 73 patients had myopathy, 13 from an earlier report (Ghosh and Milone, 2015). The mean time to myopathy clinical visit was 25.1 years (range: 1–48 years).

EMG. Of the 73 patients, 54 had undergone an EMG study at our institution all clinically with

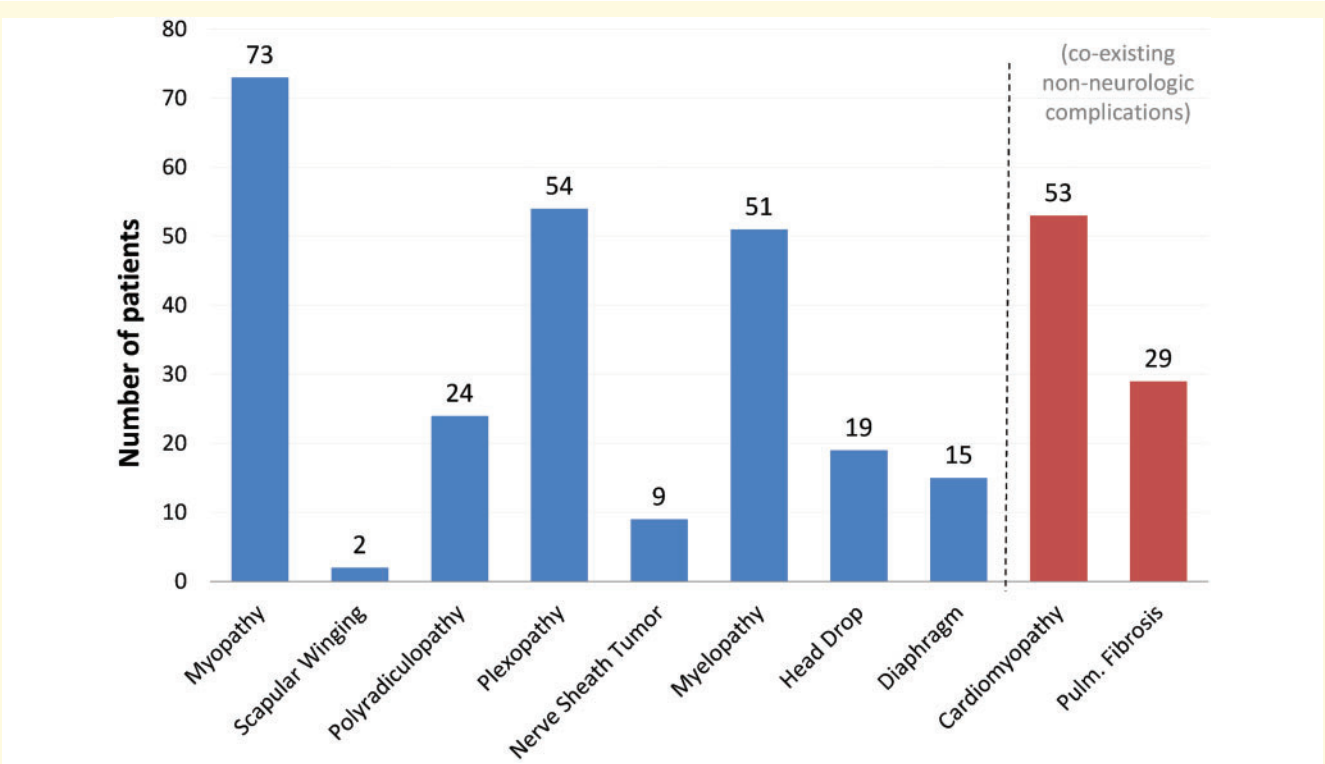


Figure 2 Radiotherapy neuromuscular complication types in HL survivors. Shown in blue are frequencies of each neurologic complication related to radiation therapy from a total cohort of 189 affected patients, with some persons having more than one complication. In red within this same cohort are the frequencies of post-radiation cardiomyopathy and pulmonary fibrosis complications.

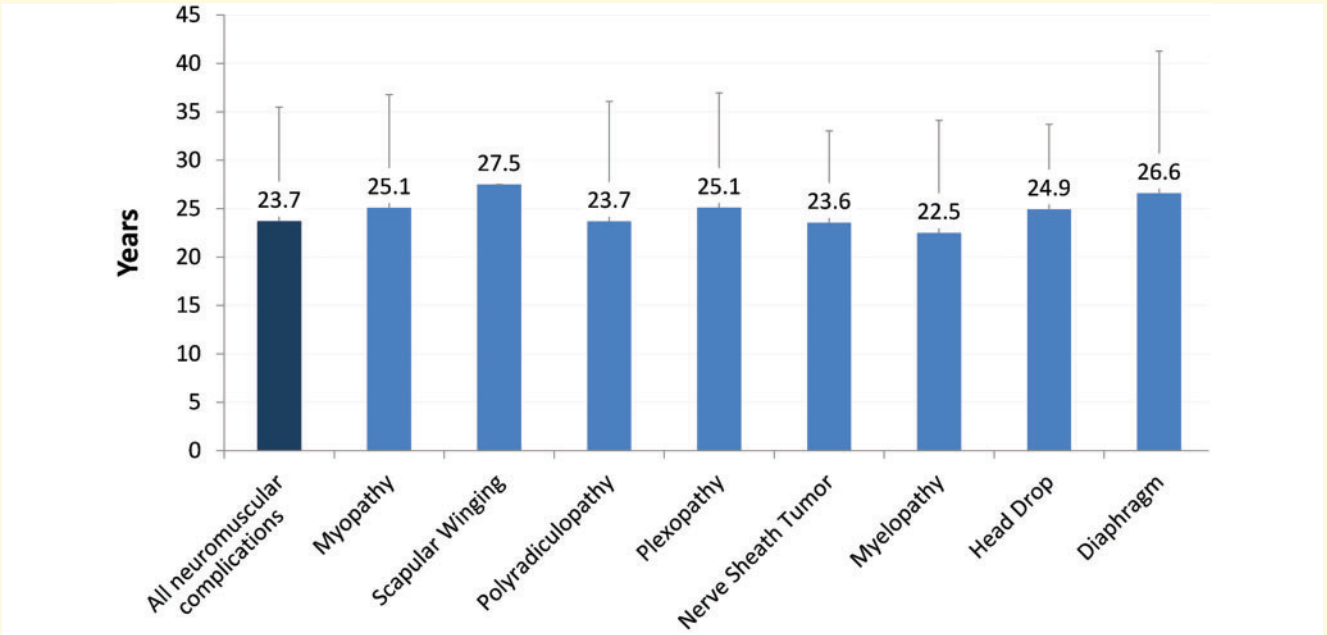


Figure 3 Average time in years to physician recognition of radiotherapy neuromuscular complications in HL survivors. Shown in dark blue is the average year to onset of first recognized neuromuscular radiotherapy complications for all types combined (average 23.7 years). In light blue are the divergent complications seen and their average time to recognition. Error bar equals 1 SD.

axial-predominant involvements, and post-radiation myopathy was specifically mentioned as likely in 18 cases on the EMG. Fibrillation potentials were commonly witnessed in at least one muscle having myopathic features (reported in 28).

Muscle biopsy. Thirteen patients underwent a muscle biopsy. The biopsy report most commonly reported nonspecific features frequently finding denervation atrophy ($n = 10$). Type-1 fibre atrophy was noted in one patient, whereas type-2 fibre atrophy was noted in four patients. Fibrosis was noted in perimysium ($n = 8$) and endomysium ($n = 5$).

Plexopathy

A total of 54 patients were identified with plexopathy; mean time to clinical recognition of 25.1 years since HL (range: 1–50 years). There were 34 patients with brachial plexopathy, 18 patients with lumbosacral plexopathy and 1 patient with both brachial and lumbosacral plexopathy. The majority of patients had pan-plexus involvements 67% (36/54) motor predominant and painless; one also with bilateral phrenic involvements. Of the remaining 18 cases (7 had lower trunk or posterior cord brachial plexopathy, 7 had nerve sheath tumours (see below), 4 undocumented). When laterality was documented, in 13 cases the presentation was bilateral, whereas in 39 cases the presentation was unilateral (evenly split between right and left). All had painless motor-only slowly progressive presentations.

Myelopathy

A total of 51 patients were noted to have myelopathy after HL diagnosis; mean time to recognition was 22 years (range: 2–45 years). In 26 of the patients, the myelopathy was localized to cervical segment, whereas 21 were localizable to the thoracolumbar segment (not determined in the remaining 4 patients). Five cases had compressive myelopathy from tumours detailed below.

Compressive myelopathy secondary to spinal neoplasm. Four patients were noted to have compressive meningiomas in the thoracic spine (Fig. 4). These patients were diagnosed with meningioma anywhere between 17 and 38 years since the diagnosis of HL, and all four were biopsy-confirmed WHO grade-I without atypical or anaplastic features (WHO grade II–III). One biopsy-proven meningioma was recurrent, and the neurologist concluded that the tumour was likely radiation-induced. There was also a single case of a biopsy-proven high-grade leiomyosarcoma in the T_3–T_5 vertebra and causing paraplegia, developing 45 years after radiotherapy. Insidious progressive spasticity with weakness was the major feature experienced by all patients.

Polyradiculopathy

A total of 24 patients were diagnosed with polyradiculopathy of some form, with mean time to diagnosis of 23.7 years since HL (range: 1–45 years). Sixteen patients underwent an EMG for confirmation of this process. No cases had isolated thoracic radiculopathy. There was a single case of a multiple lumbar radiculopathies from

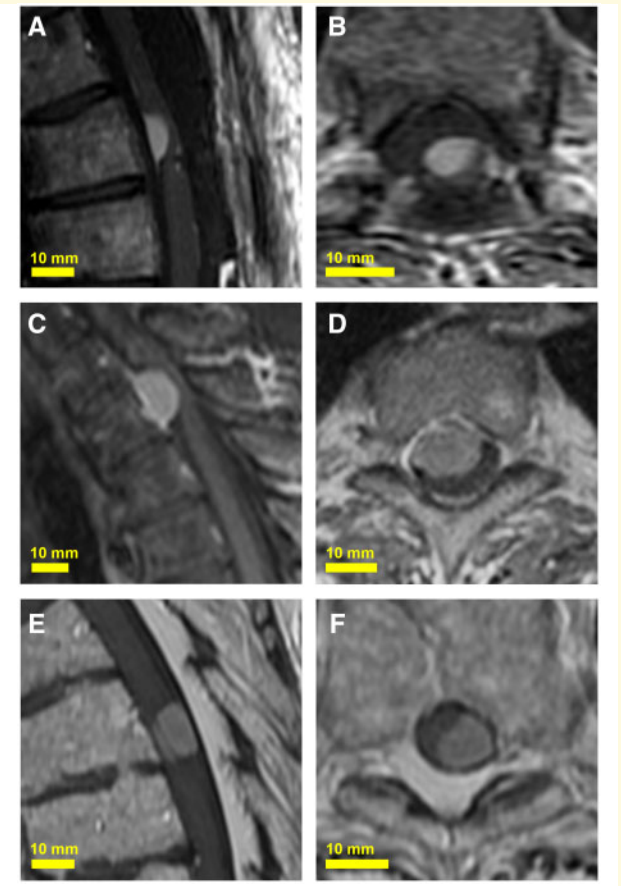


Figure 4 Examples of spinal meningioma in radiotherapy-treated HL survivors. Three representative examples with MRI imaging T_1 post-gadolinium showing both sagittal and axial thoracic views. (**A**, **B**) T_6 meningioma in a 38-year-old woman, with radiation 17 years prior. (**C**, **D**) T_2 meningioma in a 60-year-old woman, with radiation 27 years prior. (**E**, **F**) $T_{6–7}$ meningioma in a 69-year-old man, with radiation 26 years prior. All yellow bars are scaled to 10 mm in length.

diffuse cavernous malformations in a 61-year-old male patient, 20 years after the radiotherapy. Details of this case have been published previously (Rastogi *et al.*, 2017). Similar to this case all had motor predominant involvements slowly progressive over months and years without pain.

Nerve sheath tumour

A total of nine patients were identified with a nerve sheath tumour, with mean time to recognition of 25 years since HL (range: 18–33 years). Of these, four were malignant; there was also one schwannoma, one benign neurofibroma, one epithelioid mesothelioma and one unbiopsied, 'possibly schwannoma'. The location was variable, ranging from the brachial plexus (four patients), to thoracic spine (one), to lumbar root (one), to individual nerves such as sciatic or radial nerve (two). Pain and sensory involvements were present in addition to weakness in all these cases.

Mononeuropathies

Diaphragm/phrenic neuropathy—15 patients were noted to have phrenic neuropathy. Mean time to neuromuscular diagnosis was 26.6 years (range: 3–49 years). Scapular winging/long thoracic neuropathy—two patients; one diagnosed 24 years, the other diagnosed 31 years after onset of HL. All had insidious progressions over years motor-only without pain.

Myokymic discharges on EMG

Of the 189 patients reviewed, 129 had undergone an EMG at some point. Of these, 18 patients had documented myokymic discharges in at least one EMG report, whereas reports from 26 patients declared absence of myokymia. While not all of the EMG session among the 129 patients were necessarily directed towards search for radiation-related changes (and instead may have been requested to address unrelated conditions such as carpal tunnel syndrome), it is noted that only about 41% (18/44) of the patients had myokymia even when the electromyographer was actively aware of the radiation therapy as risk factor.

Neuromuscular complications at the time of HL radiation therapy

There were 14 additional cases with neuromuscular presentations, occurring within the same year as the HL diagnosis that we did not include in the delayed complication HL radiation cohort. This includes direct infiltration or mass effect of HL onto neuromuscular structures, suspected paraneoplastic involvement, or post-treatment complications and side effects (e.g. secondary to critical illness neuromyopathy). Incidentally, none of the patients reviewed here developed any delayed neuromuscular complications at a later date.

Myopathy. Five patients had myopathy in the same year as HL diagnosis. Two of these patients had critical illness myopathy (acutely ill in the context of HL), one patient had steroid myopathy (receiving steroids as part of HL treatment), one patient was thought to have inflammatory or paraneoplastic myopathy in context of HL and one patient had unspecified progressive myopathy.

Myelopathy. Two patients were diagnosed with HL as a cause of myelopathy, via direct compression. One was an 80-year-old female with symptomatic cervical cord compression, whereas the other case was an 81-year-old male with paraparesis due to thoracic cord compression.

Plexopathy. There was a single case of an infiltrating HL to the left brachial plexus in a 45-year-old female patient.

Polyradiculopathy. Five patients had polyradiculopathy; four of the cases were due to direct infiltration/leptomeningeal spread, whereas one was initially suspected to be

of paraneoplastic aetiology. In the latter, a specific autoantibody was not found.

Phrenic nerve involvement. There was a single case in a 33-year-old male patient where the lymphoma compressed against the right phrenic nerve, and was felt to cause paralysis of the hemidiaphragm.

Region of radiation exposure

Of the 189 patients treated with radiation, a vast majority of the patients had radiation to the chest (84.1%; 159/189), as well as head/neck (75.6%; 143/189). This was largely due to many patients undergoing mantle radiation therapy, which includes both the neck and chest as part of the radiation field. In total, 31.7% or 60 patients received radiation to the abdomen/pelvis. In 7% of the patients (14/189), the radiation modality could not be determined. A total of 32 patients (16.9%) were exposed to radiation in single region only (head/neck, chest or abdomen/pelvis), 98 patients (51.9%) received radiation in two regions (again, with most cases due to mantle radiation) and 45 patients (23.8%) received radiation to all three regions.

Excluding all cases where the radiation exposure site was unknown, head drop (19 patients) and nerve sheath tumour (9 patients) were always associated with radiation to both neck and chest. While only two patients with scapular winging were identified, both had radiation to head/neck and chest regions as well. Similarly, diaphragmatic involvement (13 patients) was always associated with radiation to the chest. Beyond this, there were no clear differences in radiation exposure sites, when comparing between neuromuscular complications. All cases of cardiomyopathy (51 patients) and pulmonary fibrosis (29 patients) were associated with radiation to the chest.

Cardiopulmonary complications

Cardiomyopathy. Within our patient group with pre-specified neuromuscular complications, 53 patients were noted to have cardiomyopathy at some point. Most of the reviewed cases were restrictive cardiomyopathy rather than ischaemic in aetiology, and radiation was commonly suspected as a culprit. Mean time to recognition was 28.4 years after HL diagnosis (range: 1–48 years).

Pulmonary fibrosis. Within our patient group with pre-specified neuromuscular complications, 29 patients were noted to have pulmonary fibrosis. Mean time to diagnosis was 27.4 years after HL diagnosis (range: 2–52 years). When pulmonary fibrosis was noted, the aetiology was almost universally documented as radiation-driven (96.6%).

Neurologist recognition of HL history based on documentation

Among the 189 patients who had a radiation neuromuscular complication after HL treatment, a total of 336 clinical notes (either an inpatient consult note, or an inpatient admission note, or outpatient clinic initial visit note) were composed under 'Department of Neurology', between 149 patients. Neurology notes were only included if written at least a year after HL diagnosis. Of the 336 notes, 285 (84.8%) included the keyword 'Hodgkin' among 139 patients (seen in the department). The remaining 48 notes did not mention HL (14.3%). Additionally, 10 patients (6.7%) never had HL acknowledged by neurology during their post-HL radiation visits with subsequent non-neurological notes making the diagnosis.

Disability

A total of 120 patients were identified who had (i) been seen by a neurologist, (ii) completed a pre-visit questionnaire that includes self-reported degree of disabilities, (iii) completed within 2 years of the first neurologist visit and (iv) without any notable cardiopulmonary complications. Of the 123 patients, 67 patients (55.8%) had e-MRS of 0–1, 7 patients (5.8%) with e-MRS of 2–3 and 46 patients (38.3%) with e-MRS of 4–5.

Clinical visits related to HL

A total of 302 outpatient visits and 109 emergency department or inpatient visits were reviewed among 60 patients identified to receive their primary care in our health care system. In both emergency department/inpatient and outpatient settings, patients more frequently saw a clinician for cardiopulmonary complications coded to be from radiation rather than neuromuscular complaints, attributable to radiation (Fig. 5). The frequency of emergency department/inpatient visits for neuromuscular complaints attributable to radiation were (emergency department/inpatient in 22/1109, or 20.0%; outpatient in 55/302, or 18.2%).

Discussion

To the best of our knowledge, this is the first large-scale single institution effort to comprehensively characterize the frequency and clinical burden of all neuromuscular complications in HL from radiation. The study identifies that plexopathy and myelopathy are seen almost as frequently as myopathy. Additionally, emphasized is the common occurrence of multiple neuromuscular post-radiation complications in the same patient. Disabilities are frequently severe, and these complications can be seen in patients also with cardiopulmonary complications of radiation which translates into multiple doctor visits and hospitalizations. Our findings support the need to expand awareness of these complications, including the inclusion of the now quantified broader neuromuscular issues in HL survivorship guidelines (Ng, 2014).

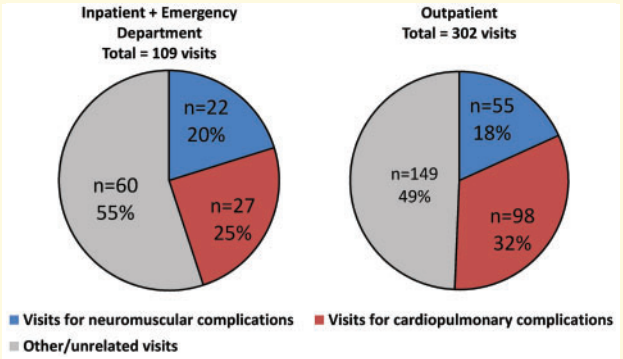


Figure 5 Frequency of care visits among HL patients with neuromuscular post-radiation complications. Shown is the number of outpatient and inpatient visits accrued among 60 patients identified to receive their primary health care in our medical health system over the period of 1 January 2003 to 31 December 2017.

The relatively young age at cancer diagnosis and high survival rates translates into potential for long-term radiation complications. Attempts to reduce radiation exposure are being embraced through more precise delivery of radiation and optimization of chemotherapy (Ferme *et al.*, 2007; Specht *et al.*, 2014; Yahalom, 2014; Petersen *et al.*, 2015; Brockelmann *et al.*, 2018; Longo and DeVita, 2018). However, the benefits of these modern approaches may only be realized in decades as we observed the time of neuromuscular complications occurred on average 25 years (range 1–50 years) after radiation therapy, and modern radiation practices only began over the past 15–20 years. Additionally, we did witness three patients receiving these modern radiotherapies with bulky tumour burdens developed post-radiation complications. Interestingly, the timeline of onset symptoms appeared relatively invariant regardless of the neuromuscular complication. Specifically, we observed significant lag in all neuromuscular complications seen including with myopathy, myelopathy, plexopathy, polyradiculopathy, plexopathy and mononeuropathy.

Inevitably, there is an inherent level of uncertainty in declaring suspected radiation-induced neuromuscular complications—especially for clinicians seeing the patient for the first time. Also for many patients, the HL may be a distant memory that may be seldom re-explored or forgotten altogether during a limited office visit or acute hospital setting. The patient may have medical problems or undergo treatments that are more recent and unrelated to their distant HL history, and this generates other plausible explanations for their neuromuscular complaints—for instance, blaming the myopathy on recent use of statins or steroids, rather than the remote radiotherapy. Given that 14.4% of neurology notes failed to document a prior radiation exposure suggests an opportunity to better recognize remote radiotherapy in patients with unexplained neuromuscular and myelopathic disorders. EMG remains a valuable tool for assessing the aetiology and localization of neuromuscular weakness in these settings, but the sensitivity of the needle exam could be swayed by the clinical question, the electromyographer's suspicion, and the study design. Myokymic discharges on EMG can be suggestive of radiation injury (Gutmann, 1991), but this was only seen in a minority of our cases, even when the electromyographer was actively aware of potentially encountering myokymia throughout the study. We note all patients without secondary tumour involvements had painless insidious progressive motor predominant involvements regardless of their localizations. Because head drop and axial myopathy are well described post-radiation complications this may contribute to increased physician ascertainment in our cohort (Rowin *et al.*, 2006; Ghosh and Milone, 2015; Stubblefield, 2017). The combination of aforementioned factors raises significant concern that post-radiotherapy neuromuscular complications is probably under-recognized at-large.

It is expected, but still interesting to note that the prevalence of nerve sheath tumours increases decades after the radiotherapy, presumably secondary to radiation damage. The four cases of thoracic spinal meningiomas and a single case of spinal leiomyosarcoma implicate earlier radiation in cause. Radiation-induced meningiomas are well recognized following scalp or brain radiation (Munk *et al.*, 1969; De Tommasi *et al.*, 2005) but only a single case report of meningioma in the spinal region (in the conus medullaris) following radiotherapy for bladder cancer is reported (Oikonomou *et al.*, 2011). Post-radiation leiomyosarcomas have also been documented in rare cases (Grabowska *et al.*, 2007), but never in the spine causing neurologic deficits. It is open to speculation whether this was in fact post-radiation effect or purely an incidental and highly unusual tumour. The single case of cavernous malformation developed 20 years after the radiotherapy has been published previously by one of the authors (Rastogi *et al.*, 2017).

Importantly, this study highlights the range of disability of patients. At diagnosis e-MRS was quite varied: 0–1 (55.8%); 2–3 (5.8%); 4–5 (38.3%). Admittedly, even though co-morbid cardiopulmonary problems were automatically excluded, other causes of disability (e.g. severe orthopaedic issues or unrelated neurologic conditions) could not be fully excluded, and occult cardiopulmary process also cannot be excluded. The significant disability and morbidity among these patients highlights the need for timely recognition, which could expedite the diagnosis and proper management avoiding unnecessary testing and treatments. Cardiac (28%; 53/189) and pulmonary (15%; 29/189) complications were documented in the minority, which may also delay neuromuscular diagnosis. Another metric of the seriousness of radiation complications and

neuromuscular disease is the number of hospital and outpatient visits for radiotherapy complications among 60 patient receiving primary care in our system; neuromuscular (19%; 77/411 visits) compared to cardiopulmonary (30%; 125/411 visits).

We recognize there may be an unknown number of patients who were seen at our institution for their neuromuscular complaint following radiotherapy for HL, but the history of HL was never documented in our medical record for various reasons (e.g. because the patient was treated elsewhere long ago and was overlooked during the evaluation) and therefore never entered our patient cohort.

Although not the primary focus of our study, we were able to identify multiple cases in which HL caused a neuromuscular complication around the time of diagnosis. Most of these were due to direct compression from the HL of nervous system structures, causing myelopathy, plexopathy, polyradiculopathy or mononeuropathy. This appears consistent with descriptions in prior literature (Higgins and Peschel, 1995). These patients were noted and excluded from the radiation complication group who had steroid myopathy or critical illness as part of HL treatment chemotherapy regimen.

Out study demonstrates that post-radiation neuromuscular complications can be diverse in presentation, often with overlaps in manifestation, and have variable onset time; yet the timing of diagnosis averages 24 years following the radiation exposure for all neuromuscular complications. The crucial history of lymphoma and radiation may be occasionally missed by neurologists, possibly due to its temporal remoteness. Nevertheless the condition is associated with significant morbidity, both in terms of overall disability as well as frequency of outpatient and hospital encounters, and most will present with motor predominant insidious progressive involvements. Because modern radiation approaches which reduce the risk of radiation complications have only been instituted in the past 15–20 years the reductions of these complications will likely not be realized until the next decades. Future HL survivorship guidelines should reflect the potential neuromuscular complications and morbidity of the condition.

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Competing interests

The authors report no competing interests.

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