Proton therapy in the management of non-Hodgkin lymphoma

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Abstract
Proton therapy (PT) is a highly conformal type of radiation therapy that can target the tumor while sparing dose to surrounding normal tissues. This study reviews a single institution’s experience managing patients with non-Hodgkin lymphoma (NHL) treated with PT. Eleven patients with NHL were treated with PT from January 2008 to January 2014 on an institutional review board-approved outcomes tracking protocol, and included patients with indolent orbital lymphoma (n = 4), primary mediastinal B-cell lymphoma (n = 3), plasmablastic lymphoma (n = 2) and natural killer (NK) T-cell lymphoma (n = 2). The median follow-up was 38 months. The 2-year rate of local control was 91%, with one patient with NK T-cell lymphoma having recurrence in-field. Toxicities were limited to grade 2 at highest, during follow-up. PT is a feasible and effective treatment for NHL. Early outcomes are favorable. Longer follow-up and more patients are needed to confirm our findings.

Keywords: Lymphoma and Hodgkin disease, radiation, outcomes, proton beam therapy

Introduction
Non-Hodgkin lymphoma (NHL) consists of a heterogeneous group of malignancies with varied clinical presentation and biological behaviors. The estimated number of new cases in 2014 is 70,000, which represents 4% of all cancers diagnosed and 3% of cancer deaths in the United States [1]. The histological subtypes of NHL are typically classified as indolent and aggressive histologies.

Although NHL is predominantly managed with chemotherapy, radiation therapy is used as definitive treatment among patients with early-stage indolent lymphoma and natural killer (NK) T-cell lymphoma. Radiation therapy is also used as consolidative treatment in patients with early-stage and bulky aggressive histologies following chemotherapy. Despite growing evidence of the benefit of radiation therapy for patients with NHL, concerns regarding radiation-associated late toxicities persist and, consequently, radiation therapy is omitted in the management strategy of many patients for whom it may be of benefit.

In an effort to reduce radiation-related toxicity, several important modifications have been made to traditional historic radiation treatment. These include reducing the dose of radiation in both definitive and consolidative radiotherapy [2], smaller field sizes [3] and using modern radiotherapy techniques, such as intensity-modulated radiation therapy [4,5]. Proton therapy is another way to potentially reduce radiation-associated toxicity. There are several studies examining the dosimetric benefits of proton therapy in patients with Hodgkin lymphoma (HL) [6–8]; however, there are limited published data reporting outcomes of patients with NHL treated with proton therapy.

The present study evaluated the disease control, toxicities and radiation dose delivered to various organs at risk (OARs) using proton therapy either definitively or in combination with chemotherapy among a cohort of consecutively treated patients with NHL.

Materials and methods
Between January 2008 and January 2014, 11 patients with NHL were treated with definitive (n = 6) or consolidative radiation therapy (n = 5). All patients were treated on an institutional review board-approved outcomes tracking protocol with proton therapy. Prospectively collected data in the charts were extracted, including patient and disease characteristics prior to treatment, chemotherapy, proton treatment plan and acute and late side effects and disease control. This cohort included four patients with indolent orbital lymphoma, three patients with primary mediastinal lymphoma, two patients with plasmablastic lymphoma and two patients with NK T-cell lymphoma. Table I outlines patient characteristics, involved sites of disease and treatment details.

Patients were simulated supine with custom immobilization devices including VacLok™ bags (Civco Medical Solu-
## Table I. Patient and tumor characteristics.

| Patient no. | Age (years) | Role of proton treatment | Chemotherapy | Follow-up (months) | Status | Radiation dose |
|-------------|-------------|--------------------------|--------------|-------------------|--------|----------------|
| 1           | 56          | None                     | None         | 58                | NED    | 30.6 Gy (RBE) in 1.8 fx |
| 2           | 46          | None                     | None         | 57                | NED    | 30.6 Gy (RBE) in 1.8 fx |
| 3           | 48          | Definitive               | Hyper-CVAD   | 53                | NED    | 56 Gy (RBE) in 1.5 fx in 1.2 fx BID |
| 4           | 46          | Definitive               | R-CHOP       | 57                | NED    | 54 Gy (RBE) in 2 fx |
| 5           | 36          | Definitive               | R-ICE        | 57                | NED    | 50.4 Gy (RBE) in 1.2 x 2c |
| 6           | 36          | Consolidative            | R-ESHAP      | 57                | NED    | 50.4 Gy (RBE) in 1.2 x 2c |
| 7           | 24          | Consolidative            | Hyper-CVAD   | 57                | NED    | 50.4 Gy (RBE) in 1.2 x 2c |
| 8           | 42          | Hyper-CVAD               | CHOP         | 57                | NED    | 50.4 Gy (RBE) in 1.2 x 2c |
| 9           | 66          | Plasmablastic            | CHOP         | 57                | NED    | 50.4 Gy (RBE) in 1.2 x 2c |
| 10          | 4           | NK-T-cell                | CHOP         | 57                | NED    | 50.4 Gy (RBE) in 1.2 x 2c |
| 11          | 57          | NK-T-cell                | CHOP         | 57                | NED    | 50.4 Gy (RBE) in 1.2 x 2c |

**Results**

The median follow-up for all patients was 38 months, and seven of the nine living patients have more than 2 years of...
follow-up. Two events occurred. One patient with NK T-cell lymphoma had progressive disease immediately after completing radiation therapy and died. Another patient with plasmablastic lymphoma was diagnosed with a gastrointestinal junction tumor outside the radiation field during follow-up and died 6 years following treatment. The 3-year overall survival rate for the cohort was 91% and the 3-year local control rate was 91%. Table II summarizes acute and late radiation-associated toxicities for the entire cohort of 11 patients.

Four patients were treated with definitive proton therapy for indolent orbital lymphoma in an effort to reduce the dose to the brain. Two of these patients had mucosa-associated lymphoid tissue (MALT) lymphoma and received 30.6 Gy (relative biological effectiveness, RBE) in 1.8 Gy fractions. The other two patients had low-grade follicular lymphoma and received 24 Gy (RBE) in 1.5 Gy fractions. All four patients tolerated proton therapy well, with grade 1–2 dermatitis \( (n = 4) \), grade 1–2 headache \( (n = 2) \) and/or grade 1 fatigue \( (n = 2) \). There were no instances of grade 3 or greater acute toxicities. There were no local recurrences at the time of last follow-up. Three patients later developed grade 3 cataracts in the treated eye. In these patients, the lens had been either entirely in the PTV \( (n = 2) \) or partially in the PTV \( (n = 1) \). One patient developed late grade 1 anhidrosis and another patient developed late grade 1 epiphora.

Three patients were treated with consolidative proton therapy for primary mediastinal B-cell lymphoma to reduce the radiation dose to the heart, lungs, esophagus and breasts. Their ages ranged from 19 to 36 years. Two of these patients had a complete response to six cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy and one patient required second-line cyclophosphamide, doxorubicin, vincristine and prednisone. Their ages ranged from 19 to 36 years. Two of these patients had a complete response to six cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy and one patient required second-line cyclophosphamide, doxorubicin, vincristine and prednisone. One patient completed radiation therapy and died. Another patient with follicular lymphoma had progressive disease immediately after completing treatment. Acute toxicities were grade 1–2 dermatitis \( (n = 3) \), grade 1 fatigue \( (n = 3) \) and other grade 1 gastrointestinal \( (n = 2) \) and pulmonary toxicities \( (n = 2) \). At the time of last follow-up there were no grade 2 or greater late toxicities.

Two patients were treated with consolidative proton therapy for plasmablastic lymphoma. This included one located in the head and neck and the other in the stomach and left adrenal gland. There were no recurrences at the time of last follow-up. The patient with the head and neck site developed a GE junction cancer out-of-field a few years following treatment and died approximately 6 years following proton therapy. Acute toxicities were grade 1 nausea \( (n = 1) \), grade 1 mucositis \( (n = 1) \) and grade 2 dermatitis \( (n = 1) \). There were no grade 2 or greater late toxicities.

Finally, two patients received definitive proton therapy for treatment of NK T-cell lymphoma of the head and neck region in an effort to reduce the dose to the parotid glands, oral cavity and brain. One patient had progressive disease and died 5 months later, while the other patient is a 4-year-old boy with involvement extending from the nasopharynx to hypopharynx, who is free of disease at 9 months after completing treatment. Acute toxicities were grade 1–2 dermatitis \( (n = 2) \), grade 2 mucositis, grade 2 laryngeal edema requiring steroids, grade 3 dysphagia \( (n = 1) \) and grade 2 anorexia \( (n = 1) \).

**Discussion**

This study is the first to report on a cohort of patients with NHL treated with proton therapy [11]. Proton therapy led to local control rates similar to what is expected with photon radiation, but was delivered with the objective of reducing the long-term side effects of radiation. Several published studies have evaluated the use of proton therapy in HL, but there are few data regarding outcomes of patients treated with proton therapy for NHL. Three studies have evaluated the dosimet-

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**Table II. Acute and late radiation associated toxicities.**

|                  | Acute |          |          |          | Late |          |          |          |
|------------------|-------|----------|----------|----------|------|----------|----------|----------|
|                  | Grade 1 | Grade 2 | Grade 3 | Grade 4  | Grade 1 | Grade 2 | Grade 3 | Grade 4  |
| Skin             |        | 4       | 6       | 0       | 0     | 9       | 0       | 0       |
| Fatigue          |        | 6       | 0       | 0       | 0     | 2       | 0       | 0       |
| Nausea/vomiting  |        | 3       | 0       | 0       | 0     | 0       | 0       | 0       |
| Esophagitis      |        | 3       | 0       | 1       | 0     | 1       | 0       | 0       |
| Xerostomia       |        | 2       | 0       | 0       | 0     | 1       | 0       | 0       |
| Mucositis        |        | 2       | 0       | 0       | 0     | 0       | 0       | 0       |
| Weight loss      |        | 0       | 1       | 0       | 0     | 0       | 0       | 0       |
| Cough/dyspnea    |        | 2       | 0       | 0       | 0     | 1       | 0       | 0       |
| Dyspepsia        |        | 1       | 0       | 0       | 0     | 0       | 0       | 0       |
| Cataracts        |        | 0       | 0       | 0       | 0     | 0       | 3       | 0       |
| Epiphora         |        | 0       | 0       | 0       | 0     | 1       | 0       | 0       |
| Dry eye          |        | 0       | 0       | 0       | 0     | 0       | 1       | 0       |
| Dermatitis       |        | 1       | 6       | 0       | 0     | 0       | 0       | 0       |
| Alopecia         |        | 2       | 0       | 0       | 0     | 0       | 0       | 0       |
| Headache         |        | 1       | 1       | 0       | 0     | 0       | 0       | 0       |
| Anxiety/depression|      | 1       | 0       | 0       | 0     | 1       | 0       | 0       |
| Dysphagia        |        | 0       | 0       | 1       | 0     | 0       | 0       | 0       |
| Dysarthria       |        | 1       | 0       | 0       | 0     | 1       | 0       | 0       |
| Anorexia         |        | 0       | 1       | 0       | 0     | 0       | 0       | 0       |
| Tinnitus         |        | 0       | 0       | 0       | 0     | 1       | 0       | 0       |
| Oralgia          |        | 0       | 0       | 0       | 0     | 1       | 0       | 0       |
| Hypothyroidism   |        | 0       | 0       | 0       | 0     | 1       | 0       | 0       |

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ric impact of using proton therapy in NHL, including studies from Massachusetts General Hospital (MGH; Boston, MA), M. D. Anderson Cancer Center (MDACC; Houston, TX) and University of Florida (UF; Jacksonville, FL) and there is a case report from Loma Linda University Medical Center (LLUMC; Loma Linda, CA). The study from MGH included four patients with diffuse large B-cell NHL involving the mediastinum treated with proton therapy, and showed reduced cardiac, lung, spinal cord and integral doses with excellent disease control and minimal acute toxicities [12]. The study from MDACC discussing proton therapy in mediastinal lymphoma included two patients with NHL and showed similar results [13]. The UF study evaluating the dosimetric benefit of proton therapy compared with 3D conformal radiotherapy in two patients with primary mediastinal B-cell lymphoma demonstrated a clinically meaningful reduction in dose to the heart, lungs and esophagus [14]. Finally, a case report from LLUMC demonstrated that proton therapy can minimize the volume of normal brain tissue receiving low- to moderate-dose radiation in a patient with primary B-cell lymphoma [15]. These dosimetric studies provide a rationale for the use of proton therapy in the treatment of NHL to potentially reduce the risk of late radiation toxicities. This approach is also supported by the work of Chung et al. [16], who demonstrated a 50% reduction in secondary cancer development among patients treated at MGH with proton therapy compared with matched patients from the Surveillance, Epidemiology, and End Results (SEER) program registry.

All three patients with primary mediastinal B-cell lymphoma had an excellent response to consolidative proton therapy and no evidence of disease during follow-up. Patients with primary mediastinal B-cell lymphoma generally present at a young age, similar to those with HL involving the mediastinum, and would likely derive the same benefits with proton therapy as patients with HL. In a prospective study, Hoppe et al. [17] demonstrated significant and clinically meaningful dose reduction with proton therapy when compared with 3D and intensity-modulated radiation therapy. These patients with NHL represent an important cohort who should be considered for consolidative treatment with proton therapy. Furthermore, many of these patients are being treated with dose-dense chemotherapy regimens in an effort to avoid radiation therapy and its associated toxicities [18]. Therefore, in the few patients receiving radiation therapy as part of their treatment, proton therapy should be strongly considered.

In patients with orbital lymphoma, local disease control outcomes were favorable and consistent with outcomes described in the literature [19–21]. Given that the majority of patients with indolent orbital lymphoma achieve long-term survival, it is important to minimize the potential for late treatment-associated toxicities. The patients in this cohort had similar rates of subacute toxicities (i.e. cataracts, anhidrosis) to patients treated with photon therapy. Proton therapy has the advantage of sparing the dose to the pituitary, ipsilateral temporal lobe and ipsilateral hippocampal head, all of which receive low-dose radiation with similarly fractionated conventional photon therapy.

Other effective strategies for treating orbital lymphoma have been investigated. In 2011, Lowry et al. [2] published their results of 361 sites of indolent NHL randomized to 40–45 Gy in 20–23 fractions or 24 Gy in 12 fractions and 640 sites of aggressive NHL randomized to 40–45 Gy in 20–23 fractions or 30 Gy in 15 fractions. There was no difference in overall response rate, progression-free survival or overall survival between the standard- and low-dose arms in either group. Fasola et al. [22] analyzed a cohort of 20 patients with NHL with ocular adnexal involvement treated with low-dose radiation consisting of two fractions of 2 Gy. At a median follow-up of 26 months, the overall response rate was 96% and the complete response rate was 85%. The treatment was well tolerated, with mild acute side effects in 30% and no late toxicities. Furthermore, patients treated with this low-dose regimen have the option of re-irradiation in the case of local-regional relapse. With conjunctival MALT lymphoma (provided there is no disease behind the equator of the globe on high-quality orbital MRI), patients can be treated effectively with an anterior orthovoltage field (250–300 kV) [20]. Considering that very low doses for orbital lymphoma are emerging as an effective alternative, the true value of its use in patients with indolent histologies still remains to be seen. However, more aggressive histologies of the orbit require higher doses, which would benefit from proton therapy.

Although this study demonstrates that proton therapy can be safely and effectively delivered to patients with NHL involving other anatomic areas, including the abdomen and head and neck region, NHL includes a broad range of anatomic disease locations and histologic subtypes, making it difficult to generalize the benefits of a particular radiation modality among all cases of NHL. While low-grade indolent lymphoma (predominantly MALT and follicular lymphoma) and NK T-cell lymphoma can be effectively treated with radiation therapy alone, aggressive histologies (diffuse large B-cell lymphoma, plasmablastic and Burkitt lymphoma) require individualized chemotherapy regimens in combination with radiation therapy. Current National Comprehensive Cancer Network (NCCN) guidelines include photons, electrons or protons as appropriate treatment modalities for NHL, depending on clinical judgement. Although ideal, a randomized controlled trial comparing proton and photon therapy based on a primary endpoint of late toxicity is unlikely because of the numerous potential sites of disease, the long time interval between treatment delivery and manifestation of late side effects, and the shrinking role of radiation owing to persistent concerns of radiation-associated toxicities by medical oncologists. In addition to offering lower radiation doses and involved site radiation therapy, proton therapy may allow more patients to receive the most effective and safe treatment.

The major limitations of the present study are its small sample size and the diversity of primary disease sites and histologies among patients with NHL. Despite NCCN endorsement for the use of proton therapy in cases where the dose to the OARs can be reduced significantly compared with photon radiation, many patients evaluated at our center for proton therapy for whom the proton plans were superior to the photon plans could not obtain insurance coverage for the treatment of their NHL with protons. These experiences
illustrate the challenges that researchers face when investigating the role of proton therapy for different diseases.

The present study did not examine all possible clinical scenarios in which proton therapy may benefit patients with NHL; the patients included in this study represent a typical cross-section of disease presentations encountered by radiation oncologists. More long-term follow-up of all surviving patients included in this study is essential for continued monitoring of disease status and late toxicities.

**Conclusion**

Proton therapy is a feasible and effective treatment for NHL. Early outcomes are favorable. Longer follow-up and additional patients are needed to confirm our findings. Given the variable disease locations, histologies and biologic behaviors of NHL, prospective studies evaluating proton therapy in the treatment of this disease will be complex, and likely require pooled data from multiple institutions to demonstrate adequate local control and lower rates of late toxicities.

**Potential conflict of interest:** Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

**References**

[1] Surveillance, Epidemiology, and End Results Program. SEER Stat Fact Sheets: Non-Hodgkin Lymphoma. 2014. Available from: http://seer.cancer.gov/statfacts/html/nhl.html

[2] Lowry L, Smith P, Qian W, et al. Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: a randomised phase II trial. Radiother Oncol 2011;106:86–92.

[3] Specht L, Yahalom J, Illidge T, et al. Modern radiation therapy for Hodgkin lymphoma: field and dose guidelines from the International Lymphoma Radiation Oncology Group (ILROG). Int J Radiat Oncol Biol Phys 2014;89:554–62.

[4] Bi XW, Li YX, Fang H, et al. High-dose and extended-field intensity modulated radiation therapy for early-stage NK/T-cell lymphoma of Waldeyer’s ring: dosimetric analysis and clinical outcome. Int J Radiat Oncol Biol Phys 2013;87:1086–1093.

[5] Xu LM, Li YX, Fang H, et al. Dosimetric evaluation and treatment outcome of intensity modulated radiation therapy after doxorubicin-based chemotherapy for primary mediastinal large B-cell lymphoma. Int J Radiat Oncol Biol Phys 2013;85:1289–1295.

[6] Holtzman A, Hoppe BS, Li Z, et al. Advancing the therapeutic index in stage III/IV pediatric Hodgkin lymphoma with proton therapy. Int J Particle Ther 2014;1:343–356.

[7] Hoppe BS, Flampouri S, Su Z, et al. Consolidative involved-node proton therapy for stage IA-IIIB mediastinal Hodgkin lymphoma: preliminary dosimetric outcomes from a phase II study. Int J Radiat Oncol Biol Phys 2012;83:260–267.

[8] Hoppe BS, Flampouri S, Zaiden R, et al. Involved-node proton therapy in combined modality therapy for Hodgkin lymphoma: results of a phase 2 study. Int J Radiat Oncol Biol Phys 2014;89:1053–1059.

[9] Illidge T, Specht L, Yahalom J, et al. Modern radiation therapy for nodal non-Hodgkin lymphoma-target definition and dose guidelines from the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys 2014;89:49–58.

[10] Parikh RR, Moskowitz BK, Maher E, et al. Long-term outcomes and patterns of failure in orbital lymphoma treated with primary radiotherapy. Leuk Lymphoma 2015 Jan 28. [Epub ahead of print]

[11] Sachsman S, Flampouri S, Li Z, Lynch J, Mendenhall NP, Hoppe BS, et al. Proton therapy in the management of non-Hodgkin lymphoma. Leuk Lymphoma 2015;6:1–20. [Epub ahead of print] PubMed PMID: 25669925.

[12] Chen Y, Adams J, Abramson JS, et al. Preliminary experience with proton radiotherapy in mediastinal lymphoma. Int J Radiat Oncol Biol Phys 2010;78(3 Suppl.1):S547.

[13] Li J, Dabaja B, Reed V, et al. Rationale for and preliminary results of proton beam therapy for mediastinal lymphoma. Int J Radiat Oncol Biol Phys 2011;81:167–174.

[14] Hoppe B, Flampouri S, Dang N, et al. Advantages of Proton therapy in the management of primary mediastinal B-cell lymphoma (PMBCL). Br J Haematol 2012;159(Suppl. 1): Abstract 61.

[15] Ronson B, Rossi C, Johnson S, et al. Locoregional proton radiotherapy of a primary cavernous sinus non-Hodgkin’s lymphoma: case report. Technol Cancer Res Treat 2006;5:281–284.

[16] Chung CS, Yock TI, Nelson K, et al. Incidence of second malignancies among patients treated with proton versus photon radiation. Int J Radiat Oncol Biol Phys 2013;87:46–52.

[17] Hoppe BS, Flampouri S, Su Z, et al. Effective dose reduction to cardiac structures using protons compared with 3DCRT and IMRT in mediastinal Hodgkin lymphoma. Int J Radiat Oncol Biol Phys 2012;84:449–455.

[18] Dunleavy K, Pittaluga S, Maeda LS, et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. N Engl J Med 2013;368:1408–1416.

[19] Bhatia S, Paulino AC, Buatti JM, et al. Curative radiotherapy for primary orbital lymphoma. Int J Radiat Oncol Biol Phys 2002;54:818–823.

[20] Bolek TW, Moryes HM, Marcus RB Jr, et al. Radiotherapy in the management of orbital lymphoma. Int J Radiat Oncol Biol Phys 1999;44:31–36.

[21] Zhou P, Ng AK, Silver B, et al. Radiation therapy for orbital lymphoma. Int J Radiat Oncol Biol Phys 2005;63:866–871.

[22] Fasola CE, Jones JC, Huang DD, et al. Low-dose radiation therapy (2 Gy x 2) in the treatment of orbital lymphoma. Int J Radiat Oncol Biol Phys 2013;86:930–935.