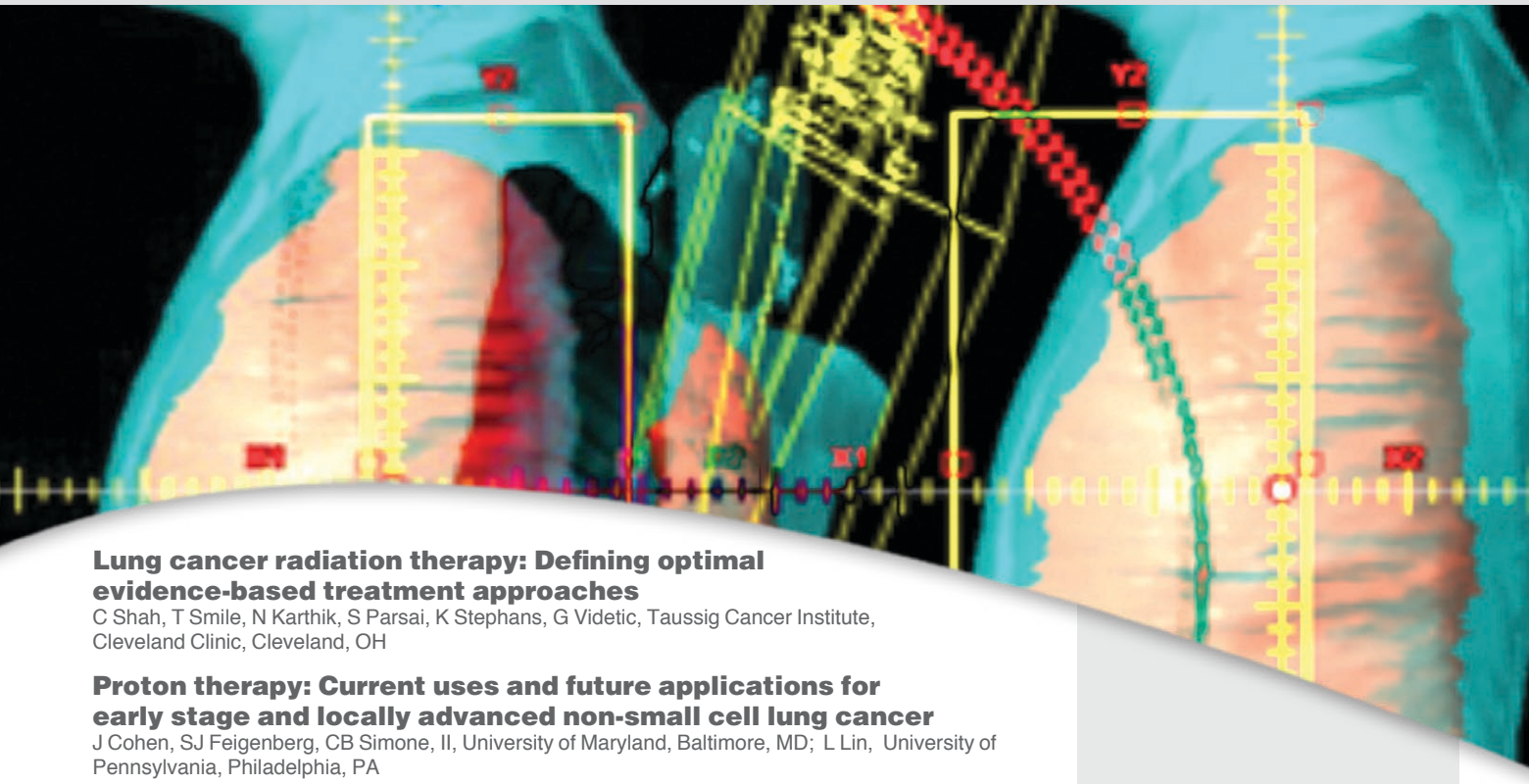
APPLIED
VOL 5 NO 4 DECEMBER 2016
RADIATION ONCOLOGY™



Lung cancer radiation therapy: Defining optimal evidence-based treatment approaches

C Shah, T Smile, N Karthik, S Parsai, K Stephans, G Videtic, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH

Proton therapy: Current uses and future applications for early stage and locally advanced non-small cell lung cancer

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Comparison of radiation therapies for non-small cell lung cancer

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Volumetric-modulated arc therapy for malignant pleural mesothelioma

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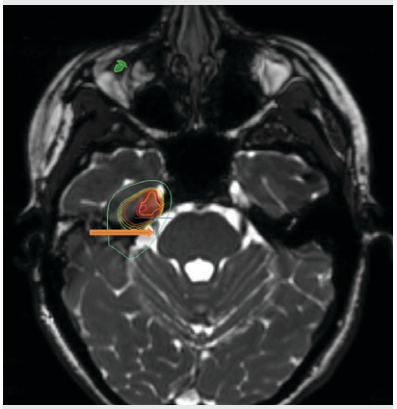

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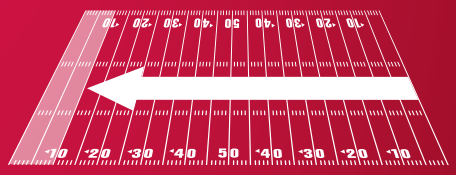

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Anderson Publishing, Ltd
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(908) 301-1995

ESSN: 2334-5446 (Online)

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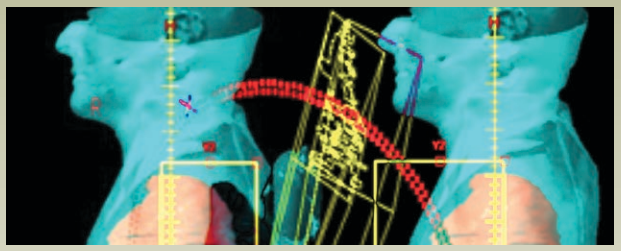
APPLIED RADIATION ONCOLOGY™

December 2016
Vol. 5, No. 4

LUNG CANCER FOCUS



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EDITORIAL

John Suh, MD, FASTRO
Editor-in-Chief

On Air: Updates in Lung Cancer RT

As we know all too well, lung cancer remains the leading cause of cancer death—by far—with more patients dying annually in the United States from this cancer than breast, prostate and colon cancers combined. Fortunately, the role of radiation therapy in lung cancer continues to evolve, increasing options—and hope—for treatment and survival.

One area of potential excitement and innovation is described in *Proton therapy for lung cancer: Current uses and future applications for early stage and locally advanced non-small cell lung cancer*. This informative and timely review article describes key studies and the rationale for proton therapy treatment, comparing passive scattering and pencil-beam techniques, while examining challenges such as intrafractional tumor motion.

We are also pleased to feature the related study, *Comparison of intensity-modulated radiation therapy (IMRT), adaptive radiation therapy, proton radiation therapy, and adaptive proton radiation therapy for small cell lung cancer (SCLC)*. This innovative study compares dose-volume histograms of target volumes and normal tissue structures to determine whether proton therapy is dosimetrically superior to photon therapy, and to assess the benefit of adaptive planning. The findings will serve as the basis for a planned phase II trial assessing toxicities in limited staged SCLC patients treated with proton therapy using adaptive planning.

A second review article, *Lung cancer radiation therapy: Defining optimal evidence-based treatment approaches,* delivers a useful framework for radiation therapy decision-making based on recent data, guidelines and treatment pathways. The article also examines the controversial role of consolidative thoracic radiation in patients with extensive stage SCLC, and discusses highly conformal treatments such as SBRT, assesses IMRT, and reviews hippocampal sparing techniques for patients undergoing prophylactic cranial irradiation.

The final article in our four-part lung focus, *Volumetric-modulated arc therapy (VMAT) for malignant pleural mesothelioma after pleurectomy/decortication* compares IMRT and VMAT delivery techniques with respect to dosimetric capabilities, MU and treatment delivery time. This interesting study also assesses planning constraints and the effects of beam angle arrangement on IMRT planning.

We hope you enjoy our focus on lung cancer and invite your comments, case reports and research findings to further evaluate data and techniques to optimize the judicious use of radiation treatment for this very common cancer.

As always, thank you for your ongoing support of ARO! We wish you a joyous holiday season and look forward to a new year of discovery, education, and collaboration across the globe in radiation oncology.

Dr. Suh *is the editor-in-chief of* Applied Radiation Oncology, *and professor and chairman, Department of Radiation Oncology at the Taussig Cancer Institute, Rose Ella Burkhardt Brain Tumor and Neuro-oncology Center, Cleveland Clinic, Cleveland, OH.*

Lung cancer radiation therapy: Defining optimal evidence-based treatment approaches

Chirag Shah, MD; Timothy Smile, BS; Naveen Karthik; Shireen Parsai, MD; Kevin Stephans, MD; Greg Videtic, MD

As the second most common cancer in the United States with an estimated incidence of more than 220,000 cases per year, lung cancer remains the leading cause of cancer mortality with 158,000 deaths annually.[1] However, lung cancer is not a homogeneous disease process, but rather a complex entity that goes far beyond traditional dichotomies of small cell (SCLC) and non-small cell lung cancer (NSCLC). Recent studies have highlighted this fact, demonstrating that even within histologic subsets of NSCLC, different treatment paradigms may be required based on tumor biology and tumor genetics.[2,3] Further, treatment techniques for surgery, radiation therapy, and systemic therapy have evolved as well, providing physicians with new modalities and treatment options for patients regardless of stage. As such, clinicians treating lung cancer are tasked with constantly re-evaluating emerging data and techniques to offer their patients evidence-based treatment options. Such innovations and paradigm shifts have been particularly evident in radiation oncology, where significant changes to treatment indications, techniques, and principles have occurred over the past decade. Therefore, the purpose of this review is to provide clinicians with a framework to make decisions regarding radiation therapy in lung cancer based on recent data as well as recent guidelines and treatment pathways.

***Dr. Shah** is associate staff and director of clinical research, **Mr. Smile** is a medical student, **Mr. Karthik** is a student, **Dr. Parsai** is a resident, **Dr. Stephans** is associate staff and **Dr. Videtic** is professor, Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH.*

Discussion

Non-Small Cell Lung Cancer

In patients with early stage NSCLC (T1-2N0), the standard of care for many years has been surgery with consideration for adjuvant chemotherapy.[4] However, many patients are deemed inoperable due to inadequate pulmonary function or other medical comorbidities, while some patients refuse surgery. Traditionally, these patients were offered definitive standard fractionation radiation therapy, which was associated with poor outcomes, even with dose escalation.[5-7] With the advent of advanced treatment planning and delivery systems in conjunction with image guidance, stereotactic body radiation therapy (SBRT) has emerged, allowing for the delivery of large doses per fraction with highly conformal dose distributions and real-time online image verification. One of the initial series evaluating SBRT came from Indiana University where an initial phase I dose escalation study was followed by a phase II study of medically inoperable patients (≤ 7 cm) with early stage (T1-2N0) NSCLC. Patients were treated with 60-66 Gy in 3 fractions and with 4-year follow-up, local control was 88% and cause-specific survival was 82%.[8,9] Importantly, however, grade 3 or greater toxicity was noted to be higher with central tumors (27% vs. 10%).[10] These promising initial findings were confirmed by additional series.[11-13] RTOG (Radiation Therapy Oncology Group) 0236 was a multi-institutional phase II trial of 55 patients (T1-2N0, < 5 cm, peripheral location, nonsurgical candidates) in which patients received SBRT (54 Gy/3 fractions); with 3-year follow-up, tumor control was 98% with a 91% rate of local (lobar) control and 87% locoregional control. Grade 3 toxicities were seen in 13% of patients with

Table 1. Key Studies Evaluating Stereotactic Body Radiation Therapy for Early Stage Non-small Cell Lung Cancer

Study	Years of accrual	Number of patients	Median F/U (months)	Radiation dose	Local recurrence	All-cause survival	Toxicity outcomes
RTOG 0236	2004-2006	55	34.4	54 Gy/3 Fx	9.4%	55.8%	Grade 3 toxicity: 12.7% Grade 4 toxicity: 3.6%
RTOG 0915	2009-2011	94	30.2	A: 34 Gy/1 Fx B: 48 Gy/4 Fx	A: 3.0% B: 7.3%	A: 61.3% B: 77.7%	Grade 3+ toxicity: A: 10.3% B: 13.3%
STARS/ROSEL	2008-2014	58	40.2	54 Gy/3 Fx 50 Gy/4 Fx	14%	95%	Grade 3+ toxicity:10%
Indiana University Phase I	2000-2003	47	27.4 19.1	54-72 Gy/3 Fx	A: 21.1% B: 21.4%	A: 87% B: 80%	Grade 3+ toxicity: 14.9%
Indiana University Phase II	Unspecified	70	50	60-66 Gy/3 Fx	11.90%	42.7%	Grade 3-5 toxicity: 10.4% (peripheral) 27.3% (central)
Cleveland Clinic Foundation	2004-2006	26	31	50 Gy/5 Fx	5.6%	52%	Grade 3 toxicity: 3.6% (dyspnea)
William Beaumont Hospital	2003-2008	124	30	48-60 Gy/ 4-5 Fx	SBRT: 9% Wedge: 27% (p>0.16)	SBRT: 72% Wedge 87%	Grade 2 or 3 radiation pneumonitis: 11%
Kyoto University	2004-2008	100	36	48 Gy/4 Fx	14%	59.9%	Grade 3-4 toxicities: 7.1%
Washington University	2004-2009	130	11 16 13	A: 45 Gy/5 Fx (central, n=9) B: 50 Gy/5 Fx (central, n=11) C: 54 Gy/3 Fx (peripheral, n=111)	LR at 1 & 2 y: A: 25%, 50% B: 0%, 0% C: 1%, 9%	1 y: 92% 2 y: 85%	Chest wall pain: 16.2%
Japanese Society of Radiation Oncology	1995-2004	257	38	18-75 Gy/ 1-22 Fx	BED > 100 Gy: 8.4% BED < 100 Gy: 42.9%	3y: 56.8% 5y: 47.2%	Pulmonary complications > Grade 2: 5.4%

4% of patients developing grade 4 toxicities and no grade 5 toxicities reported.[12] **Table 1** summarizes key studies evaluating SBRT.[8-18]

One of the greatest challenges facing clinicians is deciding on patient eligibility for SBRT as well as appropriate dose and fractionation schedules.[18-21] **Table 2** presents a summary of inclusion criteria for peripheral and central tumors as well as evidence-based fractionation schemes. An additional question facing clinicians is the role of SBRT in operable patients, as initial studies have suggested comparable outcomes.[12] Additionally, data from William Beaumont Hospital suggested lower rates of local recurrence with SBRT and comparable cause-specific survival as compared to wedge resection, while a pooled analysis of the Stereotactic Ablative Radiotherapy (SABR) in Stage I Non-small Cell Lung Cancer Patients Who Can Undergo Lobectomy (STARS) and Trial of Either Surgery or Stereotactic Radiotherapy for Early Stage (IA) Lung

Table 2. Patient Selection Criteria for SBRT

Eligibility Criteria	Peripheral Tumors	Central Tumors
Tumor Stage	T1-2	T1-2
Tumor Size	≤ 7 cm	≤ 5 cm
Nodal status	Negative	Negative
Location mediastinal/	> 2 cm from proximal bronchial tree	Within proximal bronchial tree or adjacent to pericardial pleura
Fractionation Schedules	34 Gy/1 fraction (RTOG 0915) 60 Gy/3 fractions (Indiana University/ RTOG 0236) 48 Gy/4 fractions (RTOG 0915)	50 Gy/5 fractions (RTOG 0813) 60/8 (VU University Medical Center, Netherlands)

Cancer (ROSEL) phase 3 trials evaluating SBRT in operable patients found improved survival with SBRT compared to surgery at 3 years.[16,17] Similarly, a pooled analysis from Crabtree et al found that when using propensity analyses, SBRT was associated with similar rates of local control and cancer-specific survival compared with surgery in patients with stage I disease.[22] RTOG 0618 was a phase II trial evaluating medically operable patients (T1-2N0, ≤ 5 cm, noncentral tumors) treated with SBRT (60 Gy/3 fractions) with outcomes expected in the next few years.[19]

For patients with locally advanced resectable NSCLC, neoadjuvant chemoradiation can be considered. Eligibility includes the patient being a surgical candidate with respect to medical comorbidities and pulmonary function (FEV1 > 2 L, predicted postoperative FEV > 1.2 L) with limited N2 nodal disease, and without N3 or T4 disease.[23] Patients typically receive 45-50 Gy with concurrent chemotherapy with restaging 2-4 weeks later, followed by surgery. The Intergroup 0139 trial compared this approach to definitive chemoradiation and found no difference in median or overall survival at 5 years; however, improvements in progression-free survival with neoadjuvant therapy were noted, as was improved survival for the subset of patients undergoing lobectomy.[23] An increase in treatment-related deaths was noted with neoadjuvant treatment followed by surgery (primarily in the pneumonectomy cohort), although rates of grade 3-4 esophagitis were reduced compared to definitive chemoradiation.[23]

For patients with locally advanced unresectable NSCLC who are fit for definitive therapy, chemoradiation is the standard of care.[4] This represents an evolution of treatment paradigms from radiation alone to sequential chemotherapy and radiation therapy to concurrent therapy.[4,24-26] The basis for this recommendation is several studies that have demonstrated a benefit in survival with concurrent therapy, as compared to sequential therapy.[24-26] Further, a pooled analysis comparing sequential and concurrent therapies found a 4.5% improved overall survival at 5 years with concurrent therapy, as well as reduced locoregional recurrences.[27] However, the tradeoff for this survival benefit was an increase in acute grade 3-4 esophageal toxicity (18% vs. 4%).[27] As for radiation dose, preliminary data evaluating dose escalation were promising.[28] However, RTOG 0617, a 4-arm phase III trial, found no benefit to dose escalation (74 Gy vs. 60 Gy) with a significant improvement in overall survival noted with 60 Gy, and reduced quality of life with dose escalation.[29,30] At this time, the role of dose escalation in patients receiving concurrent therapy is limited, but for patients unable to receive chemotherapy, there are data to support dose escalation when meeting organ-at-risk dose-volume constraints.[6,7,31]

While the role of postoperative radiation therapy (PORT) is often considered controversial, patients should be evaluated for adjuvant radiation therapy when there are positive margins or N2 nodal involvement (and potentially N1 patients not receiving chemotherapy).[4,32] For patients with N2 disease, while older data support a benefit to PORT, recent subset data from the ANITA (Adjuvant Navelbine International Trialist Association) trial as well as a SEER (Surveillance, Epidemiology, and End Results) analysis have also demonstrated improved survival with the addition of PORT in N2 patients, which is reflected in evidence-based guidelines.[4] Regarding sequencing, adjuvant chemotherapy is typically followed by PORT. However, in patients with positive margins, consideration for adjuvant chemoradiation should be made.[4,33-35] With respect to adjuvant chemoradiation, RTOG 9705 was a phase II trial of 88 patients (stage II/IIIA disease following surgery), with patients receiving concurrent chemotherapy (paclitaxel/carboplatin) and radiation (50.4 Gy/28 fractions, 10.8 Gy boost for nodal ECE or T3 disease). With 5-year follow-

up, local failure was 15% and median survival 57 months with an acceptable toxicity profile.[36]

Small Cell Lung Cancer

Radiation therapy has represented a standard approach to managing limited stage SCLC for several decades with the MRC trial from the 1960s demonstrating improved survival with definitive radiation as compared to surgery in operable patients.[37,38] Further, while chemotherapy remains a mainstay of treatment for SCLC, two meta-analyses have demonstrated improved survival with the addition of radiation to systemic therapy.[39,40] More recently, concurrent chemoradiation has become the standard-of-care approach, with radiation traditionally combined with cisplatin and etoposide.[38,41] The Intergroup 0096 trial randomized 417 patients to 45 Gy/25 fractions or 45 Gy/30 fractions (twice daily) with both arms receiving cisplatin/etoposide, and radiation fields that included the bilateral mediastinum and ipsilateral hilum. At 8 years, hyperfractionation was associated with improved 5-year overall survival (26% vs. 16%), with increased rates of esophagitis (27% vs. 11%) and a trend for improved local control; however, a criticism of this trial is that the two arms did not receive biologically equivalent doses, biasing the trial toward hyperfractionation.[42] Dose escalation has been evaluated, as have alternative schedules. One such regimen, which uses the concomitant boost approach (initially 1 fraction/day, then twice daily to finish within 5 weeks) was evaluated in RTOG 9712 with concurrent chemotherapy with a maximum tolerated dose of 61.2 Gy.[43] Subsequently, this regimen was evaluated on RTOG 0239 and found to have a 2-year survival of 37%, with an 18% rate of severe esophagitis and 3% treatment-related deaths.[44] Similarly, studies evaluating the maximum tolerated dose with once daily radiation therapy reached a dose of 70 Gy.[45,46] As such, the CALGB (Cancer and Leukemia Group B) 30610/RTOG 0538 trial is comparing 45 Gy/30 fractions twice daily with 61.2 Gy concomitant boost, and 70 Gy once daily with results expected in the years to come; however, the 61.2 Gy was closed leaving the hyperfractionation and the 70 Gy arms open.[47] As for the timing of chemoradiation, while individual studies have been mixed, a meta-analysis has demonstrated an improvement with early thoracic radiation therapy within 30 days of starting chemotherapy.[38,47-50]

The role of thoracic radiation therapy in patients with extensive stage SCLC remains controversial. Jeremic et al presented a randomized study of 210 patients with extensive-stage SCLC who had a complete distant response and a complete/partial response locally following chemotherapy (cisplatin/etoposide). Patients were randomized to further chemotherapy without radiation or chemoradiation (54 Gy/36 fractions twice daily with carboplatin/etoposide). The study found that median survival (17 months vs. 11 months) and 5-year survival (9% vs. 4%) improved with thoracic radiation therapy.[51] A larger multi-institutional randomized study included 498 patients with a response to chemotherapy, with patients receiving either thoracic radiation therapy (30 Gy/10 fractions) or no thoracic radiation with all receiving PCI (prophylactic cranial irradiation). With 2-year follow-up, thoracic radiation therapy improved 2-year survival (13% vs. 3%) with improved progression-free survival (24% vs. 7%) also noted.[52] However, recently RTOG 0937 was published; this was a randomized phase II trial in which patients with extensive stage SCLC (1-4 metastatic lesions, no brain metastases) who had a partial/complete response to chemotherapy were randomized to consolidative radiation therapy to the thorax and metastatic sites to a dose of 45 Gy/15 fractions (allowed to treat 30-40 Gy/10 fractions if necessary). A total of 97 patients were enrolled and with short follow-up, consolidative radiation therapy was found to delay progression with no improvement in survival noted.[53] At this time, the role of thoracic/consolidative radiation therapy remains unclear with further data required; however, its use is supported by evidence-based guidelines.[38]

PCI represents a standard-of-care treatment approach for patients with limited and extensive stage SCLC.[38] For patients with limited stage SCLC, several studies have confirmed a reduction in brain metastases with PCI in patients with a complete response to therapy, although no survival benefit was noted.[54,55] However, a meta-analysis from Auperin et al evaluated 7 randomized trials (987 patients) and found that that PCI improved OS at three years (21% vs. 15%) for patients with a complete response to therapy.[56] Additionally, larger radiation doses were associated with a greater reduction in brain metastases without survival benefit. For patients with extensive-stage SCLC, the EORTC (European Organization for Research and Treatment of Cancer) 08993 trial randomized 286 patients with extensive-stage SCLC who had any response to 4-6 cycles of chemotherapy to PCI (20 Gy/5 fractions-30 Gy/12 fractions) or no PCI. At 1 year, PCI reduced the rates of symptomatic brain metastases (15% vs. 40%) and, more importantly, improved survival (27% vs. 13%), although neuroimaging was not required beforehand.[57] Regarding dose, the standard PCI dose remains 25 Gy in 10 fractions, although alternatives have been used, including 20 Gy/5 fractions in 60% of cases in the EORTC study.[38,57] At this time, data does not support dose escalation for PCI. RTOG 0212 randomized 720 patients with limited stage SCLC who had complete response to chemoradiation to PCI with either 25 Gy/10 fractions or a higher dose (36 Gy/18 fractions or 36 Gy/24 fractions BID), with all patients receiving baseline neuroimaging. Results from this study demonstrated no difference in the incidence of brain metastases between

Table 3. Dose Volume Constraints based on SBRT Fractionation

	34 Gy/1 fraction	60 Gy/3 fractions	48 Gy/ 4 fractions	50 Gy/ 5 fractions
Lung	V7.4 Gy < 1000 cc V7 Gy < 1500 cc		V12.4 Gy < 1000 cc V11.6 Gy < 1500 cc	V13.5 Gy < 1000 cc V12.5 Gy < 1500 cc
Spinal Cord	Max Point: 14 Gy V10 Gy < 0.35cc V7 Gy <1.2 cc	Max Point: 18 Gy	Max Point: 26 Gy V20.8 Gy < 0.35cc V13.6 Gy <1.2 cc	Max Point: 30 Gy V22.5 Gy < 0.25cc V13.5 Gy <0.5 cc
Esophagus	Max Point: 15.4 Gy V11.9 Gy < 5 cc	Max Point: 27 Gy	Max Point: 30 Gy V18.8 Gy < 5 cc	Max Point: 52.5 Gy V27.5 Gy < 5 cc
Brachial Plexus	Max Point: 17.5 Gy V14 Gy < 3 cc	Max Point: 24 Gy	Max Point: 27.2 Gy V23.6 Gy < 3 cc	Max Point: 32 Gy V30 Gy < 3 cc
Heart/Pericardium	Max Point: 22 Gy V16 Gy < 15 cc	Max Point: 30 Gy	Max Point: 34 Gy V28 Gy < 15 cc	Max Point: 52.5 Gy V32 Gy < 15 cc
Great Vessels	Max Point: 37 Gy V31 Gy < 10 cc		Max Point: 49 Gy V43 Gy < 10 cc	Max Point: 52.5 Gy V478 Gy < 10 cc
Trachea/ Large Bronchus	Max Point: 20.2 Gy V10.5 Gy < 4 cc	Max Point: 30 Gy	Max Point: 34.8 Gy V15.6 Gy < 4 cc	Max Point: 52.5 Gy V18 Gy < 4 cc
Rib	Max Point: 30 Gy V22 Gy < 1 cc		Max Point: 40 Gy V32 Gy < 1 cc	
Skin	Max Point: 26 Gy V23 Gy < 10 cc	Max Point: 24 Gy	Max Point: 36 Gy V33.2 Gy < 10 cc	Max Point: 32 Gy V30 Gy < 10 cc
Stomach	Max Point: 12.4 Gy V11.2 Gy < 10 cc		Max Point: 27.2 Gy V17.6 Gy < 10 cc	Max Point: 27.2 Gy V17.6 Gy < 10 cc

regimens with improved survival with the standard PCI dose (42% vs. 37%, p = 0.05) at 2 years.[58] Concerns, however, exist regarding the potential neurotoxicity associated with PCI. Health-related quality-of-life studies from the EORTC trial demonstrated a negative impact with PCI (primarily fatigue and hair loss) with limited impact on global health status.[59] Strategies emerging to reduce PCI-related toxicity include hippocampal sparing, which is being evaluated on NRG-CC003, as well as memantine.[60,61]

Radiation Therapy Techniques

Safe and effective SBRT requires modern treatment planning and delivery techniques. Patients treated with SBRT should undergo CT simulation with respiratory motion management (4D-CT, abdominal compression, and/or gating) and immobilization. Standard volumes include a GTV (gross tumor volume, as defined on CT using lung windows), which is equal to the clinical target volume (CTV). Planning tumor volume (PTV) margins can vary depending on image guidance techniques, with RTOG 0618 using a 5-mm radial and 10-mm longitudinal expansion.[19-21] Planning can be performed using coplanar and noncoplanar beam arrangements with typically 10 or more beams; alternatively, rotational/arc-based techniques (eg, volumetric-modulated arc therapy) can be used.[19-21,62] An important consideration in SBRT planning is target volume coverage and normal tissue constraints. When reviewing target coverage, the following should be evaluated: 1) normalization to the center of mass of the PTV, 2) isodose line of 60-90% encompassing 95% of the PTV (such that 99% of the PTV receives at least 90% of prescription dose), and 3) restriction of where high dose is delivered (limit dose > 105% of prescription to PTV, all tissue outside PTV receiving > 105% of prescription should be < 15% of PTV volume) while maintaining conformality.[19-21] As for normal tissue constraints, RTOG 0618 and RTOG 0915 provide constraints for SBRT of

peripheral lesions, while RTOG 0813 provides constraints for central tumors; published constraints are available as well (**Table 3**).[19-21,63,64]

Patients treated with definitive radiation therapy for NSCLC and SCLC should undergo CT simulation with respiratory motion management (4D-CT, breath-hold, or active breathing control [ABC]) and immobilization. For NSCLC, the GTV is defined as the primary tumor and involved nodes (can use PET scan and other studies). The CTV is defined as an expansion for subclinical involvement, typically from 5-10 mm, with RTOG 1308 using an 8-mm expansion, excluding uninvolved organs.[65] Accounting for respiratory motion is the internal tumor volume (ITV), which can be done by creating a CTV on the iGTV or by creating a union of CTVs. PTV margin is typically 5 mm.[65] One question concerning CTV volume centers on the role of elective nodal irradiation (ENI). In NSCLC, data from Memorial Sloan Kettering Cancer Center identified a 6% rate of elective nodal failure when omitting ENI, confirmed by a randomized study from China.[66,67] However, a report from the International Atomic Energy Agency supports a more nuanced approach rather than completely omitting ENI, with potential utilization of ENI based on factors including stage and tumor location.[68] For treatment planning techniques, both 3-dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiation therapy (IMRT) can be used.[29] While IMRT has been shown to improve some dosimetric parameters when compared to 3D-CRT, clinical data comparing techniques are limited.[69,70] A recent secondary analysis of RTOG 0617, however, found that IMRT reduced the rates of severe pneumonitis in patients receiving chemoradiation, while a recent population-based study found improved survival with IMRT for T3/4 tumors.[71,72]

As with NSCLC, treatment techniques in SCLC have evolved over several decades. Classically, the field design from the Intergroup trial included the primary tumor as well as the ipsilateral hilum and bilateral mediastinum, extending 5 cm below the carina or to the ipsilateral hilum (whichever was lower) with the clinical volume expanded 1-1.5 cm.[42] Field arrangements included the use of oblique off-cord fields for the afternoon fraction in weeks 2 and 3. Since this study, changes have occurred concerning target volumes and treatment planning. As noted above, traditional SCLC volumes included elective nodal irradiation. However, data have emerged demonstrating low rates of elective nodal failure (< 5%), particularly when using positron emission tomography (PET) scans as part of treatment planning.[73-75] As such, current trials have moved away from elective nodal coverage and treat involved nodes only.

Another important question is whether target volumes should include prechemotherapy disease or postinduction volumes in patients not receiving radiation in conjunction with the first cycle of chemotherapy. Currently, although data remains limited, the use of postchemotherapy volumes is supported by data demonstrating no difference in the rates of marginal failures with the use of postinduction volumes.[76] Regarding the current standard of care, CALGB 30610 mandates CT-based planning with respiratory management strongly encouraged, and treatment planning with either 3D-CRT or IMRT. Target volumes include the GTV (as defined by physical exam, CT, PET and/or MRI). The ITV incorporates tumor motion during the respiratory cycle, while the CTV expansion allows for occult disease without elective nodal irradiation.[47] When delivering PCI, the standard field arrangement is opposed lateral fields covering the entire cranial contents. However, with the use of hippocampal sparing, new planning techniques are available.[60]

Conclusions

Radiation therapy represents a standard treatment option in the management of lung cancer, from early stage NSCLCs treated with SBRT to ES-SCLC, which can be treated with PCI and thoracic radiation therapy. Treatment techniques continue to evolve to help maximize the therapeutic ratio and improve not only clinical outcomes, but also toxicity profiles and quality of life for patients receiving treatment.

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Proton therapy for lung cancer: Current uses and future applications for early stage and locally advanced non-small cell lung cancer

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Lung cancer remains the leading cause of cancer death in the United States. In 2016, an estimated 224,390 new cases of lung cancer and 158,080 deaths related to lung cancer will occur.[1] Of those diagnosed, approximately 85% will be the non-small cell histologic type. Non-small cell lung cancer (NSCLC) has a very poor prognosis, with 5-year survival rates of approximately 18% across stages. Over 55% of patients are diagnosed with stage IV disease, and these patients have a particularly poor survival of only approximately 4% at 5 years.[2,3]

For patients with localized or regional NSCLC, radiation therapy is often a part of or the primary mode of treatment, with approximately 60% of patients receiving radiation.[4] In early stage disease, radiation therapy is used as definitive monotherapy most commonly in patients who are medically inoperable or refuse surgery.[5] In locally advanced disease, radiation therapy is given as bimodality definitive therapy concurrently with or sequential to chemotherapy, or it is delivered as part of trimodality therapy among patients with resectable disease.[6]

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Although treatment has become more precise, toxicity associated with thoracic radiation therapy, particularly when combined with chemotherapy, remains significant. For instance, in RTOG 0617,[7] which compared 60 Gy to 74 Gy with concurrent chemotherapy in the treatment of stage III NSCLC, 76% to 79% of patients developed grade ≥ 3 toxicity. Overall survival was inferior in the dose escalation arm, which was attributed, in part, to the high incidence of high-grade esophagitis and the higher heart doses delivered in patients receiving 74 Gy.

Treatment of NSCLC is particularly challenging since the dose needed to kill the tumor is often higher than the tolerance of the surrounding critical structures. Toxicities to healthy lung parenchyma and surrounding critical organs such as the heart, esophagus, bronchial tree, spinal cord, and brachial plexus can all be experienced with radiation therapy.[8] Compounding the issue, most lung cancer patients have a smoking history and often have pulmonary and/or cardiac disease, making them more susceptible to radiation therapy toxicities. The ideal radiation treatment plan is one that delivers a tumoricidal dose while limiting dose to normal tissue.

Proton Therapy for Lung Cancer

Unlike photon-based radiation therapy, which delivers dose throughout the course of the beam path, the physical properties of proton therapy allow for energy to be deposited at a specific depth, also called the Bragg peak. Distal to this depth, a rapid energy falloff is achieved, which allows normal tissues beyond the tumor depth to receive little or no dose of irradiation. This property gives protons better dose distributions, thus limiting dose to nearby critical structures.

In lung cancer, proton therapy can minimize dose to lung and surrounding structures, which might allow for reduced treatment toxicities. This can also allow for the treatment of tumors close to critical structures and for dose escalation,[9] which may result in better local tumor control.[10] Decreased dose to nearby healthy tissue also allows for potentially safer use of multimodality therapy and the possibility of reirradiation in the setting of local or regional recurrence.[11]

Table 1. Summary of Proton Therapy Studies for Early Stage Non-small Cell Lung Cancer

Lead author	Publication year	Stage and number of lesions treated (n)	Proton dose and Fractionation	Overall survival	Local control	Toxicity
Makita C	2015	IA (n=43) IB (n=13)	66 CGE in 10 fractions for peripheral (n=32), 80 CGE in 25 fractions for central (n=24)	3 yr 81.3%	3 yr 96.0%	16.1% grade 2 pneumonitis 1.8% grade 3 pneumonitis, no grade ≥2 esophagitis, 19.7% grade ≥2 dermatitis
Kanemoto A	2014	IA (n=59) IB (n=21) [80 tumors in 74 patients]	66 CGE in 10-12 fractions for peripheral (n=59), 72.6 CGE in 22 fractions for central (n=21)	5 yr 65.8%	5 yr 81.8%	3% grade 2 skin, 1% grade 2 esophagitis, 1% grade 3 pneumonitis, 14% rib fracture
Busch DA	2013	IA (n=47) IB (n=64)	60 CGE in 10 fraction (n=56), 51 CGE in 10 fractions (n=29), 70 CGE in 10 fractions (n=26)	4 yr 18% for 51 CGE, 32% for 60 CGE, 51% for 70 CGE	4 yr 45% for 60 CGE, 74% for 70 CGE	No grade ≥2 pneumonitis, 4% rib fractures
Iwata H	2013	IA (n=47) IB (n=23)	60 CGE in 10 fractions (n=20), 80 CGE in 20 fractions (n=14), 66 CGE in 10 fractions (n=8), 70.2 CGE in 26 fractions (n=1) [protons]; 52.8 CGE in 4 fractions (n=16), 66 CGE in 10 fractions (n=8), 68.4 CGE in 9 fractions (n=3) [carbon ions]	4 yr 58% (72% for operable patient, n=30)	4 yr 75%	3% grade ≥2 pneumonitis, 7% grade ≥2 skin, 27% rib fracture
Nakayama H	2010	IA (n=30) IB (n=28) [58 tumors in 55 patients]	66 CGE in 10 fractions for peripheral (n=41), 72.6 CGE in 22 fractions for central (n=17)	2 yr 97.8%	2 yr 97%	7% grade ≥2 pneumonitis, 2% rib fracture
Iwata H	2010	IA (n=42) IB (n=38)	60 CGE in 10 fractions (n=37), 80 CGE in 20 fractions (n=20) [protons]; 52.8 CGE in 4 fractions (n=23) [carbon ions]	3 yr 75% (74% IA, 76% IB)	3 yr 82% (87% IA, 77% IB)	12% grade ≥2 lung, 16% grade ≥2 skin, 23% rib fracture
Hata M	2007	IA (n=11) IB (n=10)	60 CGE in 10 fractions (n=18), 50 CGE in 10 fractions (n=3)	2 yr 74% (100% IA, 47% IB)	2 yr 95% (100% IA, 90% IB)	5% grade 2 pneumonitis, 10% late grade 2 subcutaneous induration/myositis
Nihei K	2006	IA (n=17) IB (n=20)	80 CGE in 20 fractions (n=17), 88 CGE in 20 fractions (n=16), 70 CGE in 20 fractions (n=3), 94 CGE in 20 fractions (n=1)	2 yr 84%	2 yr 80%	16% grade ≥2 pneumonitis/ pleural effusion
Busch DA	2004	IA (n=29) IB (n=39)	60 CGE in 10 fraction (n=46), 51 CGE in 10 fractions (n=22)	3 yr 44% (27% for 51 CGE, 55% for 60 CGE)	3 yr 74% (87% for IA, 49% for IB)	No symptomatic pneumonitis
Shioyama Y	2003	IA (n=9) IB (n=19) II (n=9) III (n=8) IV (n=1) recurrent (n=5)	Median 76 CGE in median 3.0 CGE fractions [protons alone (n=33) protons plus photons (n=18)]	5 yr 29% (70% IA, 16% IB)	5 yr 57% (89% IA, 39% IB)	8% grade ≥2 lung
Busch DA	1999	I (n=27) II (n=2) IIIA (n=8)	51 CGE in 10 fractions or 45 Gy in 25 fractions + 28.8 CGE in 16 fractions	2 yr 31% (39% stage I)	2 yr 87%	6% grade 2 pneumonitis (none for protons alone)

Early Stage NSCLC

The mainstay of treatment for early stage NSCLC is surgery, with a survival rate of 60% to 80% at 5 years.[12] However, many patients are not optimal surgical candidates due to age, poor cardiopulmonary function or other medical comorbidities, or they elect not to pursue definitive surgical management. In these patients, radiation therapy is the recommended treatment of choice. Hypofractionation and stereotactic body radiation therapy (SBRT), also termed stereotactic ablative radiation therapy (SABR), have comparable clinical outcomes to surgery for early stage NSCLC and generally more favorable clinical and toxicity outcomes compared with conventionally fractionated radiation schedules.[13,14] However, SBRT generally utilizes multiple beams or arcs, exposing larger volumes of lung to lower doses of radiation, which can result in pulmonary toxicity.[15] This makes the delivery of SBRT in patients who already have severe respiratory disease challenging. Additionally, studies have shown a higher risk of toxicities to the bronchial tree, vasculature, and surrounding critical structures when SBRT is used to treat central or ultracentral lesions.[16,17] Dose to the PTV has to be dialed back in some cases in order to avoid toxicities.[18]

The benefit of protons over photons for early stage NSCLC has been demonstrated in several planning studies[19,20] and retrospective studies in improving tumor coverage and/or reducing dose to the lungs, heart, esophagus, and spinal cord.

Many clinical studies have used protons to treat early stage NSCLC (**Table 1**). In 1999, an early prospective study was published by Loma Linda[21] in which 27 patients with early stage disease were assigned to one of two arms. Patients with adequate cardiopulmonary function received 45 Gy of photon therapy in 25 fractions to the GTV and mediastinum with a proton boost of 28.8 CGE (cobalt gray equivalents) in 16 fractions. Patients with poor cardiopulmonary function received 51 CGE of proton therapy in 10 fractions just to the GTV. At 2 years, disease-free survival was 86% and local disease control was 87%. Toxicities were minimal, with no grade > 2 esophagitis, and only 2 patients developing clinical radiation pneumonitis, both of whom had grade 2 pneumonitis that resolved with oral steroids.

Recognizing the higher rates of recurrence in patients who receive conventionally fractionated radiation therapy and the normal tissue dose constraints that limit dose escalation with photons, Loma Linda performed a phase II trial that treated stage I patients who refused surgery or were medically inoperable with hypofractionated proton therapy.[22] Twenty-two patients were treated with 51 CGE in 10 fractions over two weeks and 46 were treated with 60 CGE on the same schedule. At 3 years, local tumor control was 74% and disease-specific survival was 72%. A significant improvement in 3-year survival was noted for patients receiving 60 CGE (55% vs. 27%, $p = 0.03$). No cases of clinical acute radiation pneumonitis, acute or late esophageal toxicity, or cardiac toxicity were seen. In an updated report[23] in which 111 patients were treated with 51, 60 or 70 CGE of hypofractionated protons, the 4-year overall survival was 18%, 32%, and 51%, respectively ($p = 0.006$). For T1 tumors, 4-year local control was 86% with 60 Gy, and 91% with 70 Gy. A more notable difference was seen with a higher dose for T2 disease, with a 4-year local control of 45% with 60 Gy, and 74% with 70 Gy. There were no toxicities of grade 2 or worse.

At the University of Tsukuba in Japan, an early retrospective study reported on 28 patients with stage I disease treated with hypofractionated protons. The total equivalent doses were a median of 75.0 Gy for stage IA disease and 87.8 for IB disease.[24] Five-year overall survival was 70% for 9 stage IA patients and 16% for 19 stage IB patients, whereas 5-year infield local control was 89% for IA and 39% for IB patients. In a prospective study from University of Tsukuba, 21 patients with stage I disease were treated with hypofractionated protons to 50 or 60 Gy.[25] At 2 years, local progression-free rate was 100% and 90%, overall survival was 100% and 47%, and cause-specific survival was 100% and 70%, for stage IA and IB disease, respectively. There were no grade ≥ 3 toxicities, and only 1 patient developed a grade 2 pneumonitis. In a 2010 expanded analysis of 55 patients with stage I disease treated to 72.6 Gy in 22 fractions to central lesions and 66 Gy in 10 fractions to peripheral lesions, at 2 years, overall survival, progression-free survival, and local control were 97.8%, 88.7% and 97%, respectively.[26] In an updated 2014 report, 74 patients with 80 lesions were treated to 72.6 Gy in 22 fractions for central tumors and 66 Gy in 10 or 12 fractions for peripheral tumors.[27] At 3 years, overall survival was 76.7%, disease-specific survival was 58.6%, and progression-free survival was 58.6%. The 3-year local control was 86.3% for stage IA and 67% for stage IB, and it was 88.4% for peripheral lesions and 63.9% for central lesions. There was 1 case of grade 3 pneumonitis and 11 cases of grade 4 rib fractures.

In a retrospective report from National Cancer Center East, 17 patients with stage IA disease and 20 with IB disease were treated to 70-94 Gy in 20 fractions.[28] At 2 years, local progression-free survival was 80% and overall survival was 84%. For IA and IB disease, locoregional relapse-free survival rates were 79% and 60%, respectively.

In 2010, Iwata et al[29] published a report in which patients with stage I disease were treated with protons or carbon ions. Fifty-seven patients were treated with protons in 20 fractions to 80 Gy or 10 fractions to 60 Gy. At 3 years, overall survival was 90% and 61%, and local control was 83% and and 81% for 80 Gy and 60 Gy, respectively. In a 2013 report by Iwata el al treating larger tumors (T2A and T2B) with protons or carbon ions, the 4-year overall survival was 58%.[30]

In a recent retrospective report by Makita et al,[31] 32 patients with peripheral tumors were treated in 10 fractions to 66 Gy (6.6 Gy/fraction) and 24 patients with central tumors were treated in 25 fractions to 80 Gy (3.2 Gy/fraction). At 3 years, overall survival, progression-free survival and local control were 81.3%, 73.4% and 96%, respectively, with no significant differences between dosing regimens. No grade 4 or 5 toxicities were observed, and grade 3 toxicities were limited to a single patient (1.8%) with dermatitis and a single patient with pneumonitis.

Locally Advanced NSCLC

Dosimetric and clinical studies have demonstrated potential advantages of protons over photons in the treatment of locally advanced NSCLC. Chang et al[32] compared dose-volume histograms for protons and photons and found that protons delivered less dose to the lungs, spinal cord, heart and esophagus compared to photons (both 3-dimensional conformal radiation therapy [3D-CRT] and intensity-modulated radiotherapy [IMRT]).

A phase II study performed at MD Anderson Cancer Center enrolled 44 patients with stage III NSCLC.[33] Treatment was to 74 Gy with proton therapy at 2 Gy/fraction with concurrent carboplatin and paclitaxel. The median overall survival was 29.4 months. At 1 year, overall survival was 86% and progression-free survival was 63%. There were no grade 4-5 radiation toxicities. Grade 3 toxicities included 5 cases of dermatitis, 5 cases of esophagitis, and only 1 case of radiation pneumonitis. Of note, the median overall survival for stage III patients in RTOG 0117, in which they were treated with 74 Gy of photons plus concurrent carboplatin-paclitaxel, was relatively lower at 21.6 months,[34] similar to the 20.3 months for the 74 Gy concurrent carboplatin-paclitaxel photon radiation therapy arm of RTOG 0617.[7] In an expanded report of 84 patients, the median survival was 29.9 months. At 3 years, progression-free survival was 31.2% and overall survival was 37.2%.[35] In their 2015 report of their prospective observational study, MD Anderson investigators treated 134 patients with stage II-III NSCLC with passive scattering proton therapy (PSPT) at a dose range of 60-74.1 Gy with concurrent chemotherapy.[36] At a median follow-up of 4.7 years, median overall survival for stage II disease was 40.4 months and 30.4 months for stage III disease. Five-year disease-free rates were 17.3% and 18%, respectively.

In an analysis comparing toxicities associated with proton therapy plus chemotherapy (n = 62, median dose 74 Gy) vs. case-matched controls treated with 3D-CRT plus chemotherapy (n = 74) and IMRT plus chemotherapy (n = 66) (median dose 63 Gy for photon patients), the rates of grade ≥ 3 pneumonitis were 2% for protons, 30% for 3D-CRT, and 9% for IMRT.[37] Rates of grade ≥ 3 esophagitis were 5% for protons, 18% for 3D-CRT, and 44% for IMRT. This report suggests that chemoradiation-related toxicities can be reduced with the use of protons to treat locally advanced NSCLC.

A retrospective study was published by Nakayama et al[38] in which 35 patients with stage II-III NSCLC who were inoperable or ineligible for chemotherapy were treated with proton therapy to a median dose of 78.3 Gy at 2 Gy/fraction. Local progression-free survival at 1 year was 93.3% and at 2 years was 65.9%. Overall progression-free survival was 59.6% at 1 year and 29.2% at 2 years. Overall survival was 81.8% at 1 year and 58.9 at 2 years. There were no grade ≥ 3 toxicities. A second retrospective study from Japan reported on outcomes for 57 patients with stage III NSCLC treated with protons who were not able to receive chemotherapy due to age or medical comorbidities.[39] The median dose was 74 Gy. Median overall survival was 21.3 months, with 1- and 2-year local control rates of 79.1% and 64.1%, respectively. Six patients experienced grade ≥ 3 lung toxicities (3 acute pneumonitis, 3 late dyspnea or hemoptysis), and no grade ≥ 3 esophagitis was observed.

In a recent report using the National Cancer Data Base of patients treated from 2004-2012, capturing 243,474 patients treated with photons and 348 patients treated with protons, demonstrated on multivariate analysis that nonproton therapy was associated with inferior overall survival [HR 1.21, $p < 0.01$], with propensity-matched analysis demonstrating 5-year overall survival of 22% vs. 16% ($p = 0.025$).[40] Among stage II-III patients, photons were also associated with an increased risk of death as compared to protons (HR = 1.35, $p < 0.01$).

While the aforementioned studies generally show a benefit of protons compared to photons in LA-NSCLC, a Bayesian randomized trial presented at the 2016 American Society of Clinical Oncology Annual Meeting comparing 3DPT (PSPT) to IMRT, both with concurrent chemotherapy, demonstrated no statistically significant differences between the two modalities in a combined endpoint of grade ≥ 3 radiation pneumonitis or local recurrence.[41] Of note, patients were only randomized if both PSPT and IMRT plans satisfied normal tissue constraints. Additionally, patients treated with proton therapy generally had larger tumor volumes ($p = 0.071$), were treated to higher radiation doses, and had larger lung volumes receiving ≥ 30 Gy. These limitations underscore the need for additional investigation into the benefits of proton therapy, and particularly of pencil-beam scanning proton therapy (PBSPT).

Modalities of Proton Delivery

Two main modalities deliver protons: passive scattering proton therapy (PSPT) and PBSPT.[42] PSPT utilizes 3D planning, delivering a conformal dose to the tumor volume. In PSPT, scatterers are used, which reduce energy loss to ensure a uniform dose, and range modulation wheels create a spread-out Bragg peak to cover a tumor with a larger volume. PSPT is simpler to plan but it is not as precise as

Table 2. Currently Accruing U.S. Cooperative Group and Collaborative Group Proton Therapy Clinical Trials for Locally Advanced Non-small Cell Lung Cancer

Group	Trial Number	Trial	Stage	Proton Therapy	Chemotherapy	Primary Endpoint	Secondary Endpoints	Planned Accrual
NRG Oncology	RTOG 1308	Phase III Randomized Trial Comparing Overall Survival After Photon Versus Proton Chemoradio-therapy for Inoperable StageII-IIIB NSCLC	II-III	70 CGE in 2 CGE fractions without exceeding tolerance dose-volume limits of all critical normal structures (can reduce dose to as low as 60/2 CGE to meet constraints)	Concurrent (carboplatin and paclitaxel or cisplatin and etoposide); consolidation (required for concurrent carboplatin and paclitaxel patients)	Overall Survival	2-yr progression-free survival; grade ≥3 adverse events; quality of life; cost-effectiveness outcomes; pulmonary function changes; technological parameters	560
Proton Collaborative Group	LUN005	Phase I/II Study of Hypofractionated Proton Therapy for Stage II-III Non-Small Cell Lung Cancer	II-III	60 CGE in 24 fractions (Dose Level 1), 20 fractions (Dose Level 2), 17 fractions (Dose Level 3), 15 fractions (Dose Level 4)	Concurrent (carboplatin and paclitaxel or cisplatin and etoposide); adjuvant (optional)	Phase I: maximum tolerated dose per fraction; Phase II: 1-yr survival	Acute and late adverse events; progression-free survival and overall survival; cost-effectiveness (exploratory)	Phase I: up to 28; Phase II: 61 (inclusive of phase I patients)

PBSPT. If the tumor has an irregular shape, the thinner region will receive excessive dose compared to the thicker region, as the spread-out width must be the same. And while dose is able to conform to the distal portion of the tumor volume, conformity with PSPT proximally is more limited. Also, protons stopped by scatterers create neutrons, resulting in elevated integral dose, possibly leading to long-term toxicities such as secondary malignancies.[43,44]

In PBSPT, computer-guided magnets are used to direct the beam, painting the tumor voxel by voxel. This is a more precise technique and is, therefore, better suited for tumors with irregular shapes. With PBSPT, one can utilize either a single-field uniform optimization (SFUD), or multiple fields optimization (MFO) to create intensity-modulated proton therapy (IMPT).[45] Both SFUD and MFO use an objective function to modulate the intensities and energies of the pencil beams, delivering a targeted dose to the tumor volume while accounting for dose constraints of nearby critical structures.[46] Beam-specific planning target volume based on 4D CT can be used to ensure target margin in SFUD, and robust planning must be used to ensure target coverage in MFO.[47,48] The primary challenge of using IMPT for thoracic malignancies is overcoming the issue of respiratory motion. Due to the inhomogeneous beam with IMPT, tumor motion can result in regions of under-treatment or over-treatment, leading to the so-called interplay effect within treatment targets. However, various modalities and techniques (repainting, gating, fractionation, etc.) may correct for the uncertainty that results from intrafractional motion.[46]

Several published dosimetric studies demonstrate the benefits of IMPT.[18,49] Zhang et al[50] published a study that compared IMPT to PSPT and IMRT for inoperable stage IIIB disease. The plans of 10 patients who received 60-63 Gy with IMRT and 10 patients who received 74 Gy with PSPT were replanned using IMPT. Compared with both IMRT and PSPT, IMPT reduced dose delivered to uninvolved lungs and surrounding critical structures. Additionally, IMPT allowed for a dose escalation to 88.4 Gy without increasing the dose to the surrounding critical structures. The authors found that in the PSPT-treated patients, some of the plans required sacrificing part of the PTV due to dose constraints, and some of those patients had local failures.

As IMPT is relatively new, there are little published clinical data. One prospective study by Chang et al[46] assessed the challenges of motion analysis and management and plan optimization in treating thoracic malignancies with IMPT. IMPT was chosen for the 34 patients in that study, as these were cases of re-irradiation or that IMPT improved dose constraints over PSPT and IMRT plans. At a median follow-up of 6.5 months for these high-risk patients, 18% of patients developed grade 2 or 3 esophagitis and 15% developed grade 2 or 3 dyspnea.

Discussion

Due to the proximity to critical structures and surrounding healthy lung tissue, treating lung cancer with radiation

therapy can be challenging. Owing to their Bragg peak, protons can allow for targeted delivery of dose to lung tumors with minimal dose to surrounding tissues. With robust data demonstrating that if dose constraints can be met and toxicities can be minimized, dose escalation and hypofractionation improve local control and survival in patients with early stage NSCLC—and these interventions are continuing to be investigated in LA-NSCLC—the role of proton therapy might expand as protons may more safely allow for dose escalation and/or hypofractionation. With this and a potential toxicity reduction, protons may prove to be a cost-effective treatment modalities for thoracic tumors.[51]

As precise as protons are, this precision introduces challenges in treating lung cancer. As protons demonstrate steep dose gradients, intrafractional tumor motion can result in underdosing of tumor or overdosing of organs at risk. Breath hold, gating, or other motion-mitigation techniques or intrafractional tracking along with improved immobilization may be necessary when delivering proton therapy. Image-guided therapy is also vital for proton therapy implementation, and should undergo repeat 4D verification simulations during treatment to evaluate for anatomical and tumor motion changes that may occur during treatment and necessitate adaptive replanning.[52-53]

In comparison with IMRT planning, both the conversion of CBCT to virtual CT and the conversion of CT Hounsfield Unit to stopping power in treatment planning systems can result in the need for additional treatment margin along the proton beam direction.[52] Furthermore, although in-room CBCT/CT can be used to minimize the treatment margin perpendicular to the direction of the proton beam, additional treatment margin along the beam direction is needed to account for the proton range uncertainty related to residual patient setup inaccuracies.[54] To account for specific uncertainties related to organ motion and patient setup with proton therapy, which are often of a greater magnitude of importance compared to photon-based planning, as well as uncertainties with CT images conversion, robust and 4D optimization are emerging in treatment planning systems to enable the full capacity of IMPT.[55-56]

Future Directions

Results from prospective clinical trials are needed to be able to definitively assess for a superiority of protons compared to photons, and to identify patients most likely to benefit. RTOG 1308 is an ongoing phase III randomized trial comparing overall survival after image-guided 3D-CRT and IMRT vs. PSPT for inoperable stage II-III disease (**Table 2**). Patients are being treated up to 70 Gy (2 Gy per fraction), with the total dose reduced to as low as 60 Gy if dose constraints cannot be met. Patients in both arms will be treated with concurrent platinum-based chemotherapy, and secondary endpoints include progression-free survival, grade ≥ 3 adverse events, quality of life, cost-effectiveness outcomes, and pulmonary function testing changes.[57-58]

Another ongoing trial is Proton Collaborative Group LUN005, a phase I/II study of hypofractionated proton therapy for stage II-III NSCLC assessing the maximum tolerable dose per fraction, disease control, and toxicities/adverse events for hypofractionated proton therapy with concurrent chemotherapy.[58]

Most of the published studies utilize PSPT. PBSPT is a newer technology that employs small diameter beams to paint the tumor while taking dose constraints of nearby critical structures into account. Dosimetric studies have demonstrated the superiority of PBS/IMPT and early clinical data demonstrate it is safe and effective. As the number of centers that utilize PBS/IMPT grows, we will hopefully see more published data in the coming years.

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Comparison of intensity-modulated radiation therapy, adaptive radiation therapy, proton radiation therapy, and adaptive proton radiation therapy for small cell lung cancer

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Abstract

Background and Purpose: Proton radiation therapy for non-small cell lung cancer (NSCLC) can minimize dose to adjacent organs at risk (OARs) and potentially reduce morbidity, but limited proton data exist for small cell lung cancer (SCLC). This study compares nonadaptive intensity-modulated radiation therapy (IMRT), adaptive IMRT (AIMRT), nonadaptive proton therapy (PBT), and adaptive proton therapy (APBT) for SCLC.

Materials and Methods: Ten consecutive patients with limited-stage SCLC enrolled on an IRB-approved prospective adaptive imaging protocol treated with twice-daily photon radiation therapy to 45 Gy/30 fractions over 3 weeks were analyzed. Patients underwent repeat CT imaging after 10 and 20 fractions. Adaptive plans treated the initial CT scan to 15 Gy, second CT to 30 Gy, and third CT to 45 Gy. IMRT, AIMRT, PBT and APBT dosimetric differences were quantified (n = 40 plans).

Results: All plans provided comparable target coverage. From the simulation CT to second adaptive scan, primary and nodal GTVs decreased 54.6% and 51.9%, respectively. For photon plans, AIMRT lowered dose to lungs, esophagus, heart, and ipsilateral brachial plexus. For proton plans, APBT lowered dose to lungs, esophagus, heart, ipsilateral brachial plexus, and cord. PBT reduced dose to lungs and heart compared with IMRT and AIMRT. APBT further reduced doses to lungs, heart, and bilateral brachial plexuses compared with IMRT and AIMRT.

Conclusions: Proton therapy maintained optimal tumor coverage while significantly reducing OAR doses compared with photon plans. Adaptive planning provided dosimetric benefits for photons and protons. This study serves as the basis for a planned prospective phase II trial treating limit-staged SCLC patients with proton therapy using adaptive planning, as necessary, based on weekly verification scans.

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Table 1. Patient Clinical Characteristics and Treatment Course

Gender		
Female	8	(80%)
Male	2	(20%)
Race		
Caucasian	8	(80%)
African-American	2	(20%)
Clinical Stage		
Limited Stage	10	(100%)
Chemotherapy		
Cisplatin-Etoposide	9	(90%)
Carboplatin-Etoposide	1	(10%)
Radiation Therapy Start Timing		
Cycle 1	3	(30%)
Cycle 2	7	(70%)
Thoracic Radiation Therapy		
Twice Daily Irradiation	10	(100%)
Median Dose (Gy)	45	(100%)
Concurrent Chemotherapy	10	(100%)
3DCRT*	5	(50%)
IMRT*	5	(50%)

*Abbreviations: 3DCRT = three-dimensional conformal radiation therapy; IMRT = intensity modulated radiotherapy

Twice-daily radiation therapy with concurrent cisplatin and etoposide is standard treatment for patients with limited-stage small cell lung cancer (SCLC).[1,2] However, concurrent therapy is associated with increased toxicity, particularly when radiation therapy is administered twice daily.[3] Turrisi et al reported that among 417 patients randomized to receive twice-daily or once-daily thoracic radiation therapy with concurrent chemotherapy for SCLC, 90% of patients receiving twice-daily radiation therapy experienced grade 3 or higher toxicity, including 3% with grade 5 toxicity. Grade 3 or higher toxicities included esophagitis in 32% and pulmonary in 6%.[4]

Proton radiation therapy for non-small cell lung cancer (NSCLC) can minimize radiation dose to adjacent organs at risk (OARs), which can potentially reduce toxicities and patient morbidity.[5-10] In single-arm studies assessing survival outcomes for proton therapy to treat NSCLC, proton therapy has been reported to improve 2- and 3-year survival rates compared to historically reported rates for photon therapy.[11,12] Although early data suggest promising outcomes awith protons for NSCLC, data on proton therapy for SCLC is lacking and limited to a single case series,[13] likely due to concerns that rapid tumor volume changes during proton therapy could lead to loss of plan validity and overdosing of OARs. Such changes, therefore, might require adaptive planning if proton therapy were delivered for SCLC.

Studies in NSCLC have shown adaptive proton therapy can reduce dose to OARs. Adaptive proton therapy for NSCLC can allow for dose escalation while limiting side effects.[14] In a comparison of non-adaptive proton therapy to adaptive proton radiation therapy for NSCLC, adaptive planning showed less toxicity and more OAR sparing.[15]

To date, only limited data directly compare different radiation therapy modalities and treatment strategies for SCLC, including the use of proton and particle therapy for SCLC. Additionally, no existing reports assess adaptive photon or proton radiation therapy for SCLC. This is the first study comparing dose-volume histograms (DVHs) of target volumes and normal tissue structures in nonadaptive intensity-modulated radiation therapy (IMRT), adaptive IMRT, nonadaptive proton therapy, and adaptive proton therapy for SCLC to determine whether proton therapy is dosimetrically superior to photon therapy and to assess the benefit of adaptive planning.

Materials and Methods

Ten consecutive patients with limited-stage small cell lung cancer treated at the University of Pennsylvania, Philadelphia, with twice-daily photon radiation therapy were assessed in an Institutional Review Board-approved prospective study in which patients gave informed consent and underwent repeat imaging during radiation therapy. Patients were predominantly female and Caucasian (**Table 1**). All patients received concurrent chemotherapy and started radiation therapy with cycle 1 (30%) or cycle 2 (70%) of chemotherapy. All patients were treated to 45 Gy in 1.5 Gy twice-daily fractions (30 fractions) over 3 weeks with either 3-dimensional conformal radiation therapy (3DCRT) (50%) or IMRT (50%). Patients underwent replanning 4-dimensional CT scans after their 10th and 20th fractions of radiation therapy to evaluate treatment response.

CT data were attained with a slice thickness of 3 mm. To define target and nontarget structures, CT images were imported into photon and proton commercial treatment planning systems (Eclipse Treatment Planning Version 13.0, Varian Medical Systems, Palo Alto, California). OARs and target volumes were contoured on the initial CT data set and each subsequent re-imaging CT data set. Assessed OARs included the spinal cord, lungs, brachial plexus, esophagus, and heart.

Gross tumor volume (GTV) was defined as all gross disease determined from bronchoscopy, CT scan (nodes > 1 cm

Table 2. Changes in Gross Tumor Volumes (GTV)* and Planning Target Volumes (PTV)* During Treatment

Patient	Primary GTV_1	Primary GTV_2	Primary GTV_3	Primary PTV_1	Primary PTV_2	Primary PTV_3	Nodal GTV_1	Nodal GTV_2	Nodal GTV_3	Nodal PTV_1	Nodal PTV_2	Nodal PTV_3
1	70.4	46.0	27.9	350.1	285.6	229.4	9.9	5.6	2.5	106.8	82.9	62.7
2	0.6	0.3	0.1	42.7	34.4	29.9	36.8	21.7	15.5	170.2	140.3	126.0
3	35.8	9.7	5.3	240.4	125.3	96.0	38.9	19.2	14.9	188.8	135.5	103.1
4	5.3	2.6	2.2	82.8	62.2	58.9	110.3	92.4	68.4	378.7	351.8	308.4
5	14.5	10.2	7.6	159.0	148.6	122.5	111.2	94.5	79.3	338.3	307.7	250.2
6	162.5	114.3	92.9	607.8	480.1	407.7	26.5	15.8	13.3	131.7	109.3	101.4
7	11.1	7.0	4.5	198.9	173.3	144.2	19.5	13.5	9.3	122.8	98.5	84.3
8	34.0	27.3	22.7	302.5	281.3	268.8	58.8	40.6	30.9	314.1	266.4	223.2
9	19.3	4.4	2.2	178.3	104.2	91.4	320.1	154.7	118.1	756.8	472.1	385.8
10	18.1	5.7	3.3	162.6	96.8	91.4	26.6	15.7	12.8	214.2	180.6	143.9
Mean	37.2	22.7	16.9	232.5	179.2	154.0	75.9	47.4	36.5	272.2	214.5	178.9

*GTV_1 and PTV_1 calculated at the time of treatment planning simulation scan prior to beginning radiation therapy, GTV_2 and PTV_2 calculated at the time of replanning scan at the end of the first week of radiation therapy, GTV_3 and PTV_3 calculated at the time of replanning scan at the end of the third week of radiation therapy; volumes in cm^3

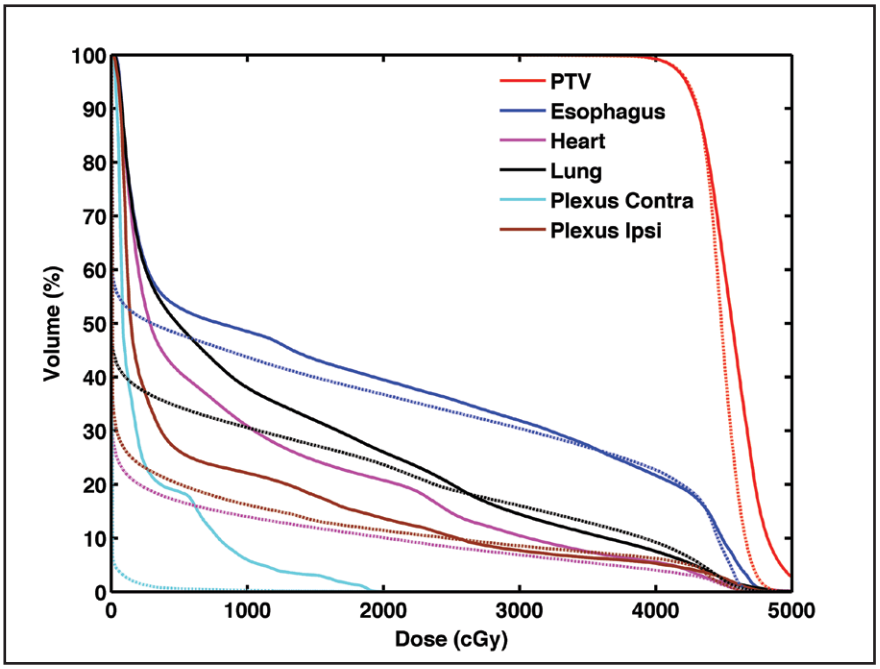

FIGURE 1. *Composite dose-volume histograms. Comparison of the mean dose-volume histograms for all nonadaptive photon (n = 10, solid lines) and nonadaptive proton (n = 10, dashed lines) treatment plans for all patients with limited-stage SCLC. Structures include PTV (red), esophagus (blue), heart (magenta), total lung minus GTV (black), contralateral brachial plexus (cyan), and ipsilateral brachial plexus (brown).*

short axis diameter), positron emission tomography (PET) scan (SUV > 3), or pathologic nodal sampling or dissection. Separate GTVs were contoured for primary tumor, designated $GTV_{Primary}$, and nodal metastasis, designated GTV_{Nodal}. To account for intrafractional motion, an internal GTV was created for each GTV, designated iGTV, by expanding the GTV based on tumor excursion seen on 4D imaging. A 10 mm expansion was added to $iGTV_{Primary}$ to account for microscopic disease to create clinical target volumes (CTV). For nodal stations involved with tumor, the entire nodal level was included in the CTV, and an additional 3-5 mm margin was added to the involved nodal station.

To account for set-up variation and organ and patient motion, a uniform 5 mm margin in all directions was added to each CTV to define planning target volumes (PTVs) $PTV_{Primary}$ and PTV_{Nodal}. $PTV_{Primary}$ and PTV_{Nodal} were combined to PTV_{Total} and planned to 45 Gy for photon plans or 45 cobalt Gray equivalents (CGE) for proton plans, with proton doses corrected with the accepted relative biologic effectiveness value of 1.1.[16]

For proton plans, beam range compensators were designed to account for properties of the proton beam and range uncertainties by providing proximal and distal margins relative to each PTV. Blocking was designed to create a lateral margin relative to each PTV, with margins individualized for each patient based on formulas by Moyers et al.[17] For the IMRT plan, dose objectives were created for PTVs and OARs. Helios Inverse Treatment Planning

Table 3. Comparison of the Average Doses to Normal Tissues Between IMRT, Adaptive IMRT, Proton Therapy, and Adaptive Proton Therapy

	Spinal Cord	Lung			Ipsilateral Brachial Plexus	Contralateral Brachial Plexus	Esophagus		Heart		
	Max	V5	V20	Mean	Max	Max	V30	Mean	1/3	2/3	Mean
IMRT	33.6	49.6	26.0	12.1	18.6	6.0	32.0	17.6	9.0	4.1	10.0
Adaptive IMRT	33.0	48.9	23.9	11.3	16.4	6.1	28.1	16.2	8.7	2.9	9.2
Proton	29.4	34.9	24.4	10.2	17.6	3.7	30.5	16.0	1.2	0.2	4.7
Adaptive Proton	27.1	33.6	21.9	9.1	15.1	2.5	26.8	14.5	0.7	0.2	4.0

Max = average maximum point dose (Gy)
V5/20/30 = volume receiving 5/20/30 Gy (percentage)

(Varian Medical Systems) was used to optimize plans to minimize dose to critical structure by increasing OAR constraints, while maintaining optimal coverage on target volumes and dose homogeneity.

Four treatment plans were created for each patient (n = 40 plans): (1) photon IMRT, with treatment planned to the target volumes and normal structures from the initial CT image set to 45 Gy; (2) adaptive photon IMRT, with treatment planned to target volumes and normal structures from the initial CT image set to 15 Gy, second CT obtained after 10 fractions of treatment to 30 Gy, and third CT obtained after 20 fractions of treatment to 45 Gy; (3) passively scattered proton therapy, with treatment planned from the initial CT image set to 45 CGE; and (4) adaptive passively scattered proton therapy, with treatment planned from the initial CT image set to 15 CGE, second CT to 30 CGE, and third CT to 45 CGE. For adaptive IMRT and proton plans, the second and third CTs were fused to the initial CT image set using deformable registration, and new OARs and target volumes were contoured on each of the successive re-planning CT scans. The same expansions to CTVs, PTVs and planning objectives were employed, and plan sums and composite DVHs were generated.

Planning was performed to achieve maximum doses (Dmax) to the spinal cord < 36 Gy and brachial plexus < 45 Gy, and the doses to 2/3 of the heart < 20 Gy and 1/3 of the heart < 35 Gy. Lung constraints were mean < 20 Gy, V5 (volume receiving 5 Gy) < 60%, and V20 < 35%, whereas esophageal constraints were mean < 20 Gy and V30 < 50%.

Statistics

The Friedman test, a nonparametric small sample test for comparing multiple treatments across dependent repeated measures, was used to compare the four treatment plans across patients. The Wilcoxon signed rank sum test was subsequently used to conduct post-hoc pairwise comparisons. No multiple testing correction was applied since these were exploratory analyses with small sample sizes. All tests were two-tailed, and results were considered to be statistically significant when $p < 0.05$.

Results

Patient statistics

The cohort mean GTV_{Nodal} from the initial CT image set obtained before concurrent chemoradiation was 75.9cm^3 (range 9.9-320.1cm^3) (**Table 2**). The mean GTV_{Nodal} from the second CT image set decreased by 37.6% to 47.4cm^3 (5.6-154.7cm^3). The mean GTV_{Nodal} from the third CT image set decreased an additional 22.9% to 36.5cm^3 (2.5-118.1cm^3), for an overall reduction of 51.9%. The corresponding mean PTV_{Nodal} were 272.2cm^3 (106.8-756.8 cm^3), 214.5cm^3 (82.9-472.1cm^3; 21.2% reduction), and 178.9cm^3 (62.7-385.8cm^3; 16.6% additional reduction, 34.3% total reduction).

Similarly, the mean $GTV_{Primary}$ from the initial CT image set was 37.2cm^3 (0.6-162.5cm^3), decreased 38.8% to 22.7cm^3 (0.3-114.3cm^3) at the second CT, and decreased an additional 25.9% to 16.9cm^3 (0.1-92.9cm^3) at the third CT, for an overall 54.6% decrease. The corresponding $PTV_{Primary}$ were 232.5cm^3 (42.7-607.8cm^3), 179.2cm^3 (34.4-480.1cm^3; 22.7% reduction), and 154.0cm^3 (29.9–407.7cm^3; 14.3% additional reduction, 33.8% total reduction).

Dose Coverage

IMRT, adaptive IMRT, proton therapy, and adaptive proton therapy plans all provided comparable and acceptable target volume coverage, with no significant difference in coverage to PTV_{Nodal} ($p = 0.32$ to $p = 0.92$ for all 6 plan comparisons), $PTV_{Primary}$ ($p = 0.44$-0.92), and PTV_{Total} ($p = 0.56$-0.95) (**Figure 1**). In all cases, 95% of the PTV_{Total} was covered by at least 99% of the prescription dose, 99% of the CTVs were covered by the prescription dose, and no point dose exceeded 120% of the prescription dose.

IMRT vs. Adaptive IMRT

Compared with IMRT plans, adaptive IMRT statistically significantly

decreased esophagus mean dose and V30 (both $p < 0.01$), lung mean ($p = 0.04$) and V20 ($p = 0.04$), and dose received by 2/3 of the heart ($p = 0.03$) **(Table 3)**. Adaptive IMRT also trended to lower the mean heart dose ($p = 0.06$) and significantly lowered the Dmax to the ipsilateral brachial plexus ($p = 0.01$), but not the contralateral brachial plexus ($p = 0.14$). There was no statistically significant difference in spinal cord Dmax ($p = 0.22$), dose received by 1/3 of the heart ($p = 0.51$), and lung V5 ($p = 0.36$).

IMRT vs. Proton Therapy

Compared with IMRT, proton therapy significantly reduced lung mean ($p = 0.03$) and V5 ($p < 0.01$), as well as heart mean and doses to 1/3 and 2/3 of the heart (all $p < 0.01$) **(Figure 1)**. Proton therapy trended to lower the contralateral brachial plexus Dmax ($p = 0.06$) but did not significantly reduce the ipsilateral brachial plexus Dmax ($p = 0.14$). The spinal cord Dmax ($p = 0.20$), lung V20 ($p = 0.44$), and esophagus mean ($p = 0.39$) and V30 ($p = 0.84$) were not significantly decreased with proton therapy.

Adaptive IMRT vs. Proton Therapy

Compared with adaptive IMRT plans, proton therapy significantly lowered lung V5, heart mean, and doses received by 1/3 and 2/3 of the heart (all $p < 0.01$). The contralateral brachial plexus Dmax ($p = 0.06$) and lung mean ($p = 0.11$) trended lower with protons. Ipsilateral brachial plexus ($p = 0.58$) and spinal cord ($p = 0.14$) Dmax and esophagus mean ($p = 0.96$) and V30 ($p = 0.28$) were not improved with proton therapy.

IMRT vs. Adaptive Proton Therapy

Adaptive proton therapy significantly lowered lung mean and V5, heart mean, and doses received by 1/3 and 2/3 of the heart (all $p < 0.01$) compared with IMRT. Adaptive proton therapy also significantly reduced the ipsilateral ($p < 0.01$) and contralateral ($p = 0.02$) brachial plexus Dmax and trended to lower spinal cord Dmax ($p = 0.07$), esophagus mean ($p = 0.09$) and V30 ($p = 0.11$), and lung V20 ($p = 0.06$).

Adaptive IMRT vs. Adaptive Proton Therapy

When compared to adaptive IMRT, adaptive proton therapy significantly reduced spinal cord Dmax ($p = 0.02$), heart mean and doses to 1/3 and 2/3 of the heart (all $p < 0.01$), and lung mean ($p = 0.03$) and V5 ($p = 0.01$). Adaptive proton therapy also significantly lowered the ipsilateral and contralateral brachial plexus Dmax (both $p < 0.01$). Esophagus mean ($p = 0.28$) and V30 ($p = 0.88$) doses did not differ.

Proton Therapy vs. Adaptive Proton Therapy

Adaptive proton therapy improved the esophagus mean and V30, ipsilateral brachial plexus Dmax, heart mean, and lung mean and V20 (all $p < 0.01$) compared with nonadaptive proton therapy. Adaptive proton therapy also significantly reduced the lung V5 ($p = 0.02$) and cord Dmax ($p = 0.04$) and trended to lower the contralateral brachial plexus Dmax ($p = 0.12$) and dose received by 2/3 of the heart ($p = 0.07$). There was no difference in dose received by 1/2 of the heart ($p = 0.14$).

Discussion

This study showed significant differences in doses to OARs when comparing nonadaptive IMRT, adaptive IMRT, nonadaptive proton therapy, and adaptive proton therapy for treatment of SCLC. Proton therapy significantly reduced dose to the lungs and heart compared with IMRT or adaptive IMRT. Adaptive proton therapy further reduced the doses to the heart and lungs compared with IMRT and adaptive IMRT, and also significantly reduced maximum doses to the bilateral brachial plexuses. When looking at the benefits of adaptive therapy within a radiation particle type, adaptive IMRT improved doses to the lung, esophagus, heart, and ipsilateral brachial plexus compared with nonadaptive IMRT, whereas adaptive proton therapy reduced doses to the lung, esophagus, heart, ipsilateral brachial plexus, and cord compared with nonadaptive proton therapy. This study also demonstrated significant shrinkage of tumor volumes during the course of radiation therapy, including > 50% reductions in GTVs and > 30% reduction in PTVs, with similar magnitude of nodal and primary tumor reductions achieved.

Colaco et al previously reported on a retrospective case series of 6 patients with SCLC who were treated with proton therapy. In that report, no acute grade ≥ 3 esophagitis or acute grade ≥ 2 pneumonitis were observed, and dosimetric comparisons with IMRT showed better sparing of lungs and esophagus with proton therapy.[13] Although the data describing the use of proton therapy to treat SCLC are extremely limited, numerous reports have demonstrated excellent survival outcomes with proton therapy for NSCLC. Xiang et al reported a median survival of 29.9 months across two prospective trials of 84 patients treated with concurrent proton therapy and chemotherapy for stage III NSCLC and found a 34.8% local recurrence-free survival, 35.4% distant metastasis-free survival, 31.2% progression-free survival, and 37.2% overall survival at 3 years.[11] Among 35 patients treated with inoperable locally advanced NSCLC with proton radiation therapy alone without chemotherapy, no grade 3 or higher toxicity was observed. The overall survival rate was 81.8% at 1 year and 58.9% at 2 years, and local progression-free survival was 93.3% at 1 year and 65.9% at 2 years.[12]

Proton therapy has also been reported in multiple studies to improve dosimetric parameters compared with photon therapy for NSCLC,[6,8,18,19] consistent with the current study findings for SCLC. Re-

duced OAR doses with proton therapy for lung cancer may reduce treatment-related toxicities for lung cancer. Sejpal et al investigated the toxicity associated with proton therapy to a median of 74 CGE with concurrent chemotherapy for NSCLC compared with toxicity for disease-stage matched patients treated with 3D-CRT or IMRT to a median of 63G y with concurrent chemotherapy. While proton radiation therapy allows for higher radiation doses, it also significantly lowers rates of grade ≥ 3 pneumonitis (2% vs. 30% vs. 9%, $p < 0.001$) and esophagitis (5% vs. 18% vs. 44%, $p < 0.001$) compared with 3D-CRT and IMRT, respectively.[10]

In efforts to decrease dose to adjacent normal tissues while maintaining optimal target volume coverage, adaptive radiation planning has been increasingly investigated. Although no published data on adaptive radiation therapy for small cell lung cancer currently exist prior to this report, adaptive radiation therapy for NSCLC has previously been evaluated. By assessing the effects of a 20-28 Gy boost to a shrunken PTV after 40 Gy in 66 patients with stage III NSCLC, Ding et al reported significant sparing of OARs compared to nonadaptive radiation therapy, which the authors reported may allow for dose escalation and an improvement in local control.[20] Similar significant reductions in lung doses and an ability to dose escalate were reported in another study of 13 patients with locally advanced NSCLC. This investigation also demonstrated a reduction in mean lung dose of 5.0% with single-plan adaptation in week 3, 5.6% with single-plan adaption in week 5, and 7.9% with adapting the plan after both weeks 3 and 5.[21,22] This benefit is in keeping with the even greater benefit seen in our study, in which the mean lung dose was reduced by 5.5% with IMRT and 11.9% with proton therapy with a single-plan adaption after 15 Gy, and by 14.7% with IMRT and 17.6% with proton therapy with a single-plan adaption after 30 Gy.

Another study that utilized PET rescanning during the course of treatment to design boost fields for NSCLC demonstrated the potential for significantly escalating doses while sparing OARs.[23] Still another study showed that adaptive image-guided radiation therapy methods for NSCLC were optimal in improving PTV coverage and decreasing dose to normal tissues, including significantly reducing the mean lung dose.[24] Other studies, however, have showed less benefit to adaptive radiation therapy, including its use for the treatment of stage I NSCLC with stereotactic body radiation therapy (SBRT).[25] However, unlike the dramatic reduction in tumor volume demonstrated during the course of treatment for SCLC in the current study, a significant tumor volume reduction would not be expected during the short course of SBRT.

More limited data exist assessing adaptive radiation therapy when delivering proton therapy. A dosimetric study that compared IMRT, adaptive IMRT, proton therapy, and adaptive proton therapy for squamous cell carcinoma of the head and neck found that proton therapy decreased doses to OARs compared to IMRT, and that adaptive proton therapy further reduced doses to OARs compared to nonadaptive proton therapy.[26] Another study of 18 patients assessing the toxicity and patterns of failure associated with adaptive proton therapy for NSCLC showed that proton therapy is well-tolerated and a promising approach to allow for higher doses while limiting side effects. No patient experienced Grade 4 or 5 toxicity, and patients most commonly experienced dermatitis (Grade 2, 67%; Grade 3, 17%), Grade 2 fatigue (44%), and Grade 2 pneumonitis (11%).[14] A third study examining the outcomes of adaptive proton therapy compared to nonadaptive proton therapy for NSCLC found less toxicity and greater OAR sparing with adaptive planning. Koay et al found adaptive planning significantly reduced NSCLC tumor volume size ($p < 0.01$) and improved sparing to the esophagus and spinal cord. However, unlike the current study, no significant reduction to the heart or lungs was observed.[15]

Although no appreciable data on adaptive radiation therapy for SCLC exist to date, to account for the rapid tumor response to therapy and to attempt to minimize radiation dose to OARs, modification of plans during SCLC treatment are being studied in Alberta, Canada, in a prospective trial. Clinical trials in Ontario, Canada, and Limburg, Netherlands, are also enrolling patients to examine adaptive radiation therapy for NSCLC. Image-guided adaptive proton therapy is being compared to photon therapy in a collaboration between Massachusetts General Hospital and UT MD Anderson Cancer Center, whereas a Stanford University trial is evaluating differences in 4DCT-based ventilation imaging during simulation and treatment. The Radiation Therapy Oncology Group (RTOG) and American College of Radiology Imaging Network (ACRIN) are investigating whether tumor dose can be escalated to improve local control when an individualized adaptive radiation treatment plan is applied by using FDG-PET/CT scans acquired at 40-46 Gy in patients with inoperable or unresectable stage III NSCLC (RTOG 1106/ACRIN 6697).[27]

Limitations

Although some radiation oncologists continue to treat SCLC with 3D-CRT, as was done in Intergroup 0096,[4] IMRT-based radiation therapy with concurrent chemotherapy for limited-stage SCLC has become increasingly utilized to decrease dose to OARs compared to 3DCRT, and IMRT is being prospectively evaluated for SCLC in the Netherlands.[27] In this study, photon plans were delivered with IMRT to maximize tumor coverage and minimize OAR

dose. It is possible that the magnitude of benefit demonstrated in this study with proton therapy over photon therapy would have been even greater had the photon plans employed 3DCRT. Furthermore, as the entire treatment course with twice daily radiation therapy was completed in 3 weeks, it is possible that greater target volume shrinkage and further reductions of dose to OARs would have been demonstrated if radiation therapy was administered once daily over 6-8 weeks instead of twice daily. Also, as 7 of the 10 patients received one cycle of chemotherapy prior to beginning radiation therapy, the magnitude of tumor volume reduction and OAR sparing may have been even greater if only chemotherapy-naïve patients were assessed. As patients treated with once-daily radiation therapy or starting radiation therapy with cycle 1 of chemotherapy may have an even greater magnitude of benefit for adaptive therapy, adaptive planning may be even more imperative when treating such patients with proton therapy.

Furthermore, all proton plans were performed using passively scattered proton therapy. It is possible that the benefit demonstrated in this study with proton therapy over photon therapy would have been even greater had the proton plans employed pencil-beam scanning proton therapy instead of passively scattered proton therapy. Additionally, all doses reported for tumor and OARs were based on the clinical proton treatment planning system. The accuracy of proton dose in a heterogeneous environment like the lung is limited due, in part, to degradation of the lateral penumbra.[28-30] As a result, the reported values may be overestimated for target dose and underestimated for dose to normal lung, and reanalysis with Monte Carlo-based dose calculation might more accurately describe the true doses to these volumes.[28,31] However, the magnitude of the effects seen in this study, including the benefit of proton therapy over IMRT and the benefit of adaptive therapy over nonadaptive therapy, would be expected to remain significant and largely proportional regardless of the dose calculation method used and out-of-field dose inaccuracies.

Additionally, given the limited data on adaptive planning in lung cancer, caution must be taken when clinically performing adaptive therapy by shrinking the target volumes, as viable microscopic disease might remain in the original treatment volume despite a strong initial response to chemoradiation. We mitigated this concern, in part, by using the same expansions to CTVs and PTVs in the adaptive plans that were used in the initial plans and by using the same field arrangements in the adaptive plans that were used in the initial plans to allow for dose delivery via beams already traversing these areas of potential microscopic residual disease. Furthermore, findings from two large studies, including a 494-patient cooperative group study, suggest that the radiation therapy treatment of smaller volumes of disease following an initial response to therapy for SCLC is not associated with reduced local control or overall survival.[32-33] Lastly, the statistical results in this study should be interpreted with caution since the sample size was limited, as this was an exploratory analysis intended to provide evidence supporting the initiation of a planned prospective clinical trial.

Conclusions

This study demonstrated a rapid shrinkage of tumor volumes during the course of radiation therapy for SCLC, which allowed for adaptive plans to be dosimetrically superior to nonadaptive plans for both photons and protons. Adaptive plans may be of more critical importance for proton therapy, and verification scans should be performed during treatment to ensure continued plan validity. Adaptive planning for proton therapy may be further facilitated using cone-beam computed tomography and deformable registration.[34] When compared with photon therapy, proton therapy allowed for the maintenance of optimal tumor coverage while significantly reducing dose to critical normal structures like lungs and heart. With decreased doses delivered to OARs, patients receiving proton therapy may experience fewer radiation-induced side effects. Prospective clinical trials are needed to determine if the dosimetric superiority of proton therapy can result in less toxicity for patients with limited-stage SCLC. Future studies should also focus on the feasibility and benefit of pencil-beam scanning and intensity-modulated proton therapy (IMPT) for SCLC to further reduce dose to OARs, including the esophagus.[35,36] The findings in this study serve as the basis for a planned phase II trial assessing toxicities in limit-staged SCLC patients treated with proton therapy using adaptive planning, as necessary, based on weekly verification scans.

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Volumetric-modulated arc therapy for malignant pleural mesothelioma after pleurectomy/decortication

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Treatment of malignant pleural mesothelioma (MPM) has historically presented a treatment challenge due to the aggressive nature of the tumor, the size and complexity of the target volume and its proximity to critical organs. Two types of surgery are performed for mesothelioma: extrapleural pneumonectomy (EPP) and pleurectomy/decortication (P/D). EPP involves an en bloc resection of the entire pleura, lung, diaphragm and ipsilateral, half of the pericardium, and is a high-risk surgery for patients with this disease. P/D is a lung-sparing surgery that involves the removal of gross tumor along with the visceral pleura, parietal pleura, pericardium and/or hemidiaphragm if needed for macroscopic complete resection, but spares the underlying ipsilateral lung.

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Studies have shown that P/D is a less morbid procedure compared to EPP, suggesting a survival benefit and, thus, is becoming increasingly used for these patients.[1,2] Surgery alone, however, does not offer adequate long-term local control or survival rates. Multimodality therapy that combines surgery, chemotherapy and radiation therapy has shown favorable clinical outcomes both for patients who have received EPP[3] or P/D[4] as part of their surgical management. Adjuvant radiation therapy with conventional techniques has been given through anterior and posterior fields that encompass the entire hemithorax.[5,6] Since the ipsilateral lung remains in situ after P/D, traditionally these techniques have attempted to spare the lung by adding a block on the central part of the lung.[6] Anterior and posterior parts of the chest wall underneath the lung are boosted with an electron field. However, this technique has resulted in disappointing local control, survival rates and high levels of toxicity.[5] Since conventional radiation techniques in these patients have been unable to provide adequate local control without compromising toxicity, we must examine advanced radiation planning and delivery techniques. Intensity-modulated radiation therapy (IMRT), a highly conformal radiation delivery technique, has been shown to effectively spare normal tissues while enabling the delivery of higher radiation doses to the tumor, potentially providing safer and less toxic treatments compared to conventional techniques.[7] Initial experience with pleural IMRT in 36 patients with 2 intact lungs has shown the safety and feasibility of this technique.[8] The risk of grade ≥ 3 pneumonitis was 20%, an acceptable result given the high risk of this patient population. An expanded analysis published using this technique in 67 patients with definitive or adjuvant hemithoracic pleural IMRT showed a median survival of 2 years from the time of diagnosis, with a 1- and 2-year overall survival (OS) rate of 85% and 50%, respectively.[9] A recent 2-center phase II trial in which 27 of 45 patients completed hemithoracic IMRT following chemotherapy and surgery reported that 8 of these patients (30%) experienced either grade 2 (n = 6) or grade 3 (n = 2) RP with no grade 4 or 5, and 1 and

Table 1. Summary of Dosimetric Criteria

Structure	Parameter	Objective
PTV	D95 (%)	94%*
	V95 (%)	≥94%*
	D05 (%)	≤120%*
Total Lung	Mean dose	≤ 20 Gy*
	V20 Gy	≤ 37% -40%
Contralateral Lung	Mean dose	≤ 8 Gy*
	V20 Gy	≤ 7%*
	V5 Gy	< 25%
Cord	max	≤ 50 Gy*
Heart	Mean (Gy)	≤ 30 Gy*
	V30 Gy	≤ 50%*
Ipsilateral Kidney	V18 Gy	≤ 33% (≤50%*)
Liver	Mean (Gy)	≤ 30 Gy (≤31Gy*)
	V30 Gy	≤ 50%*
Stomach not PTV	Mean (Gy)	≤ 30 Gy*
Esophagus	Mean (Gy)	≤ 34 Gy*
Bowel	$D_{0.5\%}$	≤ 50 Gy*

*signifies constraints used as limiting constraints, while the others are used as guidelines

2 year OS of 80% and 59% for resectable, and 74% and 25% for unresectable patients.[11] Tomotherapy has also been used for pleural IMRT with results showing encouraging survival and acceptable toxicity rates[19,20] with reports showing a correlation between the total lung V20 Gy, V30 Gy and mean dose with the incidence of grade ≥ 2 pneumonitis. Of the 69 patients, 6 experienced grade 2 pneumonitis and 7 experienced grade 3 pneumonitis. Radiation therapy delivery using multiple static-field IMRT for MPM is complex and time-consuming.[7-11] Moreover, since the treatment fields are large, the planning process often requires splitting the fields, increasing treatment fields twofold, and requiring higher monitor units (MU). Longer treatment times can cause patient discomfort and movement during treatment and, as a result, potential inaccuracies in the delivered dose. Volumetric-modulated arc therapy (VMAT) is a technique that has been investigated and clinically applied for all disease sites including head and neck, thorax, abdomen and pelvis.[12] Compared to static-field IMRT, VMAT has been shown to reduce treatment time and MU, making it an attractive RT delivery technique. Dosimetric comparison of IMRT vs. VMAT has been performed for MPM patients with 2 intact lungs,[13,14] showing that VMAT produced more homogeneous and conformal dose distributions compared with IMRT, as well as significantly reduced dose to most organs at risk (OARs) without compromising target coverage.

In this article, we assess IMRT vs. VMAT delivery techniques with respect to their dosimetric capabilities, MU and treatment delivery time. We also discuss planning details and the impact of the beam angular arrangement on IMRT planning, as well as arc range and number of arcs on the dosimetric plan quality with VMAT. Using examples of 10 left-sided and 10 right-sided cases, we compare the IMRT vs. the VMAT delivery technique. All plans in this study were designed for delivery on a Varian linac using the Eclipse treatment planning system V 11 (Varian Medical Systems, Palo Alto, California). Statistical testing was done using the Wilcoxon matched-pair sign rank test to compare the significance of dosimetric difference noted between IMRT vs. VMAT. The threshold for statistical significance was $p \leq 0.05$.

Patient simulation, volume delineation, dose constraints and planning strategy

Patients were immobilized in a supine position with their arms raised in a customized mold prior to acquiring the CT scan. All patients received a planning CT scan typically at 3 mm slice spacing. A 4-dimensional (4D) CT scan was also acquired at the time of simulation to account for respiratory motion. PET-CT scans were performed at the time of simulation and registered to the treatment planning CT scan to further delineate the target and to include areas of increased FDG (fluorodeoxyglucose) uptake. An initial PTV was defined as a rind, which surrounded the lung/chest wall interface of the entire hemithorax. The superior limit of the PTV was the thoracic inlet at the top of the T1 vertebral body and the inferior limit at the bottom of the L2 vertebral body, including the entire diaphragm and involved lymph node stations. Laterally, the PTV included the parietal pleura along the ribs and medially the mediastinal pleura and the ipsilateral hilum. Visible gross disease based on this CT scan was also included as a part of this PTV with a margin of approximately 8 mm, and the typical width

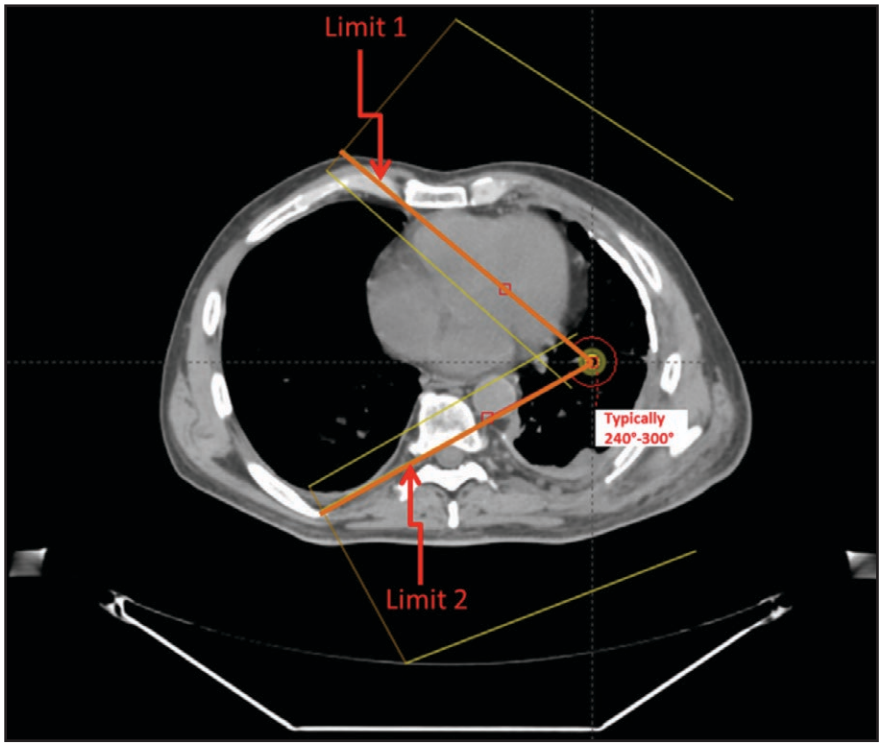

FIGURE 1. *Illustration of the concept of the lung limit. This angular range can vary 240°-300° depending on the patient's anatomy.*

of the PTV rind was 14-16 mm.[8] OARs contoured were the ipsilateral lung, contralateral lung, total lung (the union of both the ipsilateral and the contralateral lung), heart, kidneys, liver, stomach, esophagus, bowel and spinal cord. **Table 1** summarizes the dose constraints used clinically for the cohorts described in reference 8 (initial experience with pleural IMRT) and 9 (analysis of our patterns of failure and overall survival) and 11 (phase II study on pleural IMRT). Constraints for total lung, contralateral lung and heart are similar to those used during planning non-small cell lung cancer (NSCLC) cases with conventional fractionation, while constraints for the kidney, liver, stomach, esophagus and bowel are similar to those used during planning abdominal tumors with conventional fractionation. Dose constraints were classified as limits or as guidelines. While guidelines could be violated at the discretion of the treating physician, limiting constraints cannot be violated. Our clinical planning strategy was to plan to a prescription dose of 50.4 Gy while meeting target coverage (PTV D95 and V95), hotspots (PTV D05) and OAR constraints with priority given to meeting the limiting dose constraints. Guidelines could be achieved as best as reasonably possible without compromising any of the former criteria. If limiting dose constraints could not be met at 50.4 Gy, the case was discussed with the physician and the prescription dose was reduced by 1 fraction. The case was then re-optimized to see if these constraints were met. This process was repeated until the limiting constraints were met and the prescription dose was determined for the given case.

IMRT

The IMRT planning involves arranging 9 coplanar 6 MV photon beams approximately equispaced over an angular range between 200° to approximately 240°. We define a "lung limit (LL)" range, the angular limits of which are defined by the most medial anterior and posterior edges of the contralateral lung as shown in Figure 1. This range can vary from 240° to 300° depending on the patient's anatomy. The 200° range includes the ipsilateral hemithorax and extension anteriorly and posteriorly by 10° into the contralateral side. For each case in this study, IMRT plans were performed using 9 static fields uniformly distributed within the 200° range and then within the LL range. A dosimetric comparison of IMRT plans within these 2 ranges was then performed. The isocenter was placed in the middle of the ipsilateral lung. The IMRT plan delivery technique in this study was sliding window.[8,9] In our planning experience, we found that we could meet normal tissue dose constraints in **Table 1** while maintaining the PTV D95 at no lower than 94%. To form a uniform basis of comparison, all plans were normalized such that 95% of the PTV received at least 94% of the prescription dose. The homogeneity index and conformity index are typically evaluated as $D_{5\%} - D_{95\%}$, and as the ratio of the volume of the patient enclosed by 95% of the prescription isodose to the volume of the PTV receiving more than 95% of the prescription dose,[15] respectively. **Table 2** shows the comparison of IMRT planning with 9 beams arranged in the LL range vs. the 200° range for 20 patients. PTV coverage and hotspots are essentially the same with the 2 types of plans. However, restricting the beam angles to 200° rather than the LL reduced the contralateral lung V5 Gy on average by almost 25%. The dosimetric benefit of restricting the beam angle range to 200° is also seen for other contralateral structures such as the heart for right-sided cases and liver for left-sided cases. Therefore, a more restricted range of beam directions with IMRT is able to adequately cover the target volume while more efficiently sparing normal tissues, especially reducing dose to the contralateral lung. A similar trend has been observed with IMRT for

Table 2. Dosimetry for IMRT Plans With 9 Beams Uniformly Spread Over a 200° Range vs. Lung Limit (LL) Range

Structure	Parameter	IMRT_200	IMRT_LL	p value
PTV	D95 (%)	94	94	-
	V95 (%)	94	94	-
	D05 (%)	118.1±2	118.9±1.9	0.01
Ipsilateral Lung	V40 (%)	59.2±15.8	60.5±15.6	<0.01
	V30 (%)	78.3±12.8	79.2±12.4	0.02
	V20 (%)	97.4±4.6	98.1±4.1	0.16
Contralateral Lung	V20 (%)	0.1±0.5	1.2±1.6	<0.01
	Mean (Gy)	5.1±1.1	6.6±1.3	<0.01
	V5 (%)	38.9±16.4	63.7±22.1	<0.01
Total Lung	Mean (Gy)	18.6±1.5	19.8±1.5	<0.01
	V20 (%)	36.4±5.7	37.3±6.3	<0.01
Cord	Maximum point dose	45.2±4.1	46.7±3.9	<0.01
Heart (left)	V30 (%)	35.5±9.5	36.8±10.2	0.42
Heart (right)	V30 (%)	26.2±4.9	26.7±6.6	0.85
Heart (left)	Mean (Gy)	25.2±4.2	26.3±4.1	<0.01
Heart (right)	Mean (Gy)	18.5±2.4	21.9±2.2	<0.01
Ipsilateral Kidney	V18 (%)	19.1±16.4	22.1±18.9	0.03
Liver (left)	Mean (Gy)	7.8±2.6	12.1±3.9	<0.01
Liver (right)	Mean (Gy)	28±3.7	28.7±3.4	<0.01
Liver (left)	V30 (%)	3.2±4.2	8.9±8	0.02
Liver (right)	V30 (%)	43.3±9	44.2±8.9	0.38
Stomach	Mean (Gy)	16.9±8.7	19.4±7.8	<0.01
Esophagus	Mean (Gy)	25.3±6.3	27.4±5.8	<0.01
Bowel	$D_{0.5\%}$	41.4±9.1	43±8	0.01

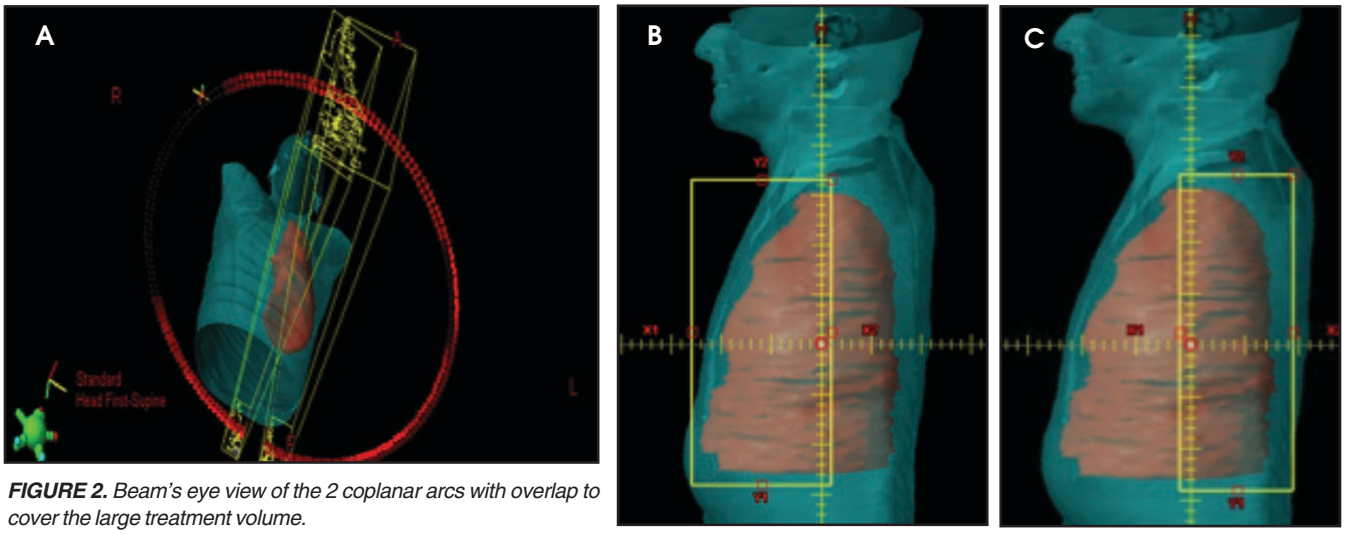

FIGURE 2. *Beam's eye view of the 2 coplanar arcs with overlap to cover the large treatment volume.*

Table 3. Dosimetry for VMAT Plans Using Lung Limit (LL) vs. 360° and 200°

Structure	Parameter	2Arcs_LL	2Arcs_360	2Arcs_200	p1*	p2^
PTV	D95 (%)	94	94	94	-	-
	V95 (%)	94	94	94	-	-
	D05 (%)	117.6±2	119.2±4.3	147.9±11.2	0.07	<0.01
Ipsilateral Lung	V40 (%)	57.4±18.8	62±17.6	85.1±11.2	<0.01	<0.01
	V30 (%)	78.9±13	81.2±11.6	96.3±4.1	0.01	<0.01
	V20 (%)	93.8±6.3	95.3±5.1	99.9±0.8	<0.01	<0.01
Contralateral Lung	V20 (%)	0.2±0.5	0.3±0.8	0.5±1.4	0.5	0.25
	Mean (Gy)	4.7±1.3	6.1±1.4	8.1±1.4	<0.01	<0.01
	V5 (%)	32.9±15.7	57.2±22.4	88.1±16.5	<0.01	<0.01
Total Lung	Mean (Gy)	18.3±1.7	19.2±1.7	25±2.8	<0.01	<0.01
	V20 (%)	35.7±5.7	37.2±6.9	39.6±8.3	<0.01	<0.01
Cord	Maximum point dose	45.3±4.7	46.4±4.4	47.8±6.1	0.6	0.09
Heart (left)	V30 (%)	35.3±11.4	34.7±10.6	41.7±12.4	0.92	<0.01
Heart (right)	V30 (%)	23±4.2	22±5.5	23.8±9.1	0.49	1
Heart (left)	Mean (Gy)	24.8±4.6	24.6±4.6	28.1±5.3	0.27	<0.01
Heart (right)	Mean (Gy)	18.8±1.7	19.4±1.9	19.9±4	0.23	0.43
Ipsilateral Kidney	V18 (%)	13.2±11.8	17.1±13.7	46.9±29.2	<0.01	<0.01
Liver (left)	Mean (Gy)	7.9±3.2	11.2±3.9	10.5±4.6	<0.01	<0.01
Liver (right)	Mean (Gy)	27±4.5	27.8±5	37.7±8.5	0.23	<0.01
Liver (left)	V30 (%)	3.5±5.2	3.2±4.9	4±6.7	0.31	0.56
Liver (right)	V30 (%)	42.8±10.8	43.7±11.2	65.9±20.6	0.56	<0.01
Stomach	Mean (Gy)	15.7±8.2	16.8±8.3	22.7±12.6	<0.01	<0.01
Esophagus	Mean (Gy)	23.6±6.4	24.0±6.1	29.9±5.7	0.18	<0.01
Bowel	$D_{0.5\%}$	41.5±8.9	42.7±8.7	51.6±14.3	0.01	<0.01

*The p1 value indicates the significance between lung limit and 360° arc. ^The p2 value indicates the significance between lung limit and 200° arc.

MPM cases that underwent EPP as part of their surgical management.[11]

VMAT

For VMAT planning, isocenter placement is the same as for IMRT plans and uses 6 MV photon arcs.[13] Since the target volumes are relatively large, and due to limitation of the MLC leaf travel within a given treatment field for some treatment machines, typically a minimum of 2 coplanar arcs are required to cover the PTV with asymmetric jaws for these types of VMAT plans.[14-16] The jaw settings of the 2 arcs are such that at the maximum dimensional projection of the PTV, both arcs together cover the PTV with a small overlap (around 2 cm) as shown in Figure 2. Since all the IMRT plans used a collimator angle of 0°,[8] in this study the collimator angle for each VMAT plan was also set at 0°. Plan normalization methods were kept the same as IMRT. Choice of the arc range in VMAT planning with these 2 coplanar arcs influences the dosimetric plan quality and thereby the ability to meet these dose constraints. **Table 3** shows the comparison of VMAT planning using 2 coplanar arcs as described earlier, arranged in the LL range (same as that used in the respective IMRT plan) vs. using the full arc (360°) vs. the 200° range for the same 20 patients. Of the 3 arc ranges, the LL provided the most homogeneous plan for the same PTV coverage. The greatest benefit of the LL range was in sparing the contralateral lung V5 Gy, which was reduced

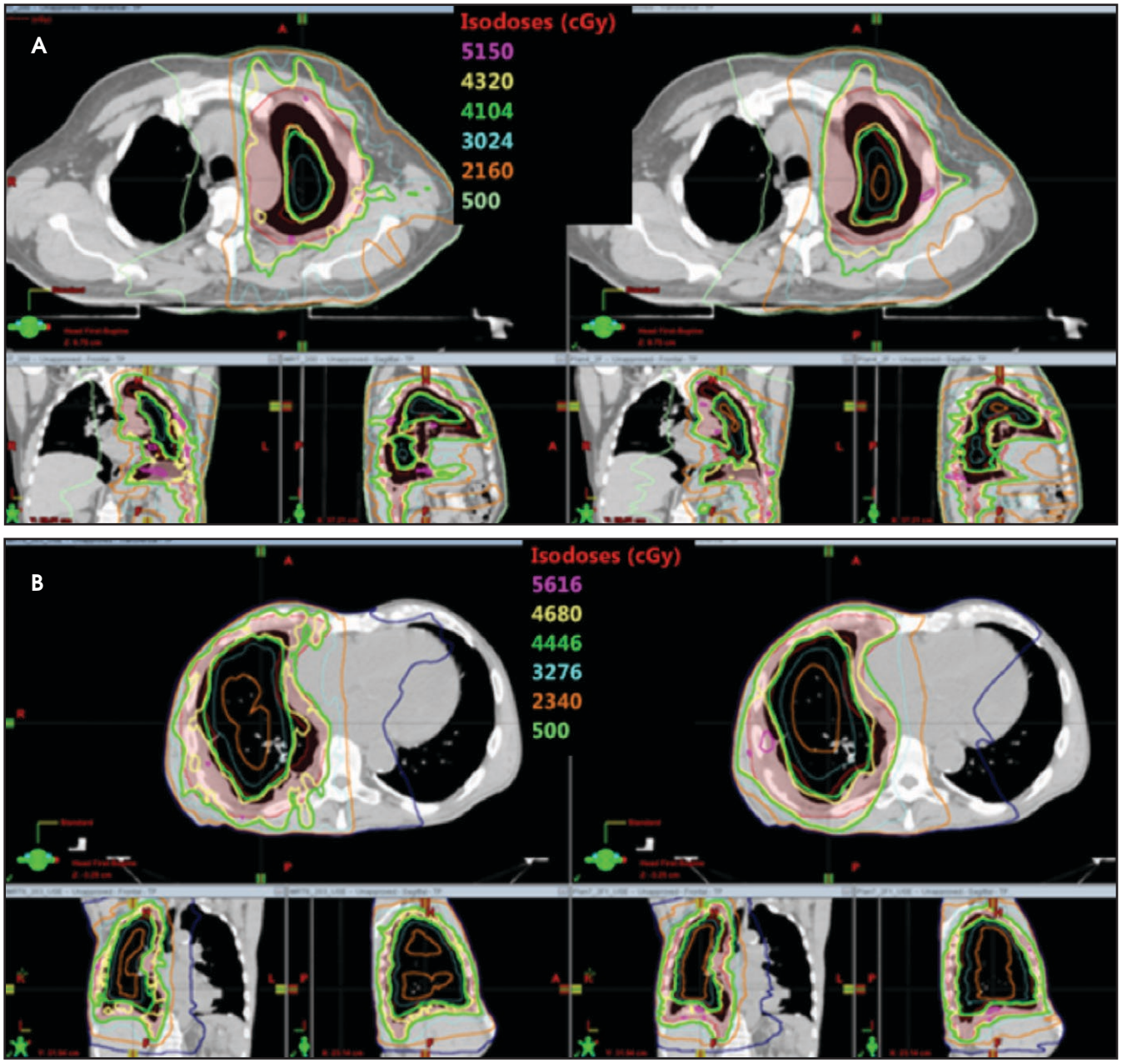

FIGURE 3. *(A) Dose distribution of IMRT on left and VMAT on right for a left-sided case. Prescription dose is 43.2 Gy in 24 fractions. The red-shaded region is the PTV. The yellow line indicates the prescription dose, while the green line indicates 95% of the prescription dose at 41.04 Gy. (B) Dose distribution of IMRT on left and VMAT on right for a right-sided case. Prescription dose is 46.8 Gy in 26 fractions. The red-shaded region is the PTV. The yellow line indicates the prescription dose, while the green line indicates 95% of the prescription dose at 44.46 Gy.*

by almost 25% compared to using full arc, and by 55% compared to restricting the arc range to 200°. A benefit of using the LL range was also seen in reducing the mean dose to the total lung. Unlike IMRT, where restricting the beam to 200° better spared the contralateral lung compared to LL, with VMAT, the opposite trend was observed. Restricting the arcs to within a 200° range significantly worsened the dosimetric plan quality with respect to PTV homogeneity and OAR sparing. All other critical organs such as the heart, liver, ipsilateral kidney, stomach, esophagus and bowel were also better spared with the LL arc range when using VMAT. As shown in **Table 4**, using 4 arcs vs. 2 did not produce a tangible improvement in the dosimetric plan quality and would only increase delivery time.

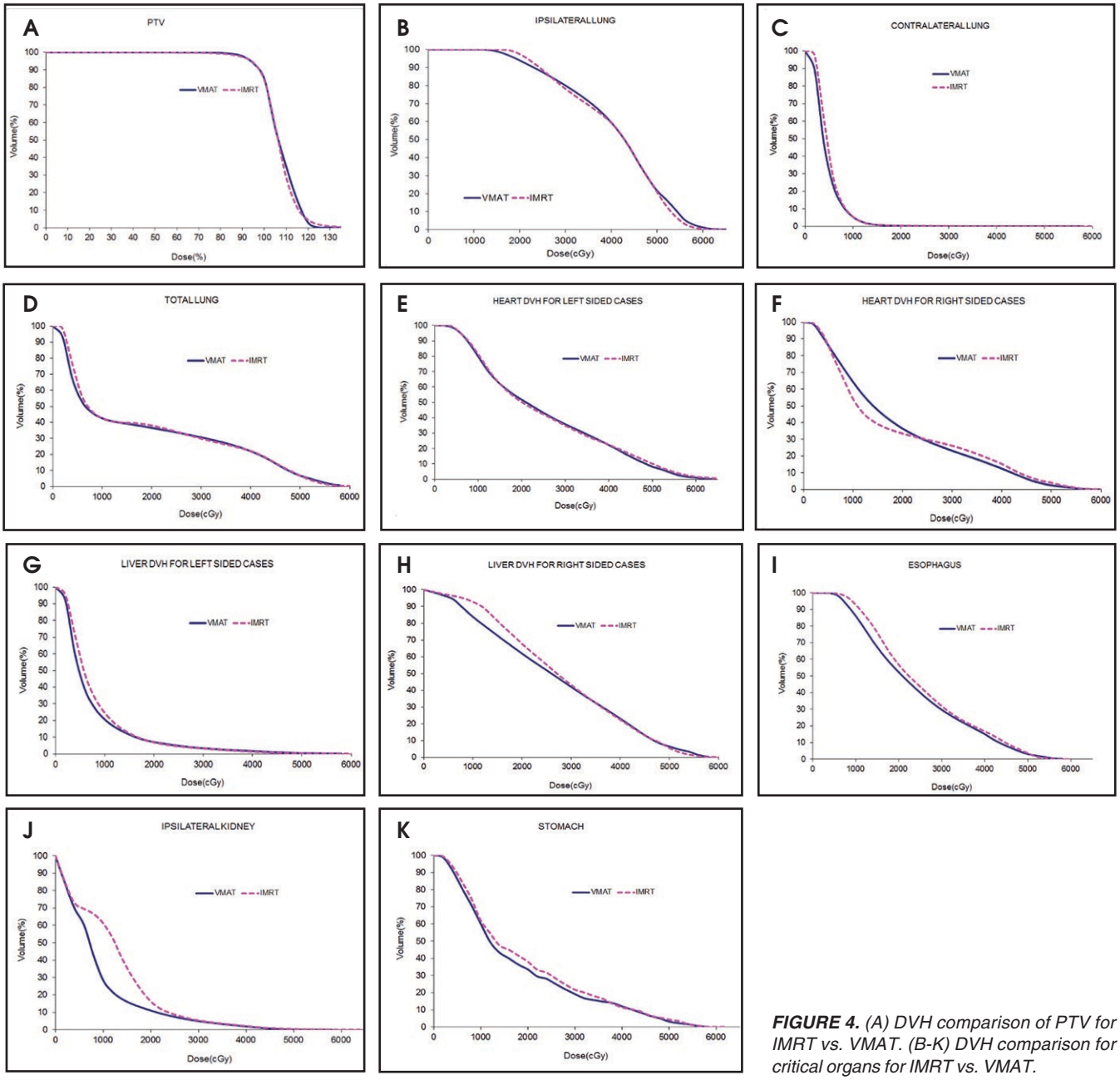

FIGURE 4. *(A) DVH comparison of PTV for IMRT vs. VMAT. (B-K) DVH comparison for critical organs for IMRT vs. VMAT.*

Comparison of IMRT vs. VMAT

Table 5 compares the dosimetric results with IMRT planning with 9 beams arranged within the 200° range vs. VMAT planning with 2 coplanar arcs within the LL range. Isodose distributions in an axial plane, a sagittal plane and a coronal plane comparing the 2 techniques are shown in Figure 3 for a left-sided case and a right-sided case. Comparison of the dose volume histograms (DVHs) is shown in Figure 4.

Both delivery techniques can produce plans with similar coverage, hotspots, conformity and homogeneity, and are able to meet all the limiting dose constraints of **Table 1**. The mean total lung dose and V20 Gy are similar among the 2 delivery techniques although are slightly lower with VMAT. Sparing of the contralateral lung with respect to the low dose, ie, V5 Gy, is significantly better with VMAT. Although sparing other critical organs such as the heart, liver, stomach, bowel, cord, esophagus and ipsilateral kidney is comparable between the 2 techniques, VMAT showed a tendency for better sparing. The average delivery time is around 15 minutes for IMRT

Table 4. Dosimetry for VMAT Plans Using 2 vs. 4 Arcs

Structure	Parameter	2Arcs_LL	4Arcs_LL	p value
PTV	D95 (%)	94	94	-
	V95 (%)	94	94	-
	D05 (%)	117.6±2	117.7±3.2	0.13
Ipsilateral Lung	V40 (%)	57.4±18.8	58±18.6	0.01
	V30 (%)	78.9±13	80.2±12.2	<0.01
	V20 (%)	93.8±6.3	95.3±4.9	<0.01
Contralateral Lung	V20 (%)	0.2±0.5	0.1±0.4	1.000
	Mean (Gy)	4.7±1.3	4.7±1.4	0.64
	V5 (%)	32.9±15.7	33.8±17.1	0.31
Total Lung	Mean (Gy)	18.3±1.7	18.6±1.7	0.01
	V20 (%)	35.7±5.7	37.2±7	<0.01
Cord	Maximum point dose	45.3±4.7	45.2±5.1	0.57
Heart (left)	V30 (%)	35.3±11.4	36.2±12	0.13
Heart (right)	V30 (%)	23±4.2	22.5±4	0.85
Heart (left)	Mean (Gy)	24.8±4.6	25±4.9	0.19
Heart (right)	Mean (Gy)	18.8±1.7	18.7±1.7	1
Ipsilateral Kidney	V18 (%)	13.2±11.8	13.9±12.6	0.06
Liver (left)	Mean (Gy)	7.9±3.2	8.1±3.7	0.22
Liver (right)	Mean (Gy)	27±4.5	27.4±4.1	0.43
Liver (left)	V30 (%)	3.5±5.2	3.9±5.9	0.13
Liver (right)	V30 (%)	42.8±10.8	42.6±10.3	0.92
Stomach	Mean (Gy)	15.7±8.2	15.6±8.5	0.46
Esophagus	Mean (Gy)	23.6±6.4	23.8±6.4	0.2
Bowel	$D_{0.5\%}$	41.5±8.9	41.4±9.3	0.81

and 5 minutes for VMAT. VMAT plans were optimized using a maximum dose rate of 600 MU/min. The average MU with IMRT is around 3000, while with VMAT it is almost 1000.

Discussion and Conclusion

The management of MPM continues to present significant challenges. P/D is increasingly becoming the surgical method of choice for patients diagnosed with this disease due to reduced morbidity relative to EPP. The proximity of critical organs including the underlying intact lung can make treatment planning a significant challenge.[14] In comparison to IMRT, VMAT is becoming a more popular delivery technique owing to the reduced MU and shorter treatment delivery time, which improves patient comfort, reduces potential error due to patent motion, and improves clinical throughput. Data reported for NSCLC patients has shown that the mean dose to the total lung (MLD) and the total lung V20 Gy are both robust predictors of RP. MLD < 20 Gy and a total lung V20 Gy < 37% are associated with a risk of pneumonitis that is considered acceptable.[17,18] Treatment of mesothelioma involves large target volumes, and the incidence of RP is a great concern among these patients. It was recently demonstrated for MPM patients having 2 intact lungs that patients who developed RP had an average MLD ≥ 21 Gy and an average V20 Gy ≥ 40%.[19] The corresponding values of these dosimetric parameters in patients who did not

Table 5. Dosimetry for IMRT Using 9 Coplanar Beams Spread Uniformly Within 200° Angular Range vs. VMAT Using 2 Coplanar Arcs Over LL

Structure	Parameter	IMRT_200	VMAT*	p value
PTV	D95 (%)	94	94	-
	V95 (%)	94	94	-
	D05 (%)	118.1±2	117.6±2	0.26
	$CI_{95\%}$	1.5±0.2	1.5±0.2	0.16
	$D_{5\text{-}95\%}$ (Gy)	10.9±1.5	10.8±2	0.6
Ipsilateral Lung	V40 (%)	59.2±15.8	57.4±18.8	0.61
	V30 (%)	78.3±12.8	78.9±13	0.44
	V20 (%)	97.4±4.6	93.8±6.3	<0.01
Contralateral Lung	V20 (%)	0.1±0.5	0.2±0.5	1
	Mean (Gy)	5.1±1.1	4.7±1.3	0.06
	V5 (%)	38.9±16.4	32.9±15.7	<0.01
Total Lung	Mean (Gy)	18.6±1.5	18.3±1.7	0.04
	V20 (%)	36.4±5.7	35.7±5.7	<0.01
Cord	Maximum point dose	45.2±4.1	45.3±4.7	0.35
Heart (left)	V30 (%)	35.5±9.5	35.3±11.4	0.85
Heart (right)	V30 (%)	26.2±4.9	23±4.2	0.04
Heart (left)	Mean (Gy)	25.2±4.2	24.8±4.6	0.13
Heart (right)	Mean (Gy)	18.5±2.4	18.8±1.7	0.49
Ipsilateral Kidney	V18 (%)	19.1±16.4	13.2±11.8	0.01
Liver (left)	Mean (Gy)	7.8±2.6	7.9±3.2	1
Liver (right)	Mean (Gy)	28±3.7	27±4.5	0.23
Liver (left)	V30 (%)	3.2±4.2	3.5±5.2	0.94
Liver (right)	V30 (%)	43.3±9	42.8±10.8	0.77
Stomach	Mean (Gy)	16.9±8.7	15.7±8.2	0.15
Esophagus	Mean (Gy)	25.3±6.3	23.6±6.4	0.01
Bowel	$D_{0.5\%}$	41.4±9.1	41.5±8.9	0.25

*VMAT plan chosen used 2 arcs and the lung limit arc range (2Arcs_LL)

develop pneumonitis were 19 Gy and 36%, respectively. Incidence of RP has also been demonstrated in patients who had a contralateral lung V5 Gy ≥ 33%.[20] It is therefore essential that dose to the total lung and the contralateral lung be kept as low as possible. Choice of the field/arc arrangement is an influential factor in deciding the plan quality and simultaneously achieving conformal and uniform target coverage and effective OAR sparing. In this article we demonstrate the influence of the choice of angular limits for IMRT and arc range and number of arcs for VMAT for MPM cases that have received P/D. For IMRT, restricting the beams to a 200° range has the highest advantage in sparing the contralateral lung with respect to the low dose, and is recommended over the LL angular range. This observation has also been made in the past with IMRT planning for cases that received EPP as part of their surgical management. Unlike with IMRT, with VMAT, the LL arc range best spares the critical organs and adequately covers the target. Using the 200° arc range produces the least acceptable plans. Moreover, using the full arc range does not improve the dosimetric results over LL range and increases low dose to the contralateral lung, making it an unfavorable choice for planning

and delivery with VMAT. With careful choice of angular/arc ranges, both IMRT and VMAT can produce acceptable plans. However, for the same target coverage, VMAT has a tendency to better spare critical organs. Additionally, reduced MU and delivery time makes VMAT a highly attractive treatment option over IMRT, improving both efficiency and patient comfort.

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Clinical realization and optimization of MR in radiation therapy

Mary Beth Massat

Interest in MR-based radiation therapy (RT) has been mounting over the past few years, and for good reason: MRI offers a host of inherent benefits, namely superior soft-tissue contrast and the ability to derive functional information, such as perfusion and diffusion data, in addition to anatomic imaging details.

"As more precise and hypofractionated techniques are being applied, oncologists are interested in going beyond anatomy with the potential to add biological or functional information, whether that be for contouring the tumor or organs at risk," says Cecile Mohr, PhD, vice president of marketing and sales for radiation oncology in the Advanced Therapies Business Area at Siemens Healthineers, Malvern, Pennsylvania.

In general, MR provides information on anatomy, tissue function and cellularity, which is particularly important as oncologists and medical physicists seek to adapt RT plans to patient-specific situations and move rapidly toward hypofractionated RT, says Dr. Mohr. Better tumor visualization can potentially reduce volumes while adding functional MR imaging data that paves the way to more personalized treatments and the development of response prediction, she adds. Two functional MR sequences she believes will become invaluable to the oncologist are diffusion-weighted imaging (DWI) and dynamic contrast-enhanced imaging, while other sequences such as spectroscopy (eg, for treatment planning of glioblastomas) are being investigated. Although not yet widely adopted, dedicated MR in RT will enable clinicians to improve patient care and investigate how tumor patterns and functional characteristics based on a multiparametric view of the cancer can be leveraged to improve local control and reduce toxicities, says Dr. Mohr.

While MR imaging has historically been used in RT to complement information obtained by PET/CT and CT simulation by fusing the images together, a change in image-guided RT is on the horizon with two systems/technologies under development: the Elekta MR-linac (Stockholm, Sweden), an investigational high-field MR-adaptive linear accelerator, and the MRIdian linac system (ViewRay, Mountain View, California), pending U.S. FDA 510(k) clearance.

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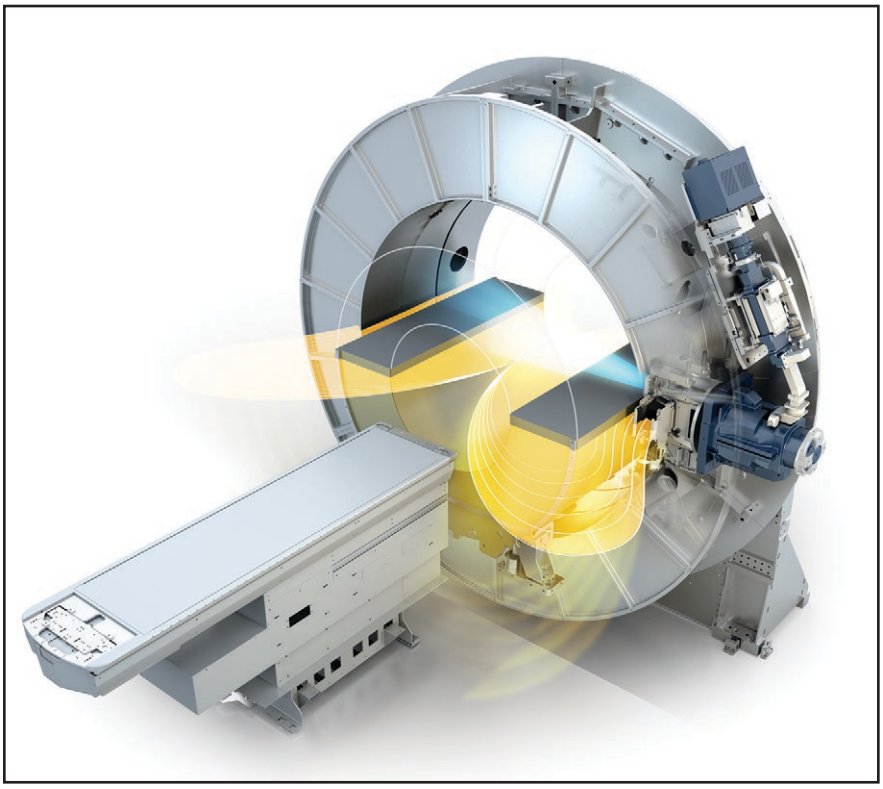
Elekta's MR-linac

It was once thought nearly impossible to combine a high-field MR system and linear accelerator because the MR magnets would interfere with the linac's radiation beams and the linac would impact the MRI. However, Elekta and its global collaborators in the MR-linac research consortium have demonstrated the feasibility of this type of system and are in the process of installing the second U.S. and fifth global site at Froedtert & the Medical College of Wisconsin (MCW) Clinical Cancer Center, Milwaukee.

"We essentially have two rooms within the [treatment] room," explains Kevin Brown, global vice president of scientific research, Elekta. The 1.5T MRI system from Elekta's technology partner, Royal Philips, lies within



MR-linac by Elekta

the static ring of the linear accelerator. Brown explains that the MR is operationally and magnetically isolated from the linac using active shielding and an RF screen. As the linac rotates in a ring around the MR scanner, the treatment beam passes through the inner MR ring. The radiation beam doesn't affect the magnetic field of the MRI, and the magnetic field of the MRI doesn't "scatter" the radiation beam. The MRI can continuously capture images while the beam is on and delivering radiation.

According to Brown, the MRI is comparable to those used in diagnostic radiology and capable of advanced functional sequences such as DWI. The digital linear accelerator is equipped with a multileaf collimator (MLC) and can continuously rotate to deliver advanced therapy techniques. Novel software includes motion management capabilities that use the continuous MR imaging and allow for adaptive planning.

At Froedtert, the department has been preparing for the new MR-linac by optimizing MR sequences and creating the functionality to perform planning based only on MR imaging, says Christopher Schultz, MD, FACR, FASTRO, professor and chairman of Froedtert's Department of Radiation Oncology.

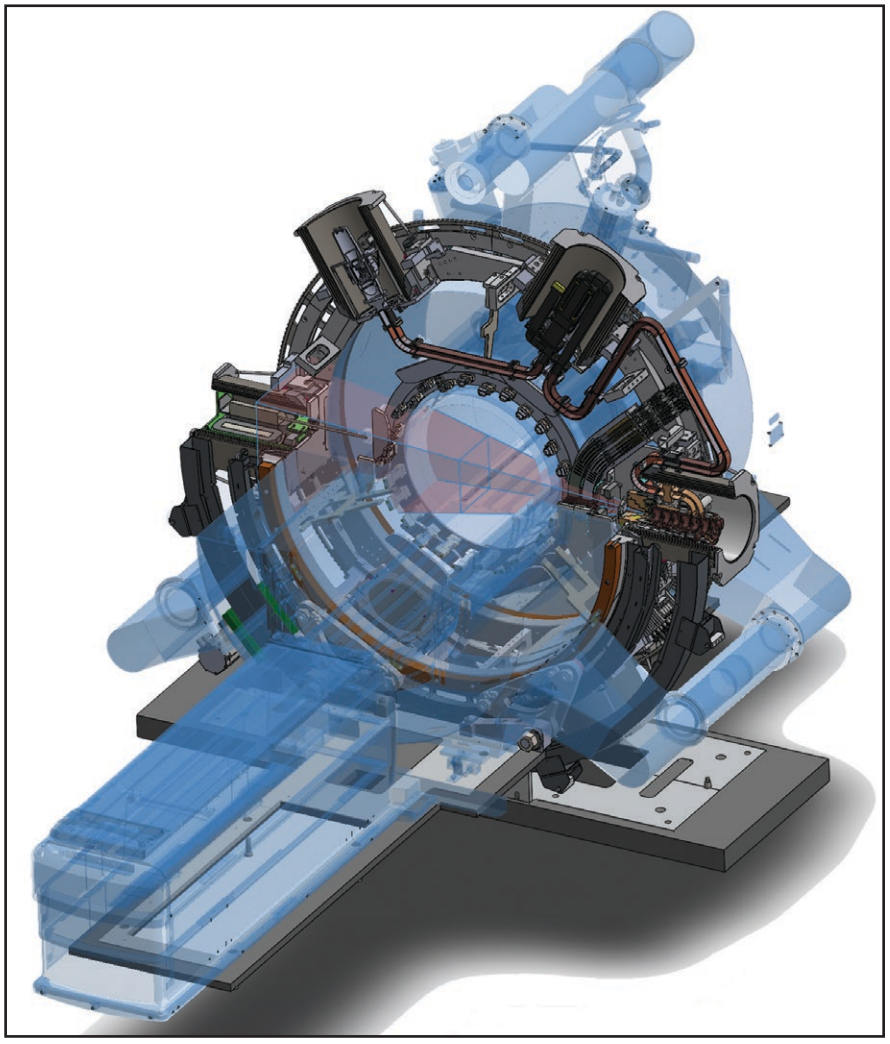
"Radiation therapy treatment planning currently relies on CT for the tissue density information that planning systems need to display how dose is distributed anatomically in a patient," Dr. Schultz says. "We are working on methods of assigning densities to the MR images and exploring MR-only workflows to allow for MR-only treatment planning. Such planning methods will be necessary to realize the full potential of MR-guided and adapted radiation therapy."

Dr. Schultz says MR-linac will be advantageous for treating the liver, pancreas, stomach, and tumors arising in the upper-abdomen in general. "The superior soft-tissue contrast and real-time motion management with MR-linac overcome the limitations of in-room, X-ray-based, image-guidance systems. This functionality will also likely expand use of hypofractionated treatments for prostate, lung and brain tumors or for entirely new sites such as kidney tumors.

"Part of our department's overarching vision is to use image guidance across the spectrum of malignancy to target tumors with minimal margins [to avoid] adjacent critical structures and decrease toxicity," he adds. While Dr. Schultz says MR will enable better visualization of soft tissues and organ motion, what's practice changing is the ability to adapt to these changes daily or weekly as needed. Key to this success is developing software tools and the clinical workflow that allow for timely adaptive changes. He notes that Froedtert's experience with online adaptive RT using a CT-on-rails RT system, as well as its use of MR imaging in RT, can be directly applied to this project.

"That's our charge as an early adopter—to define the best practices for safety and quality that need to be hardwired into the workflow," he adds.

Also of great interest to Dr. Schultz is the use of functional MR sequences, specifically DWI with its ability to create "apparent" diffusion coefficient (ADC) maps for surrogate targeting of the tumor. "When we step back and ask, 'Why a 1.5T MRI?' it is to have the whole constellation of diagnostic MR sequences, including functional imaging. So with the Elekta MR-linac, the idea was to develop a combined device without introducing any major compromises to the functionality of a standard



MRIdian system by ViewRay

1.5T MR imaging device, and also not make any significant compromises to the linac in terms of functionality and performance. Take the combined device apart and they could still work as fully functional independent devices."

The MR-linac consortium has identified nine disease sites for which the MR-linac will first be used: the brain, head and neck, esophagus, lung, breast, pancreas, cervix, prostate and rectum. These are areas where the superior soft-tissue contrast of MR and motion management may reduce uncertainty in margins and allow the clinician to more clearly see the borders that will impact treatment volumes and dose.

"This is another enabling technology and a tool in our adaptive treatment paradigm," adds Dr. Schultz.

Brown is also excited that the MR-linac could reduce uncertainty in planning. He says that cone-beam CT on a linac was a great advance in image-guided therapy, but that an onboard MR is an even bigger breakthrough. "The more we learn about MRI, the more we understand that we can see so much more at the time of treatment," he says. " We believe the old way of thinking with uncertainty can be superseded with a new way of thinking: putting the dose just where you want it and nowhere else."

Next-generation MRIdian Linac

Currently, the only FDA-cleared MR-based RT system is the MRIdian system, which uses cobalt-60 sources to deliver modulated radiation therapy. The works-in-progress MRIdian Linac system builds off this same base system yet replaces the cobalt with a conventional linear accelerator, which also removes a regulatory hurdle, says Michael Saracen, senior director of marketing at ViewRay.

By using technology similar to that in stealth aircraft, ViewRay has engineered a solution that results in no RF impact from the linac on the MRI. This is achieved using patented RF cloaking technology that consists of a copper cylinder lined with carbon fiber. When the linac emits RF noise, the copper reflects the RF and the carbon fiber absorbs it, Saracen explains. Additionally, magnetic shielding technology incorporated around the cylinder creates a "magnetic-free zone" inside the cylinder so it doesn't impact delivery of the radiation beam during treatment. The linac components are positioned inside these six ferro-magnetic "buckets," which are mounted to the gantry. Equal distribution of these buckets around the gantry, along with shimming of the magnet, maintains uniformity of the magnetic field. The result is high-quality MR images without distortion due to the radiation beam, he says.

The other important technological development in the MRIdian Linac is the double-focused MLC with two banks of curved leaves that match the divergent angle of the beam. Each photon is either shielded or passes through, significantly reducing the possibility that a photon will leak through. Saracen adds that the radiation beam doesn't pass through the magnet—there is nothing between the MLC and the patient, which reduces the beam penumbra.

Sasa Mutic, PhD, director of radiation oncology physics at Washington

University Siteman Cancer Center, St. Louis, Missouri, visited ViewRay's corporate offices and worked with the new system using phantoms. As the first site for the MRIdian cobalt-based system, Washington University has used MR-guided adaptive radiation therapy for nearly three years.

"The linac [on MRIdian] offers another advantage of superior dose distributions," Dr. Mutic says. "There is already a strong indication that the dose distribution with the new system is as good as, if not better than, what we currently have."

This is particularly important if clinicians want to pursue dose escalation based on the information obtained with MR images for adaptive planning. "Historically, our knowledge of how much dose is delivered to normal structures is poorly understood for many disease sites," Dr. Mutic says. "Treatment plans are a snapshot of the patient's anatomy at one point in time, yet it is constantly changing during treatment. What we plan and deliver is often different."

One capability that Dr. Mutic and his clinic are developing with their MRIdian system is dose recording during treatment delivery. "We can determine how much radiation each organ receives and correlate that to complications," he says. "To understand how much an organ or tissue can receive, and how much it did receive, personalizes that patient's treatment and should enable further refinements in radiation therapy."

MR-guided RT is changing not only how patients are treated but also the type of cases treated, Dr. Mutic says, noting that breast, lung, gastrointestinal and genitourinary cancer are the primary areas treated with the MRIdian at Siteman.

Systems such as MRIdian and MRIdian Linac can also help reduce treatment margins, Dr. Mutic explains. In some patients with favorable anatomic geometry, clinicians can deliver increased doses to the tumor while maintaining dose to critical structures because they can visualize the critical structures at the time of treatment and adapt treatment plans to avoid them. In partial breast irradiation, clinicians at Washington University have reduced the volume of irradiated tissue by > 55%, potentially reducing complications, notes Dr. Mutic.

Thanks to soft-tissue contrast with MRI, it may be possible to treat tumors previously deemed not-treatable due to location in and around organs or critical structures.

"The role of imaging in RT is growing, and there are new innovations that support modern treatment planning," says Dr. Mohr. "With MRI and other robust technologies, we are able to bring new benefits dedicated to radiation therapy that will support…precision medicine and personalized care."

RADIATION ONCOLOGY CASE

Congratulations to our Clinical Case Contest winner for December2016!

The trigeminocardiac reflex during linac-based hypofractionated stereotactic radiation therapy for a skull base tumor

Amit Roy, BLA; Hinrich Staecker, MD, PhD; Parvesh Kumar, MD; Fen Wang, MD, PhD

CASE SUMMARY

A 22-year old Caucasian woman presented with a recurrent right skull base paraganglioma after gross total resection. She underwent frameless linac-based hypofractionated stereotactic radiation therapy (FSRT) to 3000 cGy in 5 fractions (Figure 1). Three days after completing FSRT, the patient presented to the emergency department after experiencing syncope accompanied by diaphoresis, dizziness and nausea. Her blood pressure (BP) was 77/42 and heart rate (HR) 80 (baseline BP 110/75 and HR 110). She was given intravenous (IV) fluids and admitted for further management. Brain MRI showed no acute changes. During her 4-day hospitalization, she was managed with daily IV fluids and ondansetron. Her BP and HR normalized. Her symptoms improved throughout hospitalization and resolved by discharge. At 1-month follow-up, she remained healthy and denied further episodes.

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IMAGING FINDINGS

No specific radiologic findings are associated with the trigeminocardiac reflex.

DIAGNOSIS

Trigeminocardiac reflex

DISCUSSION

The trigeminocardiac reflex (TCR) is clinically defined as the sudden onset of cardiac dysrhythmia, arterial hypotension, asystole, apnea, or gastric hypermotility.[1] Although patients may not experience all of these autonomic symptoms, Schaller et al outlined that patients must have a > 20% decrease in mean arterial BP and HR from baseline for diagnosis of TCR.[2] As a clinical diagnosis, there is no characteristic laboratory, radiologic, or pathologic findings associated with TCR. The TCR has been reported during orbit surgery, trans-sphenoidal surgery, cranio-maxillofacial surgery, and dermatologic surgery.[1] The physiologic mechanism involves manipulation of the central or peripheral branches of the trigeminal nerve, Gasserian ganglion, or trigeminal brainstem centers and nuclei.[1,3] The clinical manifestations are generally transient and resolve after removal of stimulus during surgery.[1] However, the TCR has been associated with adverse outcomes in select cases, such as hearing loss or even death.[4] Removing the mechanical stimulus on cranial nerve V during surgery generally immediately stops the reflex.[5] This is widely considered the most important management step. If the reflex persists, based on a case report, Arasho et al suggest administration of IV atropine 0.6 mg (up to 2 doses) followed

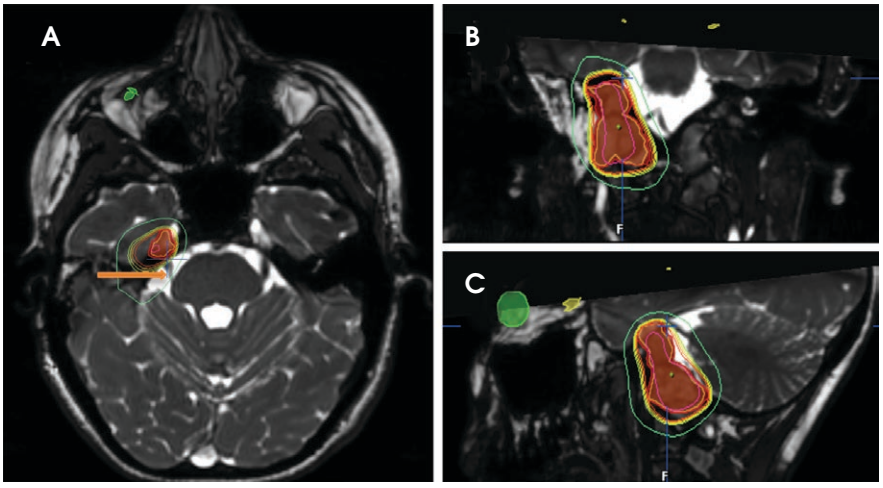

FIGURE 1. *The isodose treatment plan for framelesss linac-based hypofractionated FSRT (6 Gy x 5 fractions) to treat the patient's skull base paraganglioma on T2 MRI axial (A), coronal (B) and sagittal (C) views. The right trigeminal nerve was in the FSRT field (arrow).*

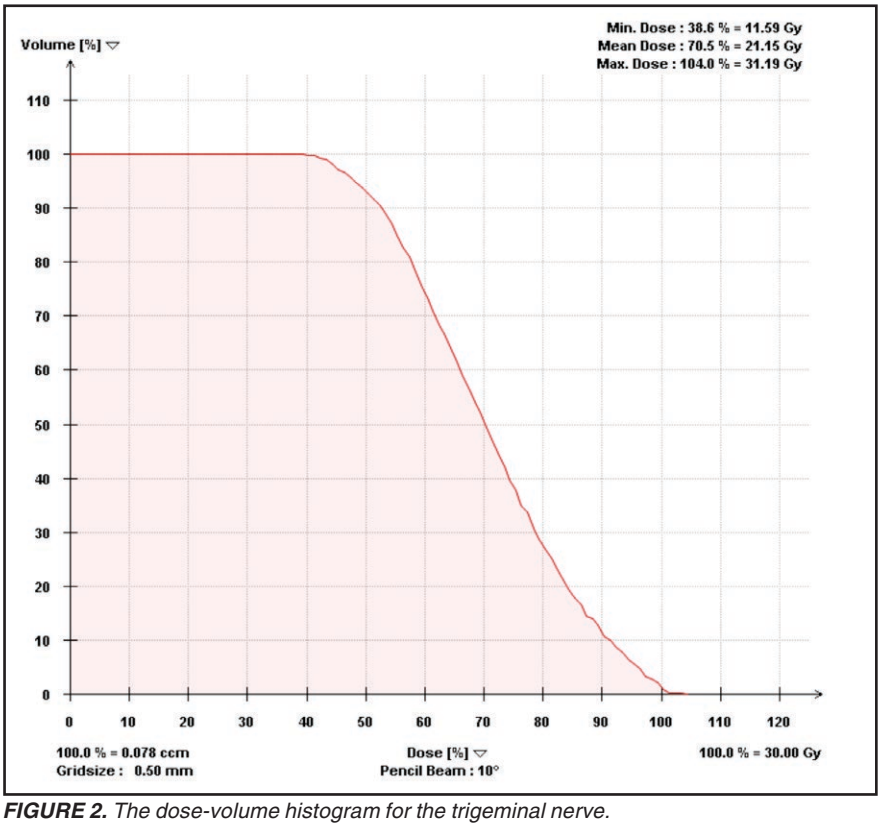

FIGURE 2. *The dose-volume histogram for the trigeminal nerve.*

by 1 dose of IV epinephrine 6 µg if no response has been achieved.[5] Several risk factors for TCR have been identified, such as age (more common in children), hypercapnia, hypoxemia, light anesthesia, narcotics such as sulfentanil, and preoperative beta-blockers or calcium-channel blockers.[5] Careful identification and modification of risk factors should be considered. There may be a role for prophylaxis in cases with planned surgical manipulation near the trigeminal nerve. Mirakhur et al found that preoperative IV or intramuscular (IM) administration of 1 dose of either atropine (10-15 mg/kg) or glycopyrrolate (5-7.5 mg/kg) decreased the incidence of the oculocardiac reflex (OCR), a variant of the TCR, during ophthalmic surgery in children.[6] Another study by Shende et al found decreased incidence and severity of OCR with local anesthetic blockade of the trigeminal nerve with bupivacaine.[7]

We believe that our patient's clinical presentation is consistent with TCR. Her decrease in mean arterial BP and HR met the criteria discussed above. The onset of her symptoms was sudden. In addition, her nausea may have been related to gastric hypermotility. Given her tumor location, the trigeminal nerve and associated structures were within her RT treatment field (Figure 1). We have included the dose volume histogram for the trigeminal nerve (Figure 2) to demonstrate the dose received. Although her symptoms resolved with supportive care, the addition of a vagolytic agent may have been useful for management. Radiation-induced toxicity to the brainstem could partially explain her symptoms of nausea and dizziness, but would not cause the hemodynamic changes seen with our patient. Her previous skull base surgery may have caused scarring that predisposed her to chronic irritation of the trigeminal nerve. The patient was fairly young (age 22), but otherwise had no other previously identified risk factors. Additionally, there were no abnormal MRI findings to suggest another etiology.

Our case does differ from the classical presentation of TCR, as the patient's symptoms manifested several days after completion of RT as a delayed TCR. Typically, the TCR presents during surgery with surgical

manipulation of the trigeminal nerve. However, Chowdhury et al reported a case of delayed-onset TCR symptoms in a patient with an orbital floor fracture.[8] The patient suffered from trauma causing a fracture of the orbital floor, and was managed conservatively. One month later, the patient developed a progressive and wide array of hemodynamic disturbances consistent with the TCR. A surgical procedure to correct the orbital fracture was performed and the patient's cardiovascular symptoms improved dramatically. The authors concluded that was the first case of a chronic OCR.[8] Compared to surgical manipulation, the intensity of stimulation on trigeminal nerve from radiation therapy (RT) in general is mild, sustained and accumulative.[9] The biological consequences of exposure to ionizing radiation are mediated by a series of physical, chemical, biochemical, and cellular responses initiated after radiation is deposited in the tissue.[10] This sustained stimulus on the trigeminal nerve and surrounding tissue occurs accumulatively during RT and persists even after RT completion.[9] Thus, the intensity of RT stimulation may not be initially strong enough to induce the TCR symptoms. After a course of RT, the cumulative intensity of radiation stimulation could reach a threshold to induce TCR symptoms as observed in this case. Our atypical presentation of TCR associated with RT appears consistent with the findings reported by Chowdhury et al.[8]

CONCLUSION

We present a case of radiation-induced TCR in a patient with a skull base tumor treated with linac-based FSRT. The TCR has not been previously reported in association with RT. The clinical presentation of radiation-induced TCR described in this case differs from the classical intraoperative presentation, as it occurred several days after RT completion. We discussed the role of supportive care and vagolytics in managing radiation-induced TCR. Because TCR has been linked to adverse clinical outcomes, radiation oncologists should be aware of TCR as a potential phenomenon when treating patients with skull base tumors. Additional reports describing TCR during RT would certainly help further our understanding.

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APPLIED RADIATION ONCOLOGY

RADIATION ONCOLOGY CASE

Examining risk factors for rectal toxicity following radiation therapy for localized prostate cancer

David Tiberi, MD, Daniel Taussky, MD, FRCPC, Carole Lambert, MD, FRCPC

Radiation-induced bowel toxicity, such as radiation proctitis, is a relatively common side effect following radiation therapy (RT) for prostate cancer. Risk factors for late radiation bowel toxicity include patient-related factors such as smoking, hypertension, diabetes and atherosclerosis.[1] Treatment-related factors include the presence of seminal vesicle and/or pelvic irradiation, RT technique and total dose, as well as specific rectal dose-volume parameters such as the V30 and V60.[2-4]

These toxicities are generally graded on a scale based on symptom severity. The RTOG (Radiation Therapy Oncology Group) classification describes the severity of acute gastrointestinal toxicity, whereas the RTOG/EORTC (European Organization for Research and Treatment of Cancer) scoring system categorizes severity of chronic gastrointestinal toxicity.[5] The vast majority of bowel toxicity (> 90%) is grade 1 or 2.[6]

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However, approximately 5% of patients will experience higher grade toxicities, which are often refractory to initial treatment strategies and require more aggressive management.[7]

The aim of this case report is to examine potential, and possibly novel, risk factors that may have contributed to the development of severe rectal toxicity in a patient treated with external-beam RT for localized prostate cancer.

CASE SUMMARY

We present the case of a 70-year-old Haitian man whose past medical history is remarkable for type II diabetes mellitus, essential hypertension, hypercholesterolemia, hemorrhoids, an ischemic stroke with no lasting sequelae, and a coronary angioplasty in 2006. The patient was investigated for prostate cancer following a rise in his prostate specific antigen (PSA) over several years. An ultrasound-guided biopsy was performed in 2014 and confirmed the presence of Gleason score 7 (3 + 4) prostate adenocarcinoma on all 12 biopsies as well as a small periprostatic foci of Gleason score 8 (4 + 4) indicating extra-prostatic invasion. The clinical stage was T2c and the PSA was 15. His International Prostate Symptom Score (IPSS) was 2 at the initial consultation. Given the patient's high-intermediate risk disease, the diagnostic workup was expanded to include a bone scan and pelvic CT, all of which were negative for metastases.

The patient was started on monthly degarelix acetate subcutaneous injections and then received external-beam volumetric modulated arc therapy (VMAT) within 2 weeks. He was treated to a total dose of 78 Gy in 39 fractions that included pelvic nodal irradiation (44 Gy). Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) dose constraints were respected.[4]

After 10 fractions of RT, the patient developed a region of moist desquamation in the intergluteal cleft. He was prescribed silver sulfadiazine cream, offering little improvement. He was referred to a dermatologist who performed a punch biopsy of the lesion. Biopsy confirmed a herpetic lesion and the patient was given oral valacyclovir. The rest of the RT course was unremarkable. Serial PSA measurements at 2, 4, 6 and 8 months after the end of RT were 2.76, 1.39, 0.71, 0.47,

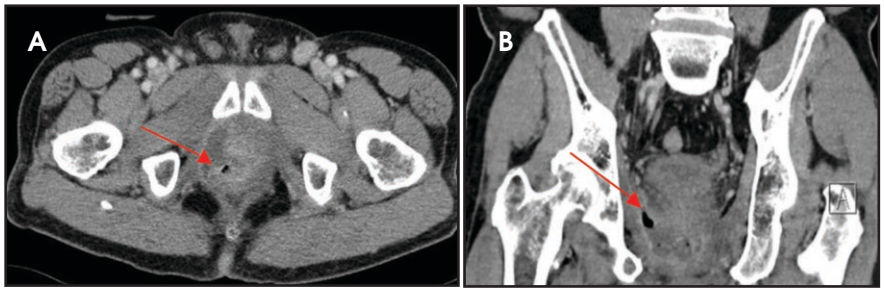

***FIGURE 1**. Axial (A) and coronal (B) CT imaging showing the perirectal abscess (arrows) at 3 months following diverting colostomy.*

respectively. After 6 months of degarelix acetate, the patient refused to pursue treatment due to the sexual toxicity.

The patient did not experience any late genitourinary side effects; however, his hemorrhoidal disease worsened, requiring a hemorrhoidectomy approximately 2 months after completing RT. Following surgery, the patient's lower digestive symptoms resolved temporarily. Unfortunately, he developed recurrent anorectal pain 6 months after completing RT (4 months after hemorrhoidectomy). A subsequent colonoscopy was performed and showed a rectal lesion suspicious of a primary rectal neoplasm. A biopsy of the lesion was performed and demonstrated a radiation-induced rectal ulcer. Initial medical therapy, including sulcralfate enemas, was ineffective.

The patient was referred and received 40 sessions of hyperbaric oxygen therapy with little to no symptomatic improvement. The patient was hospitalized to optimize his pain medication and perform a radiologic workup. CT imaging of the abdomen and pelvis revealed a perirectal abscess that required a diverting colostomy and intravenous antibiotics, as well as a recto-urethral fistula. Follow-up CT imaging at 1, 2 and 3 months after surgery and antibiotics showed no improvement in the abscess with fistulization in the levator ani muscle (Figure 1). Further surgical management of the abscess and fistula was assessed. Due to the extensive surgery that would be required and the high risk of complications, the consensus was to follow the patient with serial imaging and optimize his pain control. Currently, 8 months after the treatment with hyperbaric oxygen, the patient is followed by pain medicine specialists and requires opioids including methadone for pain management. His PSA at last follow up in May 2016 was 0.5 ng/ml.

DISCUSSION

In examining this case, several factors likely to contributed to the patient's overall toxicity and clinical course. First, the patient's multiple comorbidities including type II diabetes, atherosclerotic heart disease and hypertension are all vascular risk factors that likely increased the probability of radiation toxicity. Also, as demonstrated by several published nomograms, the use of anticoagulants, presence of hemorrhoids and use of androgen deprivation can contribute to increased lower GI toxicity.[4]

Second, the multiple biopsies and hemorrhoidectomy may have increased the patient's risk of abscess formation or fistulization. A recent review concluded that rectal biopsies may initiate chronic wounds or infections, do not contribute to the diagnosis of chronic radiation proctitis and, thus, should be avoided unless deemed necessary to eliminate suspicion of a neoplastic lesion.[8] Other studies have described fistula formation following rectal biopsies.[9-11] Interestingly, in a study by Chrouser et al, 38% of patients who developed rectal fistulas after RT had undergone a prior rectal biopsy.[11] This supports the hypothesis that in an irradiated field, further tissue damage from interventions such as a biopsy, likely increase the risk of fistula and/or abscess formation. With regard to the hemorrhoidal surgery, due to the much more proximal localization of the rectal ulcer in relation to the site of surgery, it is unlikely this intervention contributed to the development of the rectal ulcer.

Another consideration is whether the use of a high-dose-rate brachytherapy (HDR) boost may have produced a different outcome in this patient. Given that this patient's dosimetry was well within acceptable limits, there was no formal indication to favor an HDR boost over VMAT alone for this patient. However, in our experience, the use of a single-fraction HDR boost can often limit the V75 (volume of rectum receiving 75% of the prescription dose) to 1 to 2 cc since no PTV is used. In contrast, this hypofractionated technique uses a larger dose per fraction (often 15 Gy in a single fraction) and may potentially have opposite repercussions on normal tissues. Using an alpha/beta = 3 Gy, the EQD2 for an HDR boost of 15 Gy in 1 fraction is 54 Gy. To our knowledge, it is unknown what impact achieving a lower volume of irradiated rectum, and using a high dose per fraction, would have on long-term rectal toxicity. As such, it is unclear what impact an HDR boost would have had in our patient.

One may question whether the use of hyperbaric oxygen therapy (HOT) was indicated for our patient or if it may have led to increased bacterial proliferation in a patient already at risk of infection following a rectal biopsy. HOT involves patients breathing pure oxygen in a pressurized room or tube at 3 times the normal air pressure.[12] These conditions lead to highly oxygenated blood, which may be beneficial because it inhibits bacterial growth and stimulates the release of growth factors and stem cells, promoting wound healing and possibly reversing progressive changes caused by RT.[13,14] HOT is generally recommended in cases of radiation

proctitis after initial medical pharmacotherapy has failed. A Cochrane review revealed a significantly increased chance of improvement or cure following HOT for radiation proctitis (RR 1.72; 95% CI 1.0 to 2.9, p = 0.04).[15] Therefore, it does not appear likely that our patient's HOT contributed to further GI toxicity. The ideal HOT regimen is not known; however, one randomized trial used 30 daily sessions with an option for additional sessions if a clinical improvement was noted.[16]

Also, we have considered whether our patient's oral antiviral therapy may have played a role in increasing his risk of GI toxicity. Published animal and human phase I-II clinical trials have investigated the potential therapeutic effect of adenovirus mediated gene therapy combined with RT for localized prostate cancer.[17-20] This treatment approach often involves intraprostatic insertion of either an adenovirus gene vector followed by subsequent administration of an antiviral prodrug such as valacyclovir. RT was initiated 48 hours after the start of antiviral therapy. Gene therapy was not associated with any grade 3 or higher toxicity and, at 5 years, no late side effects were reported.[21] Despite these results, it remains unclear whether antiviral therapy in patients with viral lesions in noncancerous tissues may act as a radiosensitizer and increase RT toxicity.

Finally, it is well-known that the toxicity profile patients experience for a given dose of RT varies considerably, depending on differences in underlying individual normal tissue radiosensitivity.[22] Several rare genetic syndromes such as ataxia telangiectasia and Nijmegen syndrome that are characterized by mutations in genes in the detection and repair of DNA damage are associated with accrued sensitivity to ionizing radiation.[23,24]

Currently, the investigation of potential genetic differences to explain variable radiation sensitivity is an area of intense research. Genome-wide association studies (GWAS) have revealed polymorphisms associated with radiation toxicity risk.[25,26] The possibility of a genetic predictive risk "signature" is, therefore, promising. As many patient and treatment-related factors affect the overall risk of toxicity for a given dose, new risk models need to be developed that combine patient, treatment and genetic data.

CONCLUSION

In summary, our patient's clinical course represents a rather exceptional case of the development of multiple late radiation toxicities. Although this patient's comorbidities placed him at higher risk of developing radiation-related toxicities, other factors were also likely to be involved. Rectal biopsies are rarely indicated and should be avoided in the setting of GI radiation injury as they may facilitate further complications, as was the case for our patient.

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