TREATING THORACIC CANCERS WITH PROTON THERAPY
CURRENT PRACTICES, OPPORTUNITIES AND CHALLENGES

PROTECT +
ENHANCE +
SAVE LIVES

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,

Michel Closset
Clinical Director
IBA

Olivier Legrain
Chief Executive Officer
IBA

Worldwide, lung cancer is the most common cancer among men in both incidence and mortality, and among women has the third highest incidence and the second in mortality. In the United States, lung cancer remains the number one cause of cancer mortality both in men and women. Lung cancer is categorized as small cell lung cancer and non-small cell lung cancer (NSCLC), with close to 80% of patients presenting with NSCLC. Approximately 15-20% of NSCLC are surgically resectable,[1] and about 75% of patients present with locally advanced or metastatic disease at the time of diagnosis.[2] For patients with locally advanced disease, and some patients with early stage disease that are unable to tolerate surgery, the current standard therapy is radiation therapy +/- chemotherapy.[3] Other cancers of the thorax, such as thymoma and mesothelioma, are also routinely treated with radiation therapy in some scenarios.

The main challenges associated with thoracic radiation therapy are the toxicities. In order to avoid significant treatment-related morbidity and mortality, radiation dose to the heart, lungs, esophagus, spinal cord and other critical structures must be limited to avoid adversely impacting overall survival and quality of life.[4] The recent advances in photon-based radiotherapy enable an ablative dose to be delivered to small peripheral tumors which results in comparable survival to surgical resection in stage I NSCLC,[5] it is however difficult to achieve similar dose escalation for patients with larger size and centrally located tumors as well as in patients with locally advanced disease, due to normal tissue dose constraints.

Proton therapy is different from photon radiation because of the unique physical property that the maximum dose is concentrated in the Bragg peak, which could be positioned inside the tumor. Proton therapy can significantly reduce radiation exposure to organs at risk and healthy tissues which offers potential to reduce radiation-induced toxicities. This can be particularly beneficial to patients who have poor pulmonary function, patients with cardiovascular disease or recurrent disease requiring re-irradiation, and other individuals at high risk of the development of severe side effects. Another potential advantage with proton therapy is to deliver a more biologically effective dose in modest hypofractionation for locally advanced disease in order to improve local control and shorten treatment for better cost-effectiveness.[6]

Proton therapy has been used in treating lung cancer for decades. There is a substantial body of evidence as to the efficacy of proton therapy in radiation treatment for lung cancer. With the latest delivery technique, pencil beam scanning (PBS), equipped with motion mitigation and plan optimization, intensity modulated proton therapy (IMPT) achieves better conformality and greater sparing of critical structures than photon radiation. This whitepaper aims to provide existing clinical data when considering treatment options that benefit patients the most.

A) PATIENT SELECTION

The physical and biological properties of proton therapy underlie its advantageous dose distribution pattern, 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 noncancerous conditions, and their effect 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.[7]

The current model policy developed by the American Society for Radiation Oncology (ASTRO) recommends to base the patient selection 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 done with a photon-based approach. The policy provides several non-specific examples:

1. 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).

2. 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.

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

4. 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.

The published consensus statement on proton therapy in NSCLC[6] by The Particle Therapy Co-operative Group (PTCOG) Thoracic Subcommittee suggested that NSCLC patients that could benefit from proton therapy include 1) early stage with larger tumors, central tumors, tumors near the brachial plexus and multiple tumors 2) locally advanced disease with large primary tumors and with mediastinal node involvement 3) recurrent disease.

B) OVERVIEW OF BENEFITS

Protons' physical characteristics create a much different distribution of radiation dose in the body as compared to photons. Because the maximum energy of protons is deposited in the tumor, there is no radiation imparted upon the distal tissues when protons stop. This translates into to the advantage of, in the thoracic setting, sparing adjacent structures at risk namely the heart, esophagus, spinal cord, lung and brachial plexus. Radiation-induced toxicity, such as esophagitis, pneumonitis and cardiopulmonary impairment, thus can be reduced with proton therapy. In addition to decreasing toxicity, proton therapy holds the hope of improving local control and survival by allowing for delivering a higher dose.[8]

In early stage NSCLC, proton therapy is able to produce better dosimetric parameters and is more advantageous to photon-based SBRT (stereotactic body radiotherapy) technique in treating larger tumors and multiple tumors.[9] In particular, proton therapy significantly reduce the exposure of pulmonary tissues compared with photon-based IMRT and SBRT for central tumors.[10] Proton therapy is able to deliver effective high dose with hypofractionated schedule achieving excellent tumor control and improved survival without increasing toxicity. This is a significant improvement to the photon-based SBRT technique with which substantial

and severe toxicity has been reported.[11]

For locally advanced NSCLC, photon-based radiotherapy is limited in dose escalation or acceleration as shown by the study RTOG0617 where the higher dose arm was associated with poorer survival, which was linked to increased cardiac dose.[6,3,12] Proton therapy has reported excellent survival and minimal toxicity with the same dose level and chemoradiation regimen that used in RTOG0617.[2,3] Patients treated with proton therapy were more likely to complete chemotherapy and radiation treatment without a treatment break. Proton therapy has the promise of delivering dose-escalated radiotherapy and improving locoregional control and overall survival but without inducing treatment-related death.[13] A study with dose escalated (74Gy RBE) proton therapy and concurrent chemotherapy reported encouraging long-term (median follow-up 79.6 month) outcomes that both survival and toxicity compared favorably to historical data of photon-based therapy, particularly the low rates of toxic effects.[14]

Proton therapy offers also potential solution to recurrent patients that require re-irradiation treatment. Photon-based radiotherapy is often limited for the patients who had been previously irradiated due to the high risk of morbidity and mortality. The ability of sparing pre-irradiated tissues make proton therapy a promising option in delivering a definitive dose for better disease control and survival.

In the post-operative radiotherapy (PORT) setting, proton therapy has shown value both in dosimetry study and clinical outcomes. The latest study on proton therapy for mediastinal N2 disease and/or positive margins reported comparable survivals but more favorable toxicity profile compared with IMRT. [15]

C) DOSIMETRIC COMPARISON

Hoppe et al.[16] compared the SBRT treatment plans of photon-based technique and 3-dimensional conformal double-scatter proton therapy. Eight patients with medically inoperable, peripherally located stage I NSCLC treated with photon-based SBRT (xSBRT) to 48 Gy in 4 12-Gy fractions.

These patients were retrospectively re-planned using the same treatment volumes with double scattering proton (pSBRT). The analysis showed that in all eight cases, the pSBRT plans were better than the xSBRT plans with respect to total lung and ipsilateral lung V5, V10, V20, and mean dose (p = 0.01). In addition, the cardiac tissue sparing was better with pSBRT in all the eight cases, the esophageal,

trachea, ipsilateral bronchus and spinal cord were also significantly better with pSBRT.

Figure 1 illustrates the dose distribution for a typical stage III NSCLC in photon plan and proton (IMPT) plan.

Figure 2 presents the Dose Volume Histogram comparing CTV coverage and OAR doses of the Protons plan (solid line) and the Photons plan (dotted line) from Figure 1.
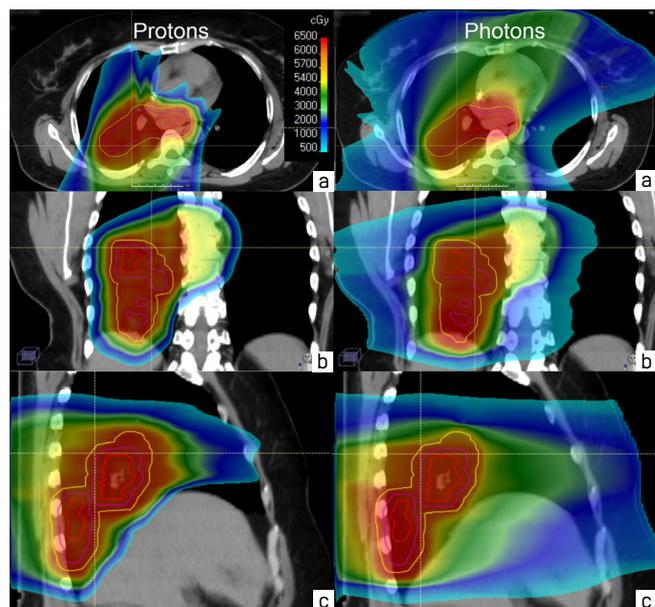

Figure 1: Isodose clouds for at typical stage III NSCLC treatement with a prescribed dose of 60Gy(RBE). Left side (protons) right side (photon) for (a) transveral, (b) coronal and (c) sagittal view.
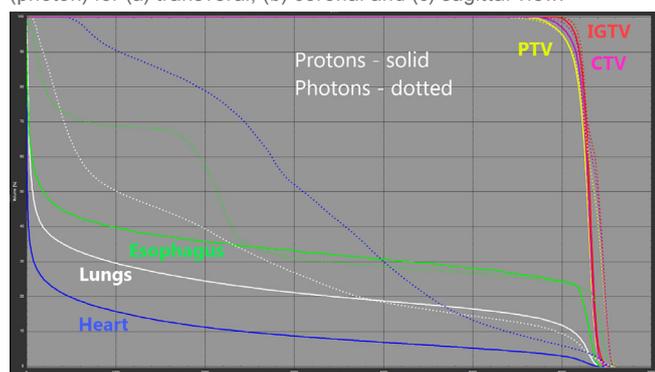

Figure 2: Dose Volume Histogram comparing CTV, PTV coverage and OAR doses of the Proton Plan (solid line) and the Photon Plan (dashed line) corresponding to plan presented in Figure 1.

Figures 1 & 2: compliments of Tony Wong, PhD Chief Medical Physicist, Seattle Proton Therapy Center

Berman et al.[17] reported the in-silico comparison of proton therapy and IMRT in postoperative radiotherapy (PORT) for completely resected (CR) stage III NSCLC. Ten patients treated with IMRT were used and optimized to deliver 50.4 Gy(RBE) in 1.8 Gy(RBE) fractions to the target volume for replanning with passive scattering proton therapy (PSPT) and intensity modulated proton

therapy (IMPT). Compared to IMRT plans, the analysis showed that PSPT plans spared the lung dose, but with a concomitant increase in the esophageal and heart doses, and an increase in the lung volume received high dose. However, IMPT plans reduced the mean esophageal dose and significantly reduced the mean heart dose by 30.7% over IMRT and all lung doses were consistently reduced with IMPT over IMRT. This study demonstrated that IMPT decreases the dose to all OARs versus both IMRT and PSPT. This decrease in dose to OARs theoretically corresponds to a decrease in the potential radiation morbidity and improvement in therapeutic index in the PORT setting.

D) CLINICAL OUTCOMES LITERATURE REVIEW

Early stage NSCLC

A retrospective review of 68 patients with stage I NSCLC treated with protons was published by Bush et al.[18] of the Loma Linda group in 2004. The median follow-up was 30 months. No symptomatic radiation pneumonitis or late esophageal or cardiac toxicities were observed. The 3-year local control and the disease specific survival rates came out at 74% and 72%. The 3-year overall survival rate was 44% for patients treated with 51 Gy(RBE) in 10 fractions and 55% for patients treated with 60 Gy(RBE).The same group updated study series in 2013 and reported their experience of 12 years in proton therapy treatment for early stage NSCLC. A total of 111 patients was treated with 3 dose schedules (51 Gy(RBE), 60 Gy(RBE) and 70 Gy(RBE)) in 10 fractions. A 4-year local control rate of 45% was achieved for the 60 Gy(RBE) group and of 74% for the 70 Gy(RBE) group. The 4-year overall survival rates turned out 18% for the 51 Gy(RBE) group, 32% for the 60 Gy(RBE) group and 51% for the group of 70 Gy(RBE).[11]

Japanese groups presented substantial experience in proton therapy for lung cancer. Nihei et al.[19] presented their study of 37 patients with medically inoperable stage I NSCLC in 2006. High doses of 70-94 Gy(RBE) were delivered in 20 fractions and led to 2-year local progression-free and overall survival rates of 80% and 84%. No serious acute toxicity was observed, but 3 patients showed late grade 2 and 3 pulmonary toxicities.

Another Japanese report published in 2007 by Hata et al.[20] showed a 2-year overall survival rate of 74%, a cause-specific survival rate of 86% and a local control rate of 95% for hypofractionated proton beam therapy administered to 21 stage I NSCLC patients. No therapy-related toxicity of grade 3 and above was observed.

Author	Pathology	Study	Outcome	Remarks
Bush et al., 2004	NSCLC, early stage	Retrospective analysis 86 patients Proton Median follow-up: 30 months Loma Linda	3-year local control, 74% disease specific survival rate, 72% 3-year overall survival rate: patients treated with 51 Gy (RBE), 44% patients treated with 60 Gy (RBE)	No symptomatic radiation pneumonitis No late esophageal toxicities No late cardiac toxicities
Nihei et al., 2006	NSCLC, medically inoperable stage I	Retrospective analysis 37 patients Proton 70-94 Gy(RBE) Median follow-up: 24 months National Cancer Center Chiba	2-year local progression-free survival, 80% 2-year overall survival, 84%	No serious acute toxicity Late grade 2 pulmonary toxicity: 3 patients Late grade 3 pulmonary toxicity: 3 patients
Hata et al., 2007	NSCLC, Stage I	Retrospective analysis 21 patients Proton Median follow-up: 25 months Tsukuba University	2-year overall survival, 74% 2-year cause specific survival, 86% 2-year local control, 95%	No therapy related toxicity of grade 3 or higher
Nakayama et al., 2010	NSCLC, medically inoperable stage I	Retrospective analysis 55 patients Proton Tsukuba University	2-year overall survival, 97.8% 2-year progression-free survival, 88.7% 2-year local control, 97%	Deterioration in pulmonary function, 3.6% Grade 3 pneumonitis, 3.6%
Bush et al., 2013	NSCLC, early stage	Retrospective analysis 111 patients Proton, 51 - 60 - 70 Gy(RBE) 10 fractions MGH	4-year local control: 60 Gy (RBE) group, 45% 70 Gy (RBE) group, 74% 4-year overall survival: 51 Gy (RBE) group, 118% 60 Gy (RBE) group, 32% 70 Gy (RBE) group, 51%	
Kanemoto et al., 2014	NSCLC, stage I	Retrospective analysis 47 patients Proton Median follow-up: 31 months Tsukuba University	3-year overall survival, 76.7% 5-year overall survival, 65.8%	Acute grade 3 pneumonitis, 1.3% Late grade 3 radiation-induced pneumonitis, 1.3%
Makita et al., 2015	NSCLC, stage I	Retrospective analysis 56 patients Proton Aichi Cancer Center	3-year overall survival, 81.3% 3-year progression-free survival, 73.4% 3-year local control, 96%	Late grade 3 toxicity, 1.5%

Nakayama et al.[21] reported in 2010 on 55 medically inoperable patients with stage I NSCLC treated with proton therapy. The 2-year overall survival rate for all patients was 97.8%, and progression-free survival came to 88.7%. Local control of all tumors at 2 years reached 97.0%. Two patients (3.6%) experienced pulmonary function deterioration, and two patients (3.6%) developed grade 3 pneumonitis.

Kanemoto et al.[22] published their series of 74 stage I patients in 2014. They reported 3-year and 5-year overall survival rates of 76.7% and 65.8%, but with 1.3% acute grade 3 pneumonitis and 1.3% late grade 3 radiation-induced pneumonitis, 1.3% grade 3 skin ulcer and 13.8% grade 4 rib fracture.

The 2015 paper by Makita et al.[23] of Aichi Cancer Center Hospital in Nagoya, Japan, reported their study of 56 stage I patients treated with 66 Gy(RBE) in 10 fractions for peripheral tumors and 80 Gy(RBE) in 25 fractions for central tumors. They reported 3-year overall survival rates, progression-free survival rates and local control rates of respectively 81.3%, 73.4% and 96% with 1,5% of late grade 3 toxicity.

In a retrospective study published in 2015, Hatayama et al.[24] assessed the efficacy, toxicity, and prognostic factors of high-dose PT in 50 patients with peripheral stage I NSCLC treated between 2009 and 2014. Median age was 72.5 years, median follow-up period was 22.8 months, clinical stages were IA in 44 (85%) and IB in 8 (15%) tumors and the total dose of PT was 66 GyE in 10 fractions for all tumors. 3-year OS rate was 87.9%, and 3-year LC and progression-free survival rates were 95.7% and 76.3% respectively. 5 patients died and only one patient experienced grade 2 pneumonitis. It was concluded that high-dose PT could be an effective and safe treatment option for patients with stage I NSCLC.

In 2016, Lee et al.[25] from the National Cancer Center of Korea evaluated the efficacy and safety of ablative dose hypofractionated PT (total dose of 50-72 CGE in 5-12 fractions a week) for stage I and recurrent NSCLC in a retrospective study including 55 patients. During a median follow-up period of 29 months (range 4-95 months), 24 patients died (43,6%), 11 from disease progression and 13 from other causes. The overall survival rate (OS) at 3 years was 54.9% and the median OS was 48.6 months (range 4-95 months). Local progression was observed in 7 patients and the median time to local progression was 9.3 months (range 5-14 months). Cumulative actuarial local control rate, lymph node metastasis-free survival, and distant metastasis-free survival rates at 3 years were 85.4, 78.4, and 76.5%, respectively. The authors concluded that ablative dose hypofractionated PT was safe and promising for stage I and recurrent NSCLC.

Locally advanced NSCLC

In Japan, Oshiro et al.[26] reported in 2012 the results of proton therapy without concurrent chemotherapy for 57 patients with stage III NSCLC. The 1 and 2-year overall survival rates were 65.5% and 39.4%. Two years later in another paper[27], the same group published their study on 15 stage III patients treated with high-dose proton therapy, with 74 Gy(RBE) to the primary site and 66 Gy(RBE) to the lymph nodes, and concurrent chemotherapy. The mean survival time was 26.7 months. Severe grade 3 and above leukocytopenia occurred in 10 patients, and late radiation grade 2 and 3 pneumonitis was observed in 2 patients.

In 2012, Hoppe et al.[28] of the Florida group published the early results for a group of 19 patients with regionally advanced NSCLC treated with concurrent chemotherapy (carboplatin and paclitaxel) and proton therapy. 7 of them were treated with induction chemotherapy, 12 without. The median proton therapy dose was 74 Gy(RBE). 12 patients received selective nodal proton therapy to the adjacent uninvolved nodal regions with a median dose of 40 Gy(RBE). The median follow-up was 15 months. One patient developed non-hematologic acute grade 3+ toxicity, and 4 presented hematologic acute grade 3+ toxicity. The authors concluded that mediastinal proton therapy with concomitant chemotherapy was associated with acceptable toxicity. These early results, although encouraging, request longer follow-up with more patients to confirm the long-term efficacy of the treatment.

MD Anderson has been publishing their extensive experience in proton therapy concurrent chemotherapy for locally advanced lung cancer. At MD Anderson, the rationale for the use of proton therapy was the recognition that concurrent chemotherapy and photon-based radiation therapy cause severe toxicity in most patients. Sejpal et al.[4] compared the toxicity of concurrent proton at 74Gy(RBE) and chemotherapy in 62 patients with locally advanced NSCLC with the toxicity of 74 patients treated with photon at 63Gy(RBE) and concurrent chemoradiotherapy. Results were published in 2011. At 2% and 5%, the rates of severe (grade 3 and above) pneumonitis and esophagitis turned out to be much lower in the proton group compared to 30% and 18% for patients treated with 3DCRT and 9% and 44% for IMRT, despite the use of a higher dose (P<0.001 for all).

Chang et al.[2] reported their series of 44 stage III patients treated with proton 74 Gy(RBE) in 37 fractions and concurrent weekly carboplatin and paclitaxel. The 1-year overall survival and progression-free survival rates were reported as 86% and 63%, but distant metastases were found in 43% patients. One year later, the same group[29] reported on a series of 18 patients with T1 central lesions or T2-3 on other locations who had their NSCLC treated with ablative dose of 87.5 Gy(RBE). The results showed a local control rate of 88.9% at a follow-up time of 4.8-36.3 months. 12 patients were alive at the last follow-up. The authors concluded that proton therapy at ablative doses was well-tolerated and produced promising local control for medically inoperable early-stage NSCLC.

Xiang et al.[30] published a larger series of 84 patients in 2012. The patients were treated with proton 74Gy(RBE) in 37 fractions and concurrent weekly carboplatin and paclitaxel. The 3-year overall survival and progression-free survival were reported as 37.2% and 31.2%, whereas the distant metastasis rate turned out to be 39% at the last follow-up. The first long-term, relatively large series of 134 patients with locally advanced disease (21 with stage II and 113 with stage III NSCLC) was reported by Nguyen et al.[3] in 2015. At a median follow-up time of 4.7 years, the median overall survival time came at 40.4 months for stage II patients and 30.4 months for stage III patients. 5-year disease-free rates came out at 17.3% for stage II patients and at 18% for the stage III group. Toxicity was tolerable, one patient developed grade 4 esophagitis and 16 patients presented grade 3 events, 2 being afflicted with pneumonitis, 6 with esophagitis and 8 with dermatitis.

In 2015, Nguyen et al.[3] from the MD Anderson group reported long-term disease control, survival, and toxicity for patients with locally advanced NSCLC prospectively treated

Author	Pathology	Study	Outcome	Remarks & Conclusion
Sejpal et al., 2011	NSCLC, locally advanced	Comparative study 62 patients treated with concurrent proton at 74 Gy (RBE) & chemotherapy 74 patients treated with concurrent 63 Gy photon & chemoradiotherapy MD Anderson		Severe grade 3 and higher pneumonitis: 2% for proton 30% for 3DCRT 9% for IMRT Severe grade 3 and higher esophagitis: 5% for proton 18% for 3DCRT 44% for IMRT
Chang et al., 2011	NSCLC T1 central lesions T2-3 other lesions	Retrospective analysis 18 patients Proton 87.5 Gy (RBE) Median follow-up: 16.3 months MD Anderson	Local control at follow-up time of 4.8 - 36.3 months, 88.9%	PT to ablative doses is well-tolerated and produces promising local control for medically inoperable early-stage NSCLC
Chang et al., 2011	NSCLC, stage III	Retrospective analysis 44 patients Proton 74 Gy (RBE) Concurrent carboplatin & paclitaxel Median follow-up: 19.7 months MD Anderson	1-year overall survival, 86% 1-year progression-free survival, 63% Distant metastasis, 43%	
Xiang et al., 2012	NSCLC, stage III	Prospective study 84 patients Proton 74 Gy (RBE) Concurrent carboplatin & paclitaxel MD Anderson	3-year overall survival, 37.2% 3-year progression-free survival, 31.2% Distant metastasis, 39% at last follow-up	
Oshiro et al., 2014	NSCLC, stage III	Retrospective analysis 15 patients High-dose 74 Gy (RBE) proton to primary site, 66 Gy (RBE) to lymph nodes, concurrent chemotherapy MGH	Mean survival time, 26.7 months 5-year local control, 74%	Severe grade 3 and higher leukocytopenia, 10 patients Late radiation grade 2 pneumonitis, 1 patient Late radiation grade 3 pneumonitis, 1 patient
Hoppe et al., 2012	NSCLC, regionally advanced	Retrospective analysis 19 patients Concurrent chemotherapy (7 with induction, 12 without) & proton (median dose 74 Gy (RBE), 12 received selective nodal therapy with median dose 40 Gy (RBE) Median follow-up: 15 months UFPTI		Non-hematologic acute grade 3 and higher toxicity, 1 patient Hematologic acute grade 3 and higher toxicity, 4 patients
Nguyen et al., 2015	NSCLC, stage II & III	Retrospective analysis 21 patients Stage II 113 patients Stage III Proton, concurrent chemotherapy Median follow-up: 4.7 years UFPTI	Median overall survival time: stage II, 40.4 months stage III, 30.4 months 5-year disease-free: stage II, 17.3% stage III, 18%	Tolerable toxicity: grade 4 esophagitis, 1 patient grade 3 pneumonitis, 2 patients grade 3 esophagitis, 6 patients grade 3 dermatitis, 8 patients
Chang et al., 2017	NSCLC, stage III	Prospective study 64 patients High dose 74 Gy (RBE) Proton, concurrent chemotherapy Median follow-up: 79.6 months	Median overall survival 26.5 months 5-year overall survival of 29% 5-year progression-free survival, 22% 5-year actuarial distant metastases, 54% Locoregional failure, 28% and 48%	Acute oesophagitis, grade 2 (28%) and grade 3 (8%) Grade 2 pneumonitis, 2% Late toxicity included grade 4 oesophagitis 2% grade 2 and 3 pneumonitis: 16% and 12% Grade 2 bronchial stricture, 3% Grade 4 bronchial fistula, 2%
Remick et al., 2017	NSCLC, stage III, postoperative, mediastinal N2 without positive margin	Retrospective analysis of 61 patients, 27 treated with PBT and 34 IMRT	At 2 years, OS for the proton cohort was 77.8% and 73.2% in the IMRT cohort. Local recurrence-free survival was similar for PBT and IMRT 3/1% and 85.7%.	No grade 4 or 5 toxicities observed. 1 patient in each cohort experienced grade 3 radiation pneumonitis. Grade 3 esophagitis was observed in 1 and 4 patients in the Proton and IMRT cohorts, respectively.

with concurrent PT and chemotherapy on a non-randomized case-only observational study. All 134 patients (21 stage II, 113 stage III, median age 69 years) received passive-scattering PT planned with 4D-CT-based simulation, and all received PT concurrent with weekly chemotherapy. At 4.7 years, median OS times were 40.4 months (stage II) and 30.4 months (stage III). 5-year disease-free survival (DFS) rates were 17.3% (stage II) and 18.0% (stage III). Toxicity was tolerable, with one grade 4 esophagitis and 16 grade 3 events (2 pneumonitis, 6 esophagitis, 8 dermatitis). This report thus indicated that this PT regimen produced excellent OS with tolerable toxicity.

In 2015, Kesarwala et al.[31] from the National Institutes of Health in Bethesda investigated the potential of protons to reduce nodal failure after radiation therapy for locally advanced NSCLC and the feasibility of IMPT for elective nodal irradiation. IMPT-involved field RT (IFRT) plans were generated with the same total dose of 66.6-72Gy(RBE) for 20 locally advanced NSCLC patients treated with photon IFRT. The study demonstrated the feasibility of IMPT for this clinical indication and showed that the potential decreased toxicity associated to IMPT could allow elective nodal irradiation while maintaining a favorable therapeutic ratio compared with photon IFRT.

Wang et al.[32] from the MD Anderson group published a longitudinal observational study in 2016 to demonstrate the ability of their Symptom Inventory to detect fine differences in symptom development among 3 chemoradiotherapy modalities used in the treatment of locally advanced NSCLC: IMRT, 3D-CRT and PT. 82 patients with unresectable primary or recurrent NSCLC underwent either 3D-CRT, IMRT or PT and their symptoms were rated weekly by the MD Anderson's Inventory for up to 12 weeks. The PT group received a significantly higher radiation target dose than the IMRT and 3D-CRT groups, and fatigue was the most severe symptom over time for all groups. The conclusion showed that PT was associated to significantly less severe symptoms than IMRT or 3D-CRT.

In 2017, Chang et al.[14] the MD Anderson group reported the longterm outcomes of unresectable stage III NSCLC treated with double scattering proton therapy and concurrent chemotherapy. With dose escalated to 74Gy(RBE), the study reported the median overall survival rate of 26.5 months, overall rates of grade 3 and above pneumonitis and esophagitis of 12% and 11% respectively. These outcomes are promising and favorable compared with historical data using photon-based radiotherapy, and have implications for

ongoing issues regarding the role of dose escalation in this patient population, further optimization of proton therapy such as IMPT, and cost-effectiveness.

In 2017 too, Remick et al.[15] published the first clinical report of postoperative proton therapy for mediastinal N2 disease and/or positive margins. Of the 61 patients enrolled in the study, 27 patients receiving PBT and 34 receiving IMRT. At 2 years, the overall survival for the proton cohort was 77.8% compared with 73.2% in the IMRT cohort. Local recurrence-free survival at 2 years was similar for PBT and IMRT (93.1%and 85.7%, respectively). Overall survival (P=.648) and local recurrence-free survival (P=.816) was not significantly different between the 2 cohorts. Grade 3 radiation esophagitis was observed in 1 and 4 patients in the PBT and IMRT groups, respectively. Grade 3 radiation pneumonitis was observed in 1 patient in each cohort. Dosimetric analysis revealed a significant decrease in the V5 and mean lung dose (P=.001 and P=.045, respectively), and maximum dose to the spinal cord (P=.010) in the proton group compared with the IMRT group. The authors stated that the study reported only the acute and subacute toxicities given the median follow-up of 26.5 months; however, it was anticipated that proton therapy would have even more sparing with regard to late adverse effects, including lung fibrosis, cardiac toxicity, and/or secondary malignancies.

A phase 2 randomized trial[33] was published in 2018 by MD Anderson and MGH, comparing passive scattering proton therapy versus photon IMRT for inoperable NSCLC. A learning curve was seen as outcomes improved over the course of the trial, but there was no difference in local control and pneumonitis between the two arms. Although passive scattering proton therapy had lower lung V5-10 Gy, V20+ Gy was higher for the proton group. Heart dose was lower with proton therapy for all dose levels. Given the improved proton dosimetry with expertise over time, as well as the newer centers using scanning beam proton therapy, this trial still leaves open the question of whether cutting edge proton therapy such as IMPT with PBS, would lead to improved outcomes compared to photon IMRT.

Small cell lung cancer (SCLC)
Colaco et al.[34] published outcomes for the first known series of limited-stage SCLC patients treated with proton therapy and a dosimetric comparison of lung and esophageal doses with IMRT. Six patients were treated and the median follow-up was 12.0 months. The one-year overall and progression-free survival rates were 83% and 66%. There were no acute grade≥3 esophagitis or acute grade≥2 pneumonitis. In

comparison to IMRT plans, proton therapy proved superior across all lung and esophageal dose levels.

A larger prospective study of 30 patients was published in 2017 by Rwigema et al.[35] Patients were treated to a median dose of 63.9 Gy(RBE) in 33 to 37 fractions with concurrent chemotherapy. At a median follow-up of 14 months, the 1- and 2-year local control rates were 85% and 69%. The median overall survival was 28.2 months, and the 1 and 2-year OS rates were 72% and 58%. There was 1 case each (3.3%) of grade 3 or higher esophagitis, pneumonitis, anorexia, and pericardial effusion. Grade 2 pneumonitis and esophagitis were seen in 10.0% and 43.3% of patients, respectively. In comparsion to the IMRT backup plans, the proton plans achieved significantly improved dosimetry for the heart and spinal cord as well as improvements in V5 and mean lung doses. The authors concluded that proton therapy in this study demonstrated encouraging efficacy and toxicity profile.

Thymoma and mesothelioma

Thymomas a rare neoplasm arising in the anterior mediastinum. Radiotherapy after surgery can improve disease free survival but mediastinal irradiation can also cause toxicities such as pneumonitis, pericarditis, and esophagitis. Proton therapy is better suited for treatment of mediastinal disease in terms of avoidance of organs at risk (OAR) compared to conventional photon-based techniques.

Parikh et al.[36] evaluated the dosimetric differences between PBT and IMRT and reported early toxicities of four patients with resected thymoma treated with PBT. Compared with IMRT plans, PBT delivered significantly lower mean doses to the lung, esophagus and heart as depicted in below table. The study reported no patients experienced greater than grade 2 toxicity during treatment. One patient developed a grade 2 skin reaction, defined as moderate to brisk erythema.

Table	Mean dose to organs at risk in PBT plan compared with analogous IMRT plan			
Organ	Mean dose in PBT plan [Gy]	Mean dose in IMRT plan [Gy]	Relative reduction %	P
Heart	6.00	10.44	42.5	.007
Lung	4.61	8.13	43.3	.02
Esophagus	5.39	20.62	73.9	.003
Breast	2.68	3.01	10.9	NS

Table 1: Courtesy to Parikh et al. (Reference 36)

Three patients experienced grade 1 skin reaction. With a median follow-up of 5.5 months, no patient had prolonged acute or subacute toxicities, including no incidence of pneumonitis.

A more recent prospective study by Vogel et al.[37] reported the treatment outcomes of 27 patients of thymoma or thymic carcinoma treated with double scattering proton therapy. This cohort of patients were treated with definitive (22%), salvage (15%) or adjuvant (63%) proton radiation to a median of 61.2/1.8 Gy(RBE). With the median clinical follow-up of 2.0 years (range 0.2–4.1 years), 100% local control was achieved and no patient experienced grade ≥ 3 acute or late toxicity. Acute grade 2 toxicities included dermatitis (37%), fatigue (11%), and esophagitis (7%). Acute grade 2 pneumonitis was observed in one patient (4%) treated after already having received 2 prior courses of thoracic radiation therapy. Late grade 2 toxicity was observed in one patient who developed chronic dyspnea. The authors concluded that this study demonstrated that patients treated with DS-PT received low doses of radiation to critical normal structures, had low rates of acute toxicities, and had excellent locoregional control. Use of proton beam radiation therapy may improve the risk–benefit ratio.

Malignant pleural mesothelioma (MPM) is another rare thoracic malignance for which treatment options are limited and outcomes are poor. Radiotherapy is widely used as an integral part of treatment strategy, but large radiation fields to an intact ipsilateral lung can be challenging because of the need to spare adjacent mediastinal structures, spinal cord, and contralateral lung. Pan et al.[38] reported their experience in treating seven patients of lung-intact MPM of who four were treated with IMPT and three by IMRT. In comparison of dosimetric parameters, the study reported that IMPT produced lower mean doses to the contralateral lung, heart, esophagus, liver, and ipsilateral kidney. Both IMRT and IMPT techniques produced similar doses to the treated lung, but mean dose to the contralateral lung was decreased by a factor of 2.9 with IMPT. The difference in contralateral lung dose largely reflected the low-dose bath from IMRT with higher V5 values. The mean dose to the heart was lower in all patients treated with IMPT. This study demonstrated the feasibility of using IMPT for intact lung MPM and the dosimatric advantages of IMPT over IMRT. Further study is necessary to determine if the dosimetric benefit translates into meaningful improvements in clinical outcomes.

E) ADDRESSING RANGE MODIFICATION AND MOTION MANAGEMENT

The technical and clinical data regarding proton therapy for NSCLC is increasing rapidly, showing that PT has the potential to decrease toxicity and enable dose escalation that potentially improve clinical outcomes in lung cancer, and holds a crucial role in settings such as re-irradiation and post-operative radiotherapy where the therapeutic window is particularly narrow. PT delivery techniques continue to improve and many of the technical challenges of sensitivity to anatomic changes and motion are being addressed, such as the sensitivity of PT to anatomic changes in the thorax and the high propensity of lung cancer patients to rapidly develop anatomic changes such as pleural and pericardial effusions or atelectasis (see Figure 3).

In 2008, Hui et al.[39] from the Texas MD Anderson Cancer Center analyzed the effects of inter-fractional anatomical changes in doses to lung tumors treated with proton therapy. Weekly 4D-CT scans were acquired for 8 patients with mobile stage III NSCLC who were treated with IMRT at the time, and a conformal PSPT plan was designed for each patient. The authors found that adaptive re-planning during proton therapy could be indicated in selected patients with NSCLC. For most patients, however, clinical target volume coverage was adequate if tumor motion was taken into consideration in the original simulation and planning processes.

In 2016, Szeto et al.[40] from the Netherlands Cancer Institute simulated and evaluated these effects in spot-scanning intensity modulated proton therapy (IMPT) for lung cancer patients. Robust IMPT plans were designed on the mid-position CT scan for 16 locally advanced lung cancer patients. Without adaptive planning, 8 patients had an under-coverage of the targets of more than 2Gy(RBE) (max; 14Gy(RBE)) on the recalculated treatment dose from the daily anatomy variations including respiration. In organs at risk, a maximum increase of 4.7Gy(RBE) in the D1 was found in the mediastinal structures. The authors concluded that an advanced planning strategy including knowledge of anatomical uncertainties would be recommended to improve plan robustness against inter-fractional variations and that adaptive therapy was mandatory for large anatomical changes.

Without mitigation techniques, intra-fractional motion-induced range variations can also lead to under-coverage of the target, both in passive scattering proton therapy (PSPT) and IMPT. This can be mitigated either using motion
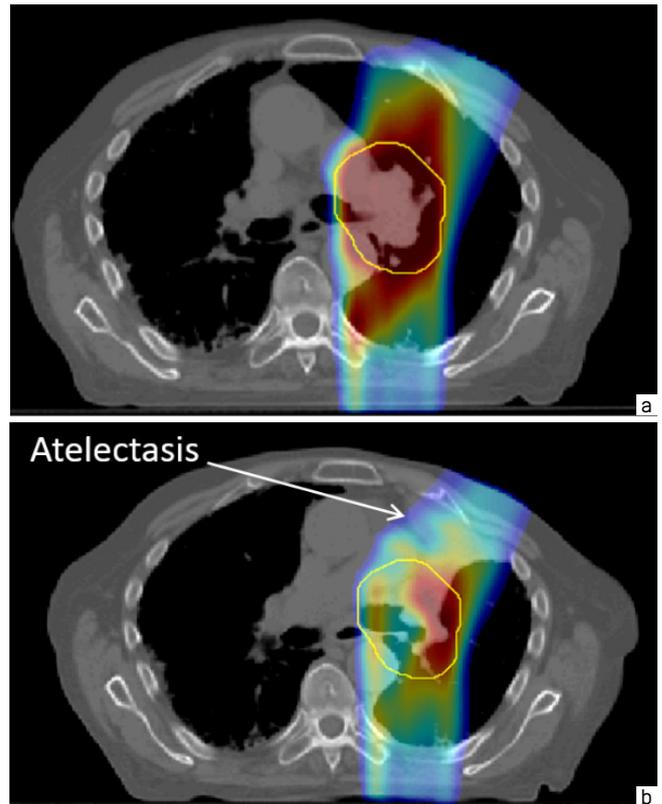
Figure 3: Illustrative example showing the sensitivity of PT to inter-fractional anatomic changes (planning study). a): robust PBS plan on planning CT. b): recalculated dose on daily CT in presence of large anatomical change in the proton beam path.

reduction techniques (e.g. gating, deep inspiration breath-hold and abdominal compression) or by taking the motion into account into the treatment planning (e.g. beam-specific planning target volume, 4D-robust optimization). Berman et al.[12] from the University of Pennsylvania established that respiratory motion quantification and motion mitigation strategies should be strongly considered, and that all patients undergoing proton therapy for NSCLC should undergo a 4D CT simulation where the tumor is observed during 8-10 phases of the breathing cycle. They showed that radiation could be delivered during a specific portion of the breathing cycle using deep inspiration breath hold or gating. Alternatively, Wang et al.[41] evaluated different strategies for PT in lung cancer based on 4D CT scans and found that planning PT was most robust when done so on the maximum intensity projection of end inhale, middle exhale, and end exhale images.

If IMPT can result in lower doses to normal tissue in comparison with intensity modulated photon radiation therapy (IMRT) and PSPT, it comes at the cost of an additional motion-induced dose uncertainty, known as the 'interplay effect'. The interplay effect is a consequence of the simultaneous motion of beam and anatomy. It has been extensively studied in scanned beam proton therapy

and strategies such as delivery sequence optimization, repainting and tumor tracking have been proposed. In 2009, Seco et al.[42] studied the effectiveness of several repainting strategies in reducing the interplay effect and showed that breath-sampled repainting was the most effective. This was further confirmed by Engwall et al.[43] in 2018, based on a comprehensive interplay simulation study on 7 NSCLC patients. Alternatively, Li et al.[44] from MD Anderson developed a delivery strategy for reducing the respiratory motion-induced dose uncertainty of spot-scanning PT. IMPT plans were generated for 10 lung cancer patients and dose uncertainties for different delivery sequences were evaluated by simulation. They showed that the maximum absolute dose error could be up to 97.2% in a single measurement with delivery sequence optimization, whereas the optimized delivery sequence resulted in a maximum absolute dose error of ≤ 11.8%. The researchers concluded that optimizing the delivery sequence could reduce dose uncertainty due to respiratory motion, assuming the 4DCT is a true representation of the patients' breathing patterns.

In 2016, Liu et al.[45] from the Mayo Clinic Arizona and the MD Anderson group conducted an exploratory study to compare the impact of uncertainties and interplay in 3D vs. 4D robustly optimized IMPT plans for lung cancer. IMPT plans were created for 11 non-randomly selected NSCLC cases. 4D robust optimization plans led to better clinical target volume coverage and homogeneity in terms of uncertainties. With interplay effect considered, 4D robust optimization produced plans with better target coverage, comparable target homogeneity, and comparable normal tissue protection. The authors concluded that compared to 3D robust optimization, 4D produced significantly more robust and interplay-effect-resistant plans for targets with comparable dose distributions to normal tissue.

F) ONGOING CLINICAL TRIALS

There are 15 ongoing clinical trials registered in clinicaltrial.gov including clinical outcome studies, a treatment planning study and a data registry.

Two studies are investigating proton therapy for early stage NSCLC with hypofractionated scheme and escalated dose. MD Anderson is leading a randomized phase II study comparing stereotactic body radiotherapy (SBRT) and stereotactic body proton therapy (SBPT) for centrally located stage I, selected stage II and recurrent NSCLC. Both arms are given 50Gy (RBE) in 4 daily treatments. The study measures treatment related toxicity and treatment

response at 2-year. University of Florida is investigating hypofractionated, image-guided proton therapy for stage I NSCLC with the primary endpoint of 1-year grade 3 or higher toxicity rate.

Ten studies look into proton therapy for locally advanced NSCLC with concurrent chemotherapy. Washington University leads a study looking into dose intensification with accelerated hypofractionated proton therapy for stage II-III patients. The study primarily measures the maximum tolerated proton dose with chemotherapy. University of Pennsylvania leads another dose escalation study for stage III patients, as well as a study investigating the side effects and best dose of proton radiation when given together with chemotherapy for patients with stage III NSCLC that can be removed by surgery MD Anderson's study is designed as phase I/II investigating the highest tolerable dose delivered by IMPT and IMRT with simultaneous integrated boost (SIB) dose escalation to gross tumor volume. Then in phase II, the study is to compare the disease control and toxicity between IMPT and IMRT.

Two trials aim to study proton therapy for recurrent diseases including MD Anderson's registry study and University of Pennsylvania's proton reirradiation for recurrent NSCLC.

Randomized and comparative studies are increasing. The Radiation Therapy Oncology Group is leading a randomized phase III trial comparing proton chemoradiotherapy to photon chemoradiotherapy for the treatment of patients with stage II-III NSCLC. Overall survival is the primary endpoint, while progression-free survival, adverse events, quality of life, cost-effectiveness and changes in pulmonary function will also be measured and compared. Although randomized studies are the optimal approach to evaluate the efficacy and toxicity of proton versus photon modalities, as the 'consensus statement'[6] by PTCOG Thoracic Subcommittee points out that there are limitations to this approach. The statement suggested that trials may need to be based on varying anatomy and personalized planning, as well as IMRT ideally should be compared with IMPT using similar volumetric image guidance and motion management strategies.

Title	Site	Type	Randomized	Comparative	PI	Endpoint
A Phase I/II Study of Hypofractionated Proton Therapy for Stage II-III Non-Small Cell Lung Cancer	Stage II-III lung	Phase I			Proton collaborative group	Safety/efficacy, maximum tolerated dose w/chemo
Comparing Photon Therapy To Proton Therapy To Treat Patients With Lung Cancer	Stage II-III lung	Phase III	Yes	Yes	RTOG	OS, PFS, toxicity, QoL, cost-effectiveness
Stereotactic Body Radiotherapy (SBRT) Versus Stereotactic Body Proton Therapy (SBPT)	Centrally located stage I and selected stage II lung		Yes	Yes	MD Anderson	Toxicity, time to response
Proton Radiation Therapy With Cisplatin and Etoposide Followed by Surgery in Stage III Non-Small Cell Lung Cancer	Stage III lung	Phase I			MGH	Establish MTD, downstaging, LC
Proton Beam Radiation Therapy and Chemotherapy in Treating Patients With Stage III Non-Small Cell Lung Cancer That Can Be Removed By Surgery	Stage III lung	Phase I II			UPenn	Feasibility, dose-limiting toxicity
Proton Therapy for Stage I Non-Small Cell Lung Cancer (LU03)	Stage I lung	Phase II		Yes	University of Florida	Toxicity, LC
Proton Beam Radiation With Concurrent Chemotherapy and Nelfinavir for Inoperable Stage III Non Small Cell Lung Cancer (NSCLC)	Stage III lung	Phase I			UPenn	Progression free survival (time frame: 2 years) Number of adverse events (time frame 2 years)
Trial of Consolidation Pembrolizumab After Concurrent Chemotherapy and Proton Reirradiation for Thoracic Recurrences of Non-Small Cell Lung Cancer	Recurrent NSCLC	Phase II		Acute		
Image-Guided Adaptive Conformal Photon Versus Proton Therapy	Stage II-III	Stage II-III lung	Yes	Yes	MD Anderson	Time to failure defined as interval from time of randomization to development of treatment-related pneumonitis (TRP) or local failure, whichever occurs first according to CTCAE v3
Intensity-Modulated Scanning Beam Proton Therapy (IMPT) With Simultaneous Integrated Boost (SIB)	Stage III lung	Phase II		Yes	MD Anderson	MTD, PFS
Photon Versus Particle Therapy for Recurrent Lung Cancer; a Planning Study Based on a Reference Dataset of Patients.	Lung	Planning study, retro-spective		Yes	Maastricht Radiation Oncology	normal tissue dose, NTCP
Reirradiation Registry Study	Lung reirradiation	Registry cohort		Yes	MD Anderson	
Hypofractionated Proton Beam Radiation Therapy, Paclitaxel, and Carboplatin in Treating Patients With Stage II-III Non-Small Cell Lung Cancer	Stage II-III lung	Phase I			Washington University	MTD, toxicity
PET-Adjusted Intensity Modulated Radiation Therapy and Combination Chemotherapy in Treating Patients With Stage II-IV Non-small Cell Lung Cancer	Stage II-IV lung	Phase II			Albert Einstein College of Medicine of Yeshiva University	Metabolic response of lesion and lymph nodes
A Trial of Integrating SBRT With Targeted Therapy in Stage IV Oncogene-driven NSCLC	Stage IV lung (target oncogenes)	Phase II			MGH	Frequency of distant failure, toxicity, OS, PFS

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THE PRESENT

We live in an exciting time in the treatment of thoracic cancers, especially lung cancer, as outcomes for all stages of lung cancer continue to improve. A large part of this has been due to improved systemic therapy, especially immunotherapy options, but the role of radiation therapy continues to evolve and grow in the management of all stages of lung cancer. In early stage lung cancer, there is increasing data for hypofractionated radiation treatment producing outcomes comparable to surgical resection. Hypofractionated radiation is now standard of care for medically inoperable patients, and is also increasingly offered to high operative risk patients, as well as operable patients who choose radiation instead of surgery. Hypofractionated radiation treatment of central tumors continues to remain challenging due to toxicity risk, and proton therapy has dosimetric advantages over photon radiation in certain scenarios. This is especially true as proton image-guidance and treatment planning approaches increasingly mirror that of photon therapy, with scanning beam proton therapy becoming more available, IMPT being deployed routinely, and cone-beam CT also becoming increasingly common at proton centers. One clear advantage of proton therapy over photon radiation is in the reduction in low dose bath, and this is even more critical as we treat more patients with multiple lung tumors, often with baseline impaired lung function.

For patients with locally advanced NSCLC, morbidity and mortality have been linked to normal tissue dose, such as heart dose, lung dose, and esophagus dose. Proton therapy can potentially decrease radiation dose to all those normal structures, without compromising target coverage. As a medical community, we have gained a tremendous amount of knowledge about treatment planning with proton therapy

in the thorax over the past 10+ years, and IMPT can now produce plans of similar conformality as photon IMRT, with less low dose to normal tissues.

As systemic therapy improves in metastatic lung cancer, we are seeing a growing role for radiation treatment in the management of metastatic cancer. Radiation has moved beyond just palliation of symptoms, to the treatment of oligometastatic cancer and oligoprogressive cancer, to improve survival. With more patients receiving immunotherapy, where pneumonitis is a known side effect, it is even more vital to minimize radiation dose to the lungs. Many patients are living longer with their cancer diagnosis, therefore re-irradiation is also becoming increasingly common, and proton therapy can have definite dosimetric advantages in this scenario.

For other cancers of the thorax, such as thymoma, where patients often have decades of survival post-treatment, protecting normal tissues from radiation is especially important. Anatomic location of thymomas typically means significant radiation dose to the heart if being treated with photon therapy, which can be decreased with proton therapy. This leads to less cardiac toxicity down the road. For mesothelioma, where normal tissue dose, especially radiation dose to the contralateral lung, can lead to fatal complications from radiation treatment, proton therapy can also decrease radiation toxicity in this scenario.

THE FUTURE

Looking ahead, we look forward to continued technologic advancements in proton therapy, helping us better target radiation while minimizing toxicity. We expect to see more clinical data being produced with modern proton technology (scanning beam with IMPT) that can show the dosimetric advantages of protons translate into improved clinical outcomes.

We also look forward to seeing more data exploring the biological differences between proton therapy and photon radiation, beyond the dosimetric differences. Since proton therapy has higher RBE (relative biological effectiveness) than photon therapy, it is possible that proton radiation produces a different type of cell kill than photons, and may interact differently with the immune system. This may have potential advantages in combination with immunotherapy. There is also increasing interest in exploring higher dose rate radiation treatment, such as ultra-high dose rate or "flash" radiation (>40 Gy/sec), which could decrease normal

tissue toxicity while having similar anti-tumor efficacy. While most standard linear accelerators cannot produce the ultra-high dose rate, many proton therapy units could. We expect exciting research on this front to continue in the coming years.

In conclusion, proton therapy will remain a valuable tool in our continuing quest to improve the therapeutic ratio for radiation therapy, to improve anti-tumor effects while minimizing toxicity. The link between the dosimetric advantages of proton therapy and clinical outcomes will continue to be established, and our understanding of the biology of proton therapy will also grow.

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