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 of information. This culture of cooperation has allowed us to work together with clinical partners to help make proton therapy available to anyone who needs it.

Our purpose is to offer more cancer patients effective treatments, decreased side effects, leading to 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, in order to gather and share information on the use of proton therapy in oncology.

We've compiled this information and written a series of white papers reflecting on 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 the highest level of integrity. While utmost care has been taken to ensure that the information contained in this publication is accurate, complete and unbiased, 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 will help you and your teams learn more about the extraordinary promise of proton therapy, and we hope you will join us in making it accessible to more patients.

We wish you good reading,

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Cancer remains one of the leading causes of morbidity and mortality in the world, accounting for 8.2 million deaths in 2012. 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. No less than 52% of every 1,000 new cancer patients will need radiation therapy as part of their treatment, and 23% of these patients will require re-treatment. Although photons are the most common source of ionizing radiation, protons are gaining increasing recognition from physicians and medical physicists as a superior treatment modality. The growing emphasis on evidence-based medicine practices 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

Hodgkin lymphoma and non-Hodgkin lymphoma are two categories of lymphomas that represent 4.8% of all cancers (excluding simple basal cell and squamous cell skin cancers) in the United States, and 47% of all blood cancers in the United States.[1] The estimated number of new cases of childhood and adolescent cancers in the United States in 2014 shows that Hodgkin lymphoma was the most common malignancy in the adolescent group (ages 15-19), accounting for 15% of the total cancers, and non-Hodgkin lymphomas were the fourth most common cancers in the children's group (ages 0-14).[2] Lymphomas are characterized by high survival rates and diagnosis at young age. Combined chemotherapy and radiotherapy achieves the best disease control for Hodgkin lymphoma and results in 85% of patients becoming long-term survivors. Up to 50% of patients with lymphoma live long enough to experience life-threatening late effects of treatment.[3]

Although chemotherapy is the primary treatment for patients with lymphoma, consolidative radiation is often used in Hodgkin lymphoma and aggressive non-Hodgkin lymphoma, while definitive treatment with radiation alone is used in a small fraction of lymphoma patients. Unfortunately, treatment-related toxicities caused by chemotherapy agents and radiation exposure to healthy tissues are major concerns for lymphoma survivors. While randomized studies confirm that radiotherapy is necessary for disease control for lymphomas, some of the radiation-induced late toxicities can occur decades after treatment, leading to some oncologists referring fewer patients for radiation.[4] These toxicities include secondary malignancies, cardiovascular disease, hypothyroidism, cerebrovascular accidents, and muscle atrophy. A 40% cumulative incidence of grade 3 to 5 chronic toxicity is attributed to chemotherapy and radiotherapy among Hodgkin lymphoma survivors 25 years following treatment.[5] Reducing irradiated volume and lowering radiation dose has become pivotal in radiation treatment because studies show this has translated into late toxicity reduction.[6]

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.[7]

This white paper aims to provide 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 increasing emphasis on evidence-based medicine practices makes it worthwhile to assess the available data supporting proton therapy over other techniques to better guide physicians and patients toward the most appropriate treatment.[8]

The current model policy developed by the American Society for Radiation Oncology (ASTRO) recommends that patient selection be 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 in close proximity to 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 the amount of dose inhomogeneity 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,[9] proton therapy is an important option for these groups of patients.

Proton therapy may offer dosimetry advantages as well as add complexity over 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.[10]

PROTON THERAPY FOR LYMPHOMAS

A) OVERVIEW 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.[11, 12]

Proton therapy is different from photon-based radiotherapy. Because of their unique physical properties, protons have no 'exit' dose and very little 'entrance' dose. Proton therapy is able to achieve statistically significant and clinically relevant dose reduction, as numerous in silico studies have demonstrated.[13] In addition to overall integral dose reduction, proton plans lend themselves best to achieving organ-specific dose reduction for heart, lung, esophagus, breast and other structures. 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.[14] 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.[15]

The number of clinical outcome studies is increasing, particularly prospective studies. Reported data 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.

B) DOSIMETRIC COMPARISON

Hoppe et al. of the University of Florida published their prospective study[16] 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.

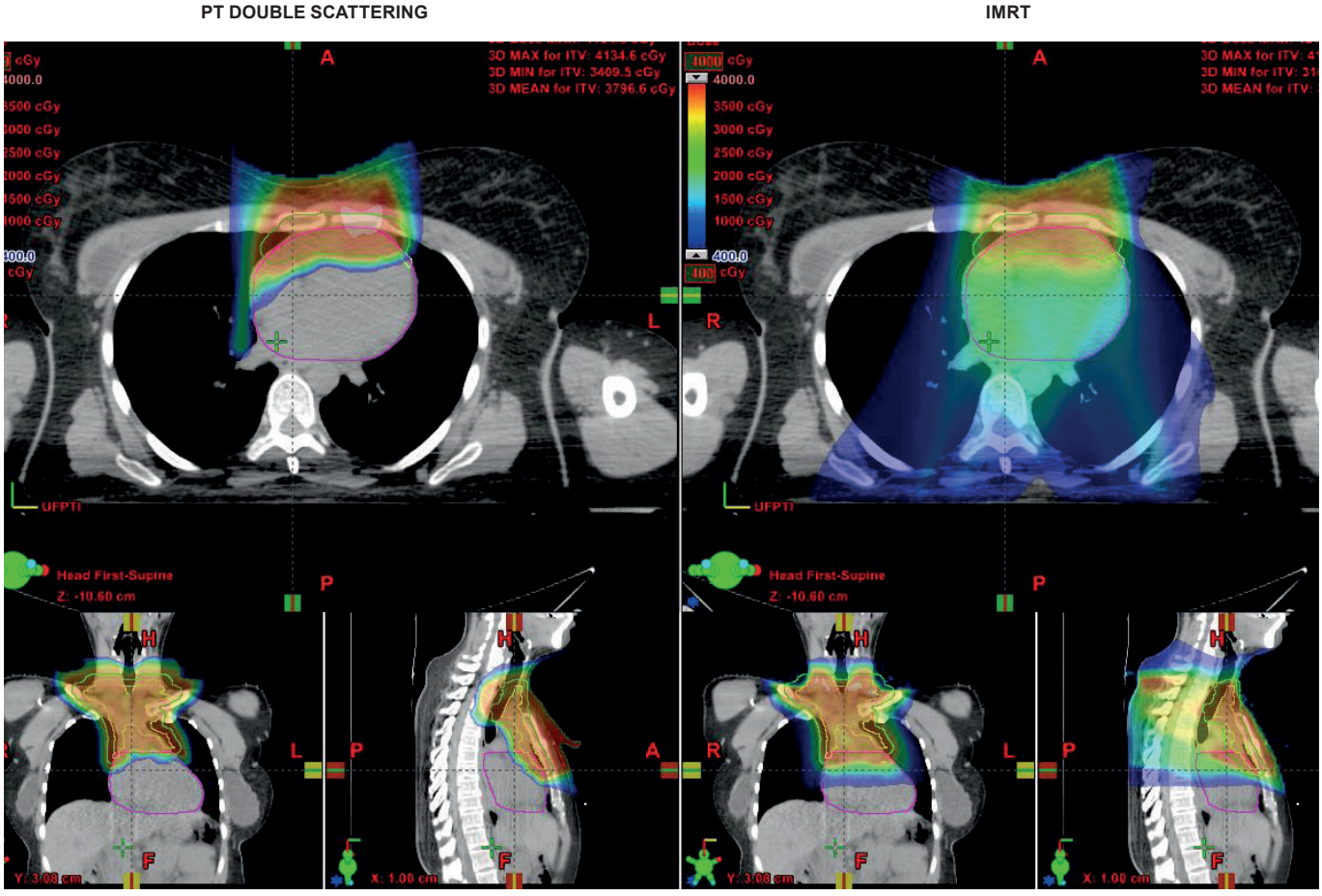
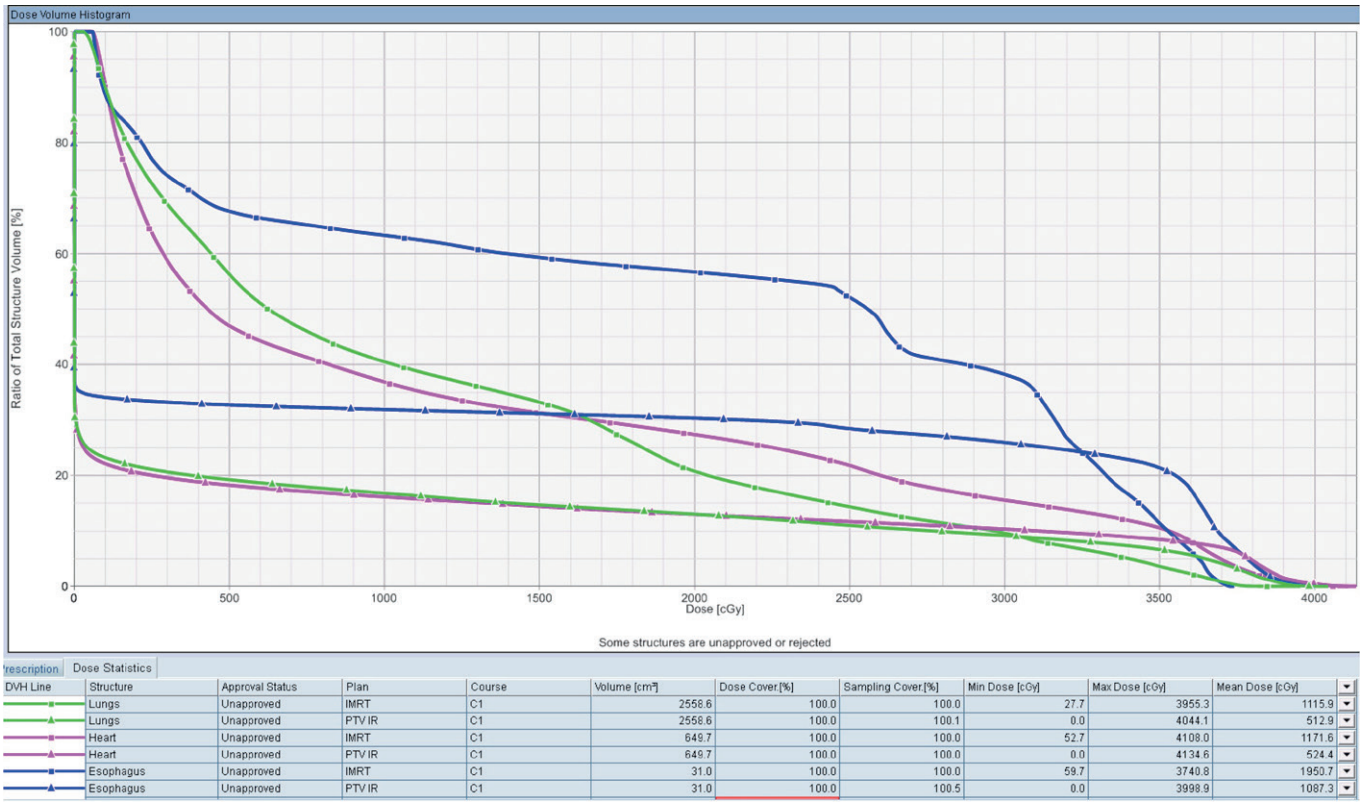


Figure 1: Radiation treatment plans comparing PT double scattering (left) and IMRT (right) for mediastinal lymphoma. The plan target volume (PTV) is in green, the heart is in pink. Proton therapy was able to better spare the heart (5.2 Gy vs. 11.7 Gy) and lungs (5.1 Gy vs. 11.2 Gy) in this young patient 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 Dr. Brad Hoppe, Associate Professor, Department of Radiation Oncology, University of Florida.

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.,[17] 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 for the past five years due to the scarcity of facilities and the difficulty of obtaining insurance coverage. With diligent follow-up, the authors argue that the clinical impact of PT can be established to improve the therapeutic ratio and to reduce late treatment-related morbidity.

• HODGKIN LYMPHOMA

In 2011, Li et al.[18] of the MD Anderson Cancer Center in Houston, Texas, published their findings on 10 patients with mediastinal masses that had been treated with protons. They compared dosimetric plans used for proton and conventional radiotherapy and found that the percentages of lung, esophagus, heart, and coronary artery (particularly the left anterior descending artery) volumes that received radiation were consistently lower in the three-dimensional proton beam therapy (3DPBT) plans for a wide range of radiation doses.

A 2014 publication by Hoppe et al.[19] 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 a three-year 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.

Author	Pathology	Study	Outcome	Conclusion
Li et al., 2011	Hodgkin lymphoma	comparison study 10 patients 3DPBT and conventional radiotherapy MD Anderson	percentage of volume that received radiation consistently lower in 3DPBT plans for wide range of radiation dose in: - lung - esophagus - heart - coronary artery (particularly left anterior descending artery)	
Hoppe et al., 2014	Hodgkin lymphoma	retrospective analysis 15 patients, 5 children - 10 adults protons University of Florida	3-year relapse-free survival, 93% 3-year event-free survival, 87% 0 acute or late grade 3 non-hematologic toxicities 1 relapse, inside & outside targeted field 1 transformation into primary mediastinal large B-cell lymphoma	proton therapy following chemotherapy in patients with Hodgkin lymphoma was well-tolerated and disease outcomes proved similar to those of conventional photon therapy
Sachsman et al., 2014	Hodgkin lymphoma	comparison study 12 patients proton therapy following chemotherapy, compared to 3DCRT & IMRT MGH	significant dose reduction with proton for: - stomach - liver - pancreas - bowel - left kidney - right kidney	dose reduction expected to translate into lower risks of secondary cancers and other late toxicities in survivors
Toltz et al., 2015	Hodgkin lymphoma	comparison study 20 patients <30 3DCRT, compared to HT & IMPT McGill University	predicted risk of cardiac mortality = in all three techniques predicted risk of secondary lung and breast cancer: - HT > 3DCRT - IMPT < 3DCRT	
Wray et al., 2016	Hodgkin lymphoma	retrospective analysis 22 patients 6-18 y old: - 7 intermediate-risk - 11 high-risk - 4 relapsed proton following chemotherapy University of Florida	2- & 3-year overall survival, 94% progression-free survival, 86% 0 PT-related grade 3 or higher acute or late complications	PT for PHL showed no short-term severe toxicity (similar short-term control to recently published large multi-institutional clinical trials)
Sachsman et al., 2015	non-Hodgkin lymphoma	retrospective analysis 11 patients: - 4 indolent orbital - 3 primary mediastinal B-cell - 2 plasmablastic - 2 NK T-cell protons University of Florida	2-year local control, 91% 1 NK T-cell patient showed recurrence in-field 0 grade 2 or higher toxicities 2-year overall survival, 53%	proton therapy = feasible and effective treatment for non-Hodgkin lymphoma, with favorable outcomes, but longer term follow-up is needed

Another University of Florida study published in the same year by Sachsman et al.[20] 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 three-dimensional conformal photon radiotherapy (3DCRT) and IMRT plans to evaluate differences in dose to organs at risk (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 a paper published in 2015, Toltz et al.[21] from McGill University in Montreal, Canada, showed that in 2010, all young patients treated at one of the 10 radiotherapy centers of the province of Quebec for intrathoracic Hodgkin lymphoma with 3DCRT could now be at risk for late treatment-related toxicities such as secondary malignancies and cardiac toxicity. All treatment plans for 20 patients with age <30 years treated were replanned with helical tomotherapy (HT) and intensity-modulated proton therapy (IMPT). The authors showed that if predicted risk for cardiac mortality was similar among the three treatment techniques (3DCRT, HT and IMPT), predicted risks of secondary lung and breast cancer were increased for HT and reduced for IMPT as compared to 3DCRT.

In 2016, Wray et al.[22] published a study on the 22 pediatric patients (six to 18 years old) treated with PT for pediatric Hodgkin lymphoma (PHL) at the University of Florida Health Proton Therapy Institute between 2010 and 2014: seven intermediate-risk patients, 11 high-risk patients, and four relapsed patients. Median follow-up was 36 months and all patients received chemotherapy before PT. The two-year

and three-year overall survival (OS) rates were both 94%, and the progression-free survival rate was 86%, and no PT-related grade 3 or higher acute or late complications were observed. The authors concluded that PT for PHL showed no short-term severe toxicity and yielded similar short-term control to recently published large multi-institutional clinical trials.

•NON-HODGKIN LYMPHOMA

Sachsman et al.[23] 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 in-field. 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.

D) REFERENCE TO ONGOING STUDIES

There is one ongoing study included in the ClinicalTrials.gov registry and results database. The Massachusetts General Hospital is investigating the possibility of using proton radiation to treat different types of lymphoma that involve mediastinum. Outcome measures include radiation dose improvement to heart and lung normal tissues, as well as disease control and toxicity profile. Primary completion data is estimated in 2017.

E) THE EXPERT'S PERSPECTIVE

Dr. Brad Hoppe,
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As an Associate Professor of Radiation Oncology at the University of Florida, Dr. Hoppe specializes in the management of patients with Hodgkin lymphoma, non-Hodgkin lymphoma, lung cancer and prostate cancer. He currently holds the James E. Lockwood, Jr. Endowed Chair of Proton Therapy; is the Chair of the Lymphoma Subcommittee of the Particle Therapy Cooperative Group (PTCOG); Secretary of the Proton Collaborative Group (PCG); and also serves on the American College of Radiology (ACR) Expert Lymphoma Guidelines Committee, the American Board of Radiology (ABR) Lymphoma Examination Board, and the American Society for Radiation Oncology (ASTRO) Education Committee. An established cancer researcher, Dr. Hoppe is the principal investigator on five clinical trials and the author of over 90 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 eight 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 a consensus statement, utilizing evidence-based information, published data and, where they are lacking, institutional experiences to describe treatment planning and the expected benefits of proton therapy in lymphoma patients. The consensus statement will be ready for submission to a radiation oncology journal in the near future.

• 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 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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DISCLAIMER

IBA: The best in proton therapy today and tomorrow

Together with our clinical partners, we brought proton therapy to clinical cancer care.

Ever since we started more than 30 years ago, our collaborations, our visionary roadmap and progressively unrivalled experience have enabled us to continue to innovate. Care givers now benefit from leading proton therapy technologies.

Today, our true continuum of Image-Guided Intensity Modulated Proton Therapy solutions can easily be integrated in most healthcare settings to make it available to all patients who need it.

Backed by IBA's unique service offer (financing, workflow optimization, education), from the single-room Proteus®ONE* to the tailor-made Proteus®PLUS*, all our solutions and robust processes (installation, operations and upgrades) are developed in collaboration with our end-users.

Tomorrow, our unique and open culture of sharing will further strengthen the clinical and patient communities we have always cared for. Working collectively, we will achieve our goal which is to offer cancer patients access to effective treatments with decreased side effects and better quality of life.

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* Proteus®ONE and Proteus®PLUS are the brand names of the Proteus®235.

Protect, enhance and save lives

iba