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# TREATING HODGKIN AND NON-HODGKIN LYMPHOMA WITH PROTON THERAPY

## CURRENT PRACTICE, OPPORTUNITIES AND CHALLENGES

Proton Therapy in Practice: Clinical Indications - Hodgkin and Non-Hodgkin Lymphoma

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# FOREWORD

Since IBA first started to develop proton therapy solutions, we have focused on collaboration and sharing information. This culture of cooperation allows us to work collectively with clinical partners to make proton therapy available to anyone who needs it.

Our purpose is simply to offer more cancer patients effective treatments, decreased late effects, and a better quality of life.

The amount of clinical data on proton therapy is increasing rapidly, making it a challenge to keep up with new findings and advancements. We decided to take advantage of our day-to-day involvement with experienced clinical teams from proton therapy centers worldwide and gather and share information on the use of proton therapy in oncology.

We have compiled this information in a series of white papers reflecting the latest scientific and clinical advances in proton therapy. The information that follows is the result of our in-depth review of the latest articles published in key scientific journals.

We have undertaken this information-gathering exercise with honesty and ethics. While utmost care has been taken to ensure that the information contained in this publication is correct, unbiased and complete, the reader should be aware that articles have been selected and data interpreted. We encourage you to interpret these data carefully and exercise your own critical and scientific judgment.

The IBA team believes in the benefits of proton therapy for patients and society. This information exemplifies the extraordinary promise of proton therapy, and we hope you will join us in making it accessible to more patients.

We wish you a good reading,

**Sofie Gillis**
*Clinical Solutions Director*
IBA

**Olivier Legrain**
*Chief Executive Officer*
IBA

# CONTACT US


**AMERICAS**
**Toll-free:** 1 877 IBA 4 PBT
**T:** +1 904 491 6080

**EUROPE, MIDDLE EAST AND AFRICA**
**T:** +32 10 203 342
**F:** +32 10 475 923

**EMAIL**
Clinical.program@iba-group.com

**RUSSIA & CIS**
**Toll-free:** +7 495 648 69 00
**E-mail:** info@iba-russia.ru

**ASIA PACIFIC**
**T:** +86 10 8080 9186

**WEBSITE**
**Visit us online at:** https://iba-protontherapy.com

Cancer remains one of the leading causes of morbidity and mortality in the world. In 2018, there were an estimated 17.0 million cases of cancer diagnosed around the world and 9.5 million cancer deaths. By 2040, the global burden is expected to reach 27.5 million new cancer cases and 16.2 million cancer deaths.[1] Fighting cancer and treating this growing number of patients with the latest medical advances is a central goal for medical professionals and healthcare policy makers. Approximately 52% of new cancer patients will need radiation therapy as part of the multi-disciplinary cancer care, and 23% of these patients will require reirradiation treatment.[2] Although photons are the most common source of ionizing radiation, protons are gaining increasing recognition from physicians and medical physicists as an advanced treatment modality. The growing emphasis on evidence-based medicine practice makes it worthwhile to assess the available evidence supporting proton therapy (PT) over other available techniques, so as to better guide physicians and patients toward the most appropriate treatment.

## HODGKIN & NON-HODGKIN LYMPHOMA

It is estimated that in 2020, 85,720 new cases of Lymphoma will be diagnosed in the United States, including both adult and children and of which 8,480 Hodgkin Lymphoma (HL) and 77,240 Non-Hodgkin Lymphoma (NHL).[3]

NHL is one of the most common cancers in the United States, accounting for about 4% of all cancers[4], whereas HL is the most common cancer in the adolescent group of 15-19 years old, accounting for 12% of all childhood cancers.[3] Lymphomas are associated with a relatively high survival rate and diagnosis at young age. Particularly, combined chemo-radiotherapy cures most HL patients, with roughly 70–80% of them surviving many decades after treatment.[5] Although chemotherapy is the primary treatment for patients with lymphoma, consolidative radiation is often used in HL and aggressive NHL, while definitive treatment with radiation alone is used only in a small fraction of lymphoma patients. Up to 50% of patients with lymphoma live long enough to experience life-threatening late effects of treatment. Hence treatment-related toxicities caused by chemotherapy agents and radiation exposure to healthy tissues are major concerns for lymphoma survivors. A 40% cumulative incidence of grade 3 to 5 chronic toxicity was attributed to chemotherapy and radiotherapy among pediatric HL survivors 25 years following treatment.[6] Radiation therapy contributes to some of these side effects, particularly damage to the heart, with increased risk of premature coronary artery disease and valvular disease and possible development of secondary malignancies of the lung, breast, and thyroid, with risks of 18% to 28% at 15–25 years post treatment.[7] Advances in the radiation therapy domain have enabled reductions in the size of the target volume, and significant reductions in the dose to nontargeted normal tissues at risk for radiation damage.[8] Advanced radiation therapy technologies such as proton therapy may offer significant and clinically relevant advantages such as sparing important organs at risk and decreasing the risk for late normal tissue damage while still achieving the primary goal of disease control. This is especially important for lymphoma patients who are being treated with curative intent and have long life expectancies following therapy.[9]

This white paper aims at providing existing clinical data on proton therapy for lymphomas, which can serve as a valuable reference when considering treatment options that would be of most benefit to patients.

## PATIENT SELECTION

The physical properties of proton therapy underlie its advantages in dose distribution, which results in improved therapeutic gains. The clinical interest lies in the comparative impact of proton beam therapy versus alternatives such as photon beam therapy, either as a curative solution or a salvage therapy for cancerous and non-cancerous conditions, and their effects on survival, disease progression, safety, health-related quality of life and other patient outcomes. The current model policy[10] developed by the American Society for Radiation Oncology (ASTRO) recommends that patient selection is based on the added clinical benefits offered by proton therapy. This comes down to considering proton therapy in cases where sparing the surrounding normal tissue is crucial and cannot be adequately achieved with a photon-based approach. The policy provides several non-

specific examples:

• The target volume is near one or more critical structures and a steep dose gradient outside the target must be achieved to avoid exceeding the tolerance dose to the critical structure(s).

• A decrease in dose homogeneity in a large treatment volume is required to avoid an excessive dose 'hotspot' within the treated volume to lessen the risk of excessive early or late normal tissue toxicity.

• A photon-based technique would increase the probability of clinically meaningful normal tissue toxicity by exceeding an integral dose-based metric associated with toxicity.

• The same or an immediately adjacent area has been previously irradiated, and the dose distribution within the patient must be sculpted to avoid exceeding the cumulative tolerance dose of nearby normal tissue.

In particular, disease sites that frequently support the use of proton therapy are those of patients with genetic syndromes that make total volume of radiation minimization crucial, such as but not limited to neurofibromatosis type 1 (NF-1) patients and retinoblastoma patients. Because of the disease characteristics of Hodgkin lymphoma and non-Hodgkin lymphoma, including a very high risk of developing a secondary cancer[11], proton therapy is an important option for these groups of patients.

The International Lymphoma Radiation Oncology Group guidelines on Proton therapy for adults with mediastinal lymphomas was published in late 2018[12]. The consensus considerations suggested that lymphoma patients who can greatly benefit from proton therapy include (1) patients with mediastinal disease that spans below the origin of the left main stem coronary artery and is anterior to, posterior to, or on the left side of the heart; (2) young female patients for whom proton therapy can reduce breast dose and risk for secondary breast cancer; and (3) heavily pretreated patients who are at higher risk for radiation-related toxicity to the bone marrow, heart, and lungs.

Proton therapy offers dosimetry advantages that may translate to clinical benefits. However, delivering proton therapy can add complexity compared with conventional radiotherapy. A comprehensive understanding of benefits and consequences is necessary for clinicians before applying proton therapy techniques. The decision to employ proton treatment also requires an informed assessment of benefits and risks.

## PROTON THERAPY FOR LYMPHOMAS

### A) OVERVIEW OF BENEFITS

Adopting the strategy of smaller target volume and lower dose in radiotherapy in order to reduce radiation-induced toxicity has translated into lower rates of toxicity, as shown by substantial published data. The advances in radiotherapy delivery technique, such as intensity-modulated radiotherapy (IMRT), enable the implementation of this strategy in practice. However, while IMRT was better able to protect the heart and coronary arteries compared to three-dimensional conformal radiotherapy (3DCRT), it caused more concern regarding increased volume of normal tissue receiving low dose, which increased the risk of breast, lung, and thyroid cancers. Studies have highlighted that the estimated increase of secondary cancer risk inherent to IMRT techniques should be carefully considered in the evaluation of a risk-adapted therapeutic strategy.[13,14]

Proton therapy is different from photon-based radiotherapy. Because of the unique physical properties, protons have little exit dose and low entrance dose. Proton therapy is able to achieve statistically significant and clinically relevant dose reduction, as numerous in silico studies have demonstrated.[15] In addition to overall integral dose reduction, proton plans are the best to achieve organ specific dose reduction for heart, lung, esophagus, breast and other structures as reported in an evidence based review of proton therapy for mediastinal lymphoma by the Particle Therapy Cooperative Group (PTCOG) lymphoma sub-committee.[16] A comparison study on estimated risks of cardiovascular disease and secondary lung and breast cancers attributable to 3DCRT, volumetric modulated arc therapy (VMAT) and proton therapy shows proton therapy as the superior modality that results in the least life years lost.[17] The latest development of proton delivery technique – pencil beam scanning (PBS) – enables further reduction of mean lung dose, mean heart dose and internal target volume.[18]

The number of clinical outcome studies is increasing, particularly prospective studies. Reported data discussed in the literature review below has shown encouraging disease control and an expected reduction in long-term adverse effects, given the minimized target volume and significant dose reduction to normal tissue. Lymphoma patients treated with proton therapy are being followed for longer term data.

PT IRMT

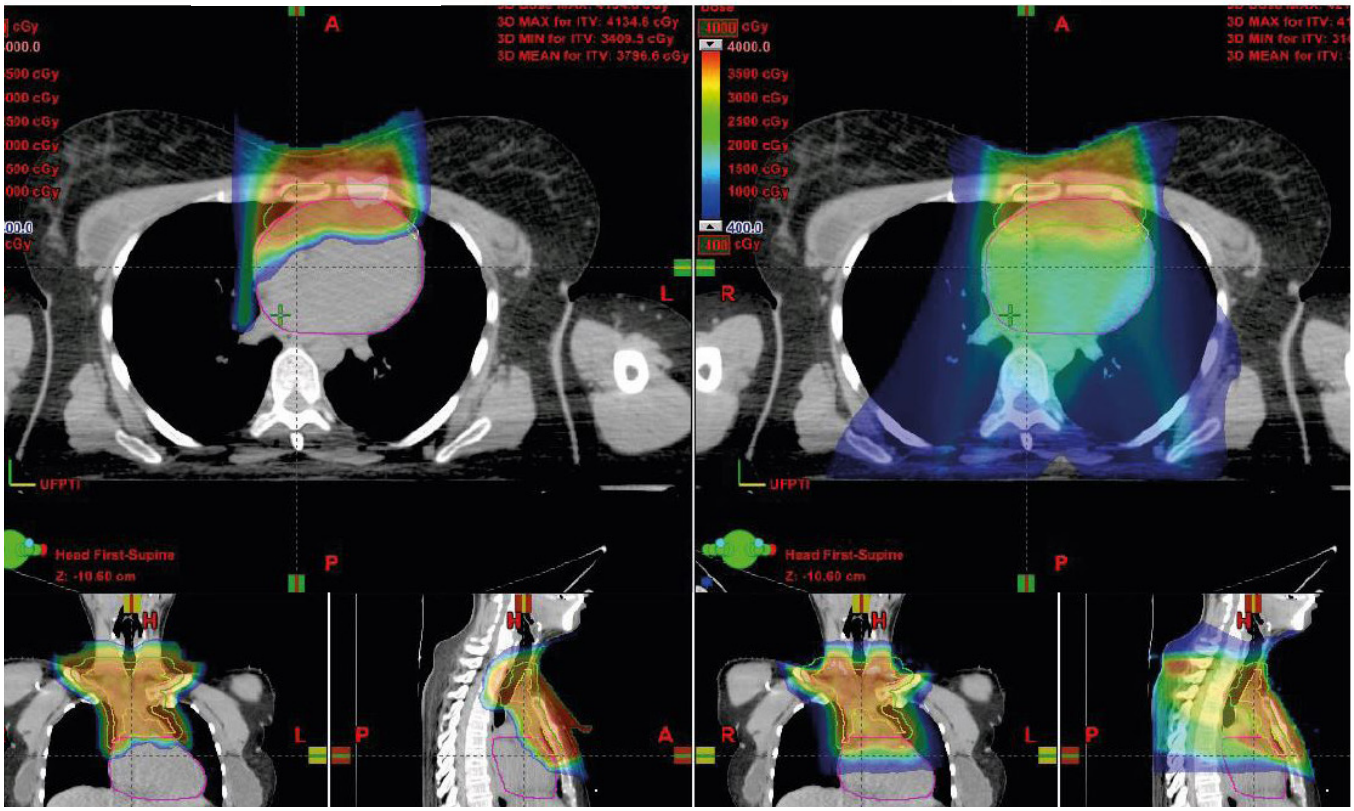
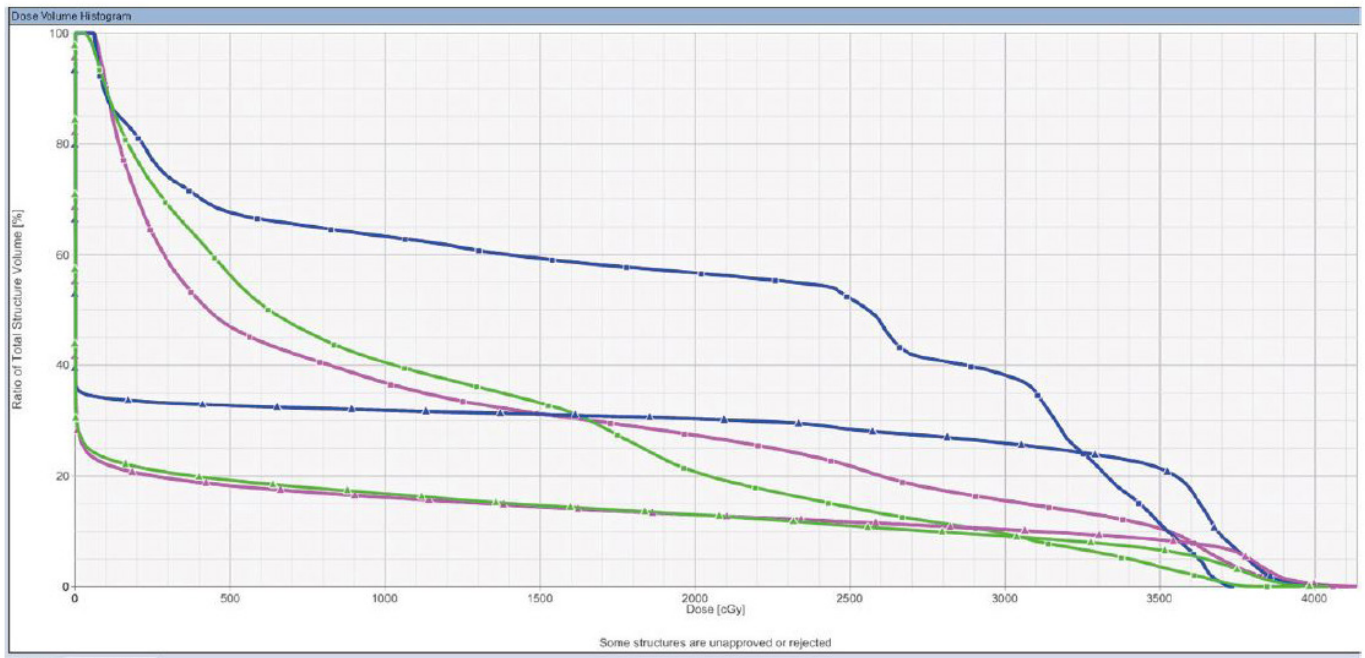



Figure 1: Radiation treatment plans comparing PT (left) and IMRT (right) for mediastinal lymphoma. The plan target volume (PTV) is in green, the heart is in pink. Proton therapy was able to better spare the heart (5.2 Gy vs. 11.7 Gy) and lungs (5.1 Gy vs. 11.2 Gy) in this young patient with mediastinal lymphoma.




| DVH Line | Structure | Approval Status | Plan | Course | Volume [cm³] | Dose Cover [%] | Sampling Cover [%] | Min Dose [cGy] | Max Dose [cGy] | Mean Dose [cGy] |
|---|---|---|---|---|---|---|---|---|---|---|
| | Lungs | Unapproved | IMRT | C1 | 2558.6 | 100.0 | 100.0 | 27.7 | 3955.3 | 1115.9 |
| | Lungs | Unapproved | PTV IR | C1 | 2558.6 | 100.0 | 100.1 | 0.0 | 4044.1 | 512.9 |
| | Heart | Unapproved | IMRT | C1 | 649.7 | 100.0 | 100.0 | 52.7 | 4108.0 | 1171.6 |
| | Heart | Unapproved | PTV IR | C1 | 649.7 | 100.0 | 100.0 | 0.0 | 4134.6 | 524.4 |
| | Esophagus | Unapproved | IMRT | C1 | 31.0 | 100.0 | 100.0 | 59.7 | 3740.8 | 1950.7 |
| | Esophagus | Unapproved | PTV IR | C1 | 31.0 | 100.0 | 100.5 | 0.0 | 3998.9 | 1087.3 |

Figure 2: Dose Volume Histogram comparison between PT double scattering (triangle) and IMRT (square) for organs at risk from the treatment illustrated in figure 1. All illustrations courtesy of Department of Radiation Oncology, University of Florida.

## B) DOSIMETRIC COMPARISON

Hoppe et al. of the University of Florida published their prospective study[19] evaluating dosimetric outcomes of 10 patients with stage IA-IIIB Hodgkin lymphoma and mediastinal involvement in 2012. For each patient, three separate optimized plans were developed: 3DCRT, IMRT and PT. The dosimetric comparison showed that the median relative reduction with proton therapy in the primary end point, body V4, was 51% compared with 3DCRT ($p = 0.0098$) and 59% compared with IMRT ($p = 0.0020$), and proton therapy provided the lowest mean dose to the heart, lungs, and breasts for all 10 patients. Consequently, all 10 patients were offered treatment with proton therapy. Figures 1 and 2 represent the dosimetric comparison between PT double scattering and IMRT for a young patient with mediastinal lymphoma (see figures on page 5).

## C) CLINICAL OUTCOMES - LITERATURE REVIEW

Survivors of Hodgkin lymphoma and non-Hodgkin lymphoma live decades after treatment with a risk of developing chemotherapy- or radiotherapy-related toxicities. Recent efforts in the field of radiotherapy have successfully reduced the radiation dose and treatment field without compromising cure rates. According to Ho et al.[20] proton therapy has the potential of further lowering treatment-related toxicities. This finding is supported by numerous dosimetric studies, however its utilization in the management of lymphoma has been limited due to the scarcity of facilities and the difficulty of obtaining insurance coverage. With diligent follow-up, the authors argued that the clinical impact of proton therapy can be established to improve the therapeutic ratio and to reduce late treatment-related morbidity.

### Hodgkin Lymphoma

In 2011, Li et al.[7] of the MD Anderson Cancer Center, Texas, published their findings on 10 patients with mediastinal masses that had been treated with protons. They compared dosimetric endpoints of proton plans and conventional radiotherapy plans, and found that PBT delivered lower mean doses to the lung (6.2 vs. 9.5 Gy), esophagus (9.5 vs. 22.3 Gy), and heart (8.8 vs. 17.7 Gy) but not the breasts (5.9 vs. 6.1 Gy) than did conventional radiotherapy. The authors suggested that for mediastinal lymphomas, the significant lower doses to the lung, esophagus, heart, and coronary arteries with proton therapy would be expected to reduce the risk of late toxicities in these major organs.

A 2014 publication by Hoppe et al.[21] collected the clinical outcomes of 15 patients, five children and 10 adults, treated with protons at the University of Florida. A three-year relapse-free survival rate of 93% and event free survival rate of 87% were observed, without any acute or late grade 3 non-hematologic toxicities. The researchers encountered one relapse, inside and outside the targeted field, and one transformation into a primary mediastinal large B-cell lymphoma. In their conclusion, the authors stated that decades of follow-up would be needed to realize the likely benefit of proton therapy in the risk reduction of radiation-induced late effects, but proton therapy following chemotherapy in patients with Hodgkin lymphoma was well-tolerated and disease outcomes proved similar to those of conventional photon therapy. Another University of Florida study published in the same year by Sachsman et al. [22] reported on proton therapy for Hodgkin lymphoma in the diaphragmatic and subdiaphragmatic regions. Twelve patients were treated with proton therapy following chemotherapy and had comparative 3DCRT and IMRT plans to evaluate differences in dose to OARs. There was significant dose reduction using proton therapy for the stomach, liver, pancreas, bowel, left kidney and right kidney. The authors stated that these dose reductions were expected to translate into lower risks of secondary cancers and other late toxicities in survivors of Hodgkin lymphoma.

In 2016, Hoppe et al.[23] analyzed the outcomes of 40 patients treated with proton therapy in the multi-center registry study (NCT01255748). 93% patients had mediastinal involvement and 65% has bulky disease. With the median follow-up of 21 months, this study reported that the two-year relapse-free survival rate was 85%, with three recurrences, including two in-field recurrences. No grade 3 acute toxicities were reported among the patients. The most common grade 2 side effects were esophagitis (10%), dermatitis (7.5%), fatigue (2.5%), and dyspepsia (2.5%). The authors concluded that the early results demonstrate an acceptable rate of recurrences. The authors also pointed out that this cohort of patients being treated with PT were those who stand to benefit the most based on the location of their disease (93% mediastinum) and young age (median age, 21 years). The dosimetric advantage of PT compared to photon techniques with respect to dose to the breast, lung, and heart may translate to significant reductions in late toxicity.

In 2017, Hoppe et al.[24] published results of the largest series of 138 patients with HL received chemotherapy followed by consolidative proton therapy. 42% patients were pediatric

(≤18 years) and 93% were under the age of 40 years. Patients predominantly had mediastinal involvement (96%) and bulky disease (57%). The 3-year relapse-free survival rate was 92% for all patients; it was 96% for adults and 87% for pediatric patients. No grade 3 radiation-related toxicities have occurred to date.

In 2018, Ntentas et al.[25] published the early outcomes of 21 patients treated with deep-inspiration breath-hold (DIBH) pencil-beam scanning (PBS) proton therapy. With the median follow-up time of 24 months, this study reported no recurrence or disease progression. Treatment was well tolerated by all patients, and no severe toxicities were reported. Minor acute toxicities were reported for some patients, including grade 1 dysphagia, radiodermatitis, mucositis, anemia and grade 2 leukopenia. The authors concluded that patients with a CTV that extends below the seventh thoracic level, female patients with axillary disease, and patients who have more extensive disease and hence a larger PTV can have significant dosimetric benefit from PBS treatments.

### Non-Hodgkin Lymphoma

Sachsman et al.[26] reviewed 11 patients with non-Hodgkin lymphoma who received proton therapy at the University of Florida from January 2008 to January 2014. The cohort included four patients with indolent orbital lymphoma, three with primary mediastinal B-cell lymphoma, two with plasmablastic lymphoma and two with natural killer (NK) T-cell lymphoma. With a median follow-up of 38 months, they reported 91% local control rate at two years. One patient with NK T-cell lymphoma showed recurrence infield. There was no grade 2 above toxicities reported. The authors concluded that proton therapy was a feasible and effective treatment for non-Hodgkin lymphoma, with favorable outcomes, but specified that longer term follow-up is needed.

In 2018, Plastaras et al.[27] reported results of 24 adult patients with mediastinal non-Hodgkin lymphoma (either primary mediastinal large B cell lymphomas or mediastinal diffuse large B cell lymphoma) treated with chemotherapy followed by proton radiation. The majority (87.5%) had bulky disease. With the median follow-up of 28 months, the local control rate was 96% and none had grade 2 or higher radiation pneumonitis.

While disease control appears to be similar between photon radiation and proton radiation for patients with lymphoma, the rationale for using proton therapy is to reduce the late effects from treatment, including second cancers and cardiac toxicity. Large cancer registry studies have been done to explore these differences. Chung et al.[28] conducted a matched paired analysis among patients treated at MGH with proton therapy with patients treated in the SEER registry, where patients were matched by sex, age, and cancer diagnosis. The results demonstrated a significant reduction in second cancers for patients treated at MGH with proton therapy. Another study by Xiang et al.[29] evaluated second cancer risk after photon or proton therapy using the NCDB database. This study also demonstrated a significant reduction in second cancers among patients treated with proton therapy, including a reduction among patients with lymphoma treated with proton therapy.

In summary, as pointed out in the International Lymphoma Radiation Oncology Group guidelines on Proton therapy for adults with mediastinal lymphomas[12], the clinical data demonstrates the promising results of proton therapy for lymphomas with mediastinal involvement. As proton treatment techniques continue to evolve, the dosimetric advantage of reducing the dose to organs at risk in certain disease distributions can be significant and highly desirable. However, until proton therapy becomes widely accessible, it requires case selection based on a clear understanding of which cases will benefit derive most from protons therapy compared to other advanced photon techniques.

## D) ONGOING STUDIES

There is no ongoing study registered in the ClinicalTrials.gov database. The clinical trial ‘Proton Therapy for Hodgkin Lymphoma’ (NCT00850200) led by University of Florida Proton Therapy Institute Jacksonville was completed in 2018. Another clinical trial ‘Proton Radiation for Lymphoma Involving Mediastinum’ (NCT01751412) led by Massachusetts General Hospital was completed in 2017. Proton therapy is allowed on cooperative group Hodgkin lymphoma trials, including Children’s oncology group (COG) studies, Southwestern oncology group, Euronet, and German Hodgkin Study Group.

## THE EXPERT'S PERSPECTIVE

*Dr. Bradfort S. (Brad) Hoppe, M.D., M.P.H*
*Professor of Radiation Oncology,*
*Particle Therapy Director*
*Department of Radiation Oncology,*
*Mayo Clinic Florida*

A Professor of Radiation Oncology and Particle Therapy Director at the Mayo Clinic Florida, Dr. Hoppe specializes in the management of patients with Hodgkin lymphoma, non-Hodgkin lymphoma, lung cancer and prostate cancer. He is the Chair of the Lymphoma Subcommittee of the Particle Therapy Cooperative Group (PTCOG); Radiation Chair of the COG Hodgkin lymphoma committee, Secretary of the Particle Therapy Co-operative Group of North America (PTCOG-NA), Steering Committee of ILROG; and also serves on the American Radium Society (ARS) Expert Lymphoma Guidelines Committee, the American Board of Radiology (ABR) Lymphoma Examination Board, and the American Society for Radiation Oncology (ASTRO) CME Committee. An established cancer researcher, Dr. Hoppe is the principal investigator on five clinical trials and the author of over 130 published manuscripts and book chapters in various peer-reviewed medical journals, including Journal of Clinical Oncology, Cancer, Journal of Thoracic Oncology, Bone Marrow Transplant, Radiotherapy and Oncology and the International Journal of Radiation Oncology Biology Physics. His research focus has been on reducing side effects of radiation and better understanding patient-reported quality-of-life outcomes among patients with lung cancer, prostate cancer and lymphoma.

## THE PRESENT

The first proposal for using proton therapy to treat Hodgkin lymphoma dates from 1976, but it wasn't actually put into clinical practice until much later with the first clinical series published in 2011. Dr. Hoppe shares his observations after twelve years of treating patients with lymphoma with proton therapy: "As is the case with proton therapy for any malignancy, using this modality potentially improves the therapeutic ratio. In Hodgkin lymphoma patients, proton therapy can help minimize toxicity and maximize the cure rate. Patients with Hodgkin lymphoma are at the highest risk of developing late complications from treatment due to their excellent cure rates and the early age at presentation (it is the most common malignancy among adolescents and young adults). In addition, many lymphomas are found in the mediastinum, adjacent to the lung, heart and breast tissue, which are all extremely sensitive to chemotherapy and radiation and can lead to second cancers and cardiac complications. Because of the fear of these long-term radiation toxicities, medical oncologists often won't send their patients for radiation. However, proton therapy can potentially reduce these late toxicities."

In describing the benefits attributed to proton therapy, Dr. Hoppe identifies potential benefits in reducing the toxicity during treatment: "Several institutions pooled their patients treated with proton therapy for Hodgkin lymphoma together to obtain data on a larger patient cohort. The follow-up isn't long enough to describe long-term effects, but the investigators found that patients who receive proton therapy are primarily younger and their disease involves the mediastinum. These are the patients who would benefit the most from a reduction of long-term side effects. We found that among 138 Hodgkin lymphoma patients treated with proton therapy – a larger cohort than any IMRT experience – the cure rate is the same as with photon-based treatment and there were no grade 3 toxicities, such as pneumonitis or esophagitis. Lymphomas are generally treated with a low dose of radiation, so in most cases severe side effects don't occur, except for some esophagitis or pain or discomfort with swallowing. Although data for direct comparison to photon-based treatment with a similar patient population are lacking, we do observe a lower radiation dose to the esophagus with proton treatment plans."

Dr. Hoppe specifies that the real benefits will probably only be established in several decades, when the reduction in therapy-related second cancers can actually be observed. "At the moment, there are not enough patients treated and there is not enough follow-up to allow us to make such observations in relation to lymphoma patients. Massachusetts General Hospital, however, has published a study showing close to a 50% reduction in second cancers amongst their proton patients compared to similar patients with various cancers treated with photons. Volumes of literature have been published showing that a higher radiation dose to the organs at risk increases the risk of late-term side effects. And at least 12 studies have shown that proton therapy significantly reduces the dose to the different organs. Consequently, one would expect less late toxicity by treating with protons. In lymphoma patients, we expect to see fewer radiation-induced cancers, including breast cancer, lung cancer and sarcomas. Owing to disease location in the chest, cardiac complications are a big cause of long-term toxicity and death in lymphoma survivors as well. As proton therapy allows for

a reduction in dose to the heart, a significant reduction of these complications may be anticipated as well." Through the Particle Therapy Cooperative Oncology Group (PTCOG), a group of radiation oncologists with an interest in proton therapy in lymphoma formed the Lymphoma Subcommittee, over which Dr. Hoppe presides. This committee has been working towards developing a cooperative approach in developing evidence for proton therapy in the management of lymphoma.

## THE FUTURE

For the future, Dr. Hoppe advocates a change in insurance policies: "Although Hodgkin lymphoma is a rare disease, it is the number one diagnosed cancer in adolescents and early young adults (AYA). Young adults gain just as much from proton therapy as pediatric patients, but are often overlooked since, in the U.S., insurance companies will only cover patients up to age 18 years, and the ASTRO policy does not include this age group in its definition of patients eligible for proton therapy. Nevertheless, as Hodgkin lymphoma is a rare type of cancer and survivors have decades of life left, proton therapy reimbursements for AYA would support cost-effective health care."

Dr. Hoppe is looking forward to an increased overall experience of treating lymphoma patients with proton therapy as more institutions adopt proton therapy and to several technologic advancements. Pencil beam scanning, already implemented and used to treat Hodgkin lymphoma patients at Penn Medicine, Mayo Clinic, and the MD Anderson Cancer Center, will bring intensity-modulated proton therapy into our scope. In addition, interesting developments in the field of in-room imaging, such as a cone-beam CT and an MRI to help with the daily alignment, will advance the sophistication of our image-guided radiation therapy (IGRT). Deep-inspiration breath-hold techniques are gaining importance as well. We have been using these to some degree, but advancements in this technique will help us to administer proton treatment safely and accurately." Because they are concerned about the side effects, medical teams opt for smaller targets with X-rays. Dr. Hoppe believes that proton therapy might allow for larger target volumes, leading to better outcomes in cure rates in the future. Furthermore, Dr. Hoppe believes that, "The realization that late effects are going to be lower than what has been seen in the past should alleviate medical oncologists' fears and encourage them to refer Hodgkin lymphoma patients for radiation."

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# NOTES

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