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Adaptive Radiotherapy for Lung Cancer Using Uniform Scanning Proton Beams

Yuanshui Zheng

Abstract

Lung cancer remains the leading cause of cancer death in North America and is one of the major indications for proton therapy. Proton beams provide a superior dose distribution due to their finite ranges, but where they stop in the tissue is very sensitive to anatomical change. To ensure optimal target coverage and normal tissue sparing in the presence of geometrical variations, such as tumor shrinkage and other anatomical changes, adaptive planning is necessary in proton therapy of lung cancer. The objective of the chapter is to illustrate the rationale, process, and strategies in adaptive lung cancer treatment using uniform scanning proton beams. In addition, practical considerations for adaptive proton planning are discussed, such as software limitations, the associated costs and risks, and the criteria on whether and how to adapt a plan.

Keywords: uniform scanning, proton therapy, lung cancer, adaptive radiotherapy

1. Introduction

Lung cancer continues to be the leading cause of cancer death in the United States, and over 158,000 lung cancer deaths were estimated in 2015 [1]. Radiation is one of the major treatment modalities for lung cancer treatment. Because of proton beams' finite range, proton beam therapy (PBT) has been increasingly used for lung cancer. Compared to 3D conformal or intensity modulated photon radiation (IMRT), proton beams can better spare the lung, esophagus, heart, cord, and other normal tissues while delivering the same or higher dose to the treatment target [2–4]. The dosimetric advantage of proton therapy could lead to potential better tumor control and less toxicity. Proton beams provide a superior dose distribution due to their finite ranges, but where they stop in the tissue is very sensitive to anatomical change. To ensure optimal target coverage and normal tissue sparing in the presence of geometrical

variations, such as tumor shrinkage and other anatomical changes, plan adaptation is often needed in proton therapy of lung cancer.

The chapter aims at illustrating the rationale and process in adaptive proton treatment of lung cancers, as well as the strategies and practical considerations in plan adaptation, with a focus on the use of uniform scanning proton beams.

2. Proton therapy system

Depending on how proton beams are spread out laterally and in depth, there are mainly three proton delivery systems in clinical use: passive scattering proton therapy (PSPT), uniform scanning proton therapy (USPT), and pencil beam scanning (PBS). In PSPT, the proton beam is spread out laterally by a static scatterer (or double scatterers) located in the beam axis, and the beam modulation in depth is typically achieved by using a rotating range modulation wheel, which is composed of multiple steps of various thicknesses. Both USPT and PBS proton therapy use scanning magnets to sweep proton beams laterally and deliver the dose to a target volume layer by layer at various depths using proton beams of various energies. The main difference between USPT and PBS is that proton beams are scanned continuously with a uniform intensity in a zigzag pattern at a fixed frequency for each energy layer in USPT, while delivered with various beam intensities from one spot to another or continuously for each layer in PBS. PBS can be further divided into single field uniform dose (SFUD) delivery, which delivers a uniform dose to the target for each field, and multiple field uniform dose (MFUD), which delivers a heterogeneous dose to the target for each field but achieves a homogeneous combined dose from all fields. MFUD is also called intensity modulated proton therapy (IMPT).

Since our main focus for this chapter is USPT, a detailed description of a USPT system at our center is described below. The proton therapy center is equipped with an IBA Cyclotron (IBA, Louvain-la-Neuve, Belgium), which accelerates proton beams to approximately 230 MeV before they are extracted to treatment rooms through a beam transportation system. The proton beam passes through an energy degrader, which can lower the energy when necessary, and an energy selection system (ESS) is then transported to a nozzle in the treatment room. After entering the nozzle, the proton beam will first pass through a first scatterer, which broadens the beam laterally to achieve the desired spot size at isocenter. The beam then passes through a range modulator wheel, which does not rotate continuously for uniform scanning beam delivery and mainly serves as an energy degrader. Together with the first scatterer, the modulator wheel lowers the proton energy to deliver a peak dose layer by layer in depth. The beam is scanned laterally with a constant frequency by two scanning magnets in a zigzag pattern to deliver a uniform dose for a near rectangular scanning area. It then passes through the main and backup ionization chambers that monitor the proton dose. At the end of the nozzle is a snout that holds an aperture and a compensator and can translate along the beam axis to achieve variable snout to isocenter positions. An aperture is used to collimate the beam to the treatment target laterally, and a range compensator is used to conform the proton penetration to the distal boundary of the treatment target. More details on this system were described by Zheng *et al.* [5]. **Figure 1** shows a schematic diagram of the uniform scanning nozzle at our proton therapy center.
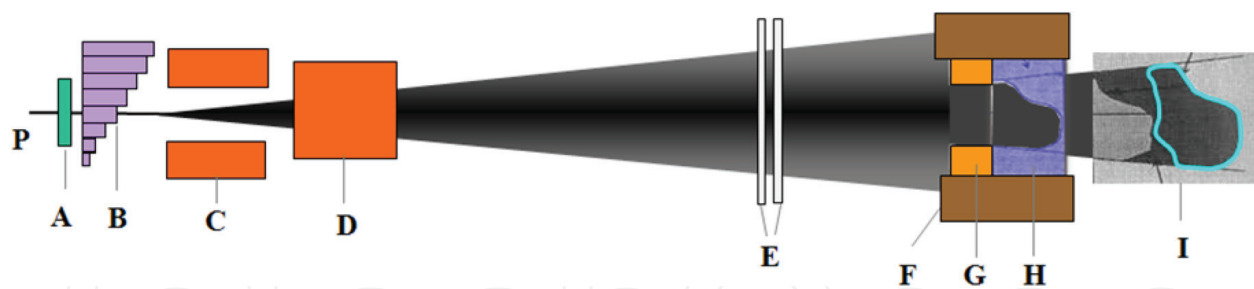
Figure 1. A schematic diagram of the uniform scanning nozzle at the ProCure Proton Therapy Center in Oklahoma City. Proton beams (P) go through a first scatterer (A), a range modulator wheel (B), two scanning magnets (C and D), the main and backup monitor unit ionization chambers (E), a snout (F), an aperture (G), a range compensator (H), and stop at the patient (I). The nozzle has a distance of about 290 cm between the first scatterer and the isocenter, and 211 cm between the effective source and the isocenter. (From Zheng *et al.* [5]).

3. Treatment techniques

3.1. Treatment simulation

Patient immobilization and simulation for lung cancer patients under proton therapy are similar to those under photon therapy. However, since proton beams are very sensitive to setup uncertainty and patient motion, the reproducibility of immobilization and proper motion management are critical in proton therapy. At our center, patients typically lie supine, are immobilized with a vacuum bag, which is on top of an index fixed framing device (wing board), and with their arms up and hands holding the pegs on the wing board, as shown in **Figure 2**. The patient is scanned at 2.5 mm slice thickness. If contrast is used, one computerized tomography (CT) scan should be taken before the contrast is injected in addition to one after the injection. The CT data with intravenous contrast will be used primarily for target delineation, and the CT data set without contrast will be used for dose calculation.

Four dimensional (4D) computerized tomography (CT) scanning is typically used for lung cancer patients in proton therapy to evaluate patient motion. The motion can be monitored by a belt system or a Varian RPM system during the 4D CT scan. The magnitude of tumor motion is typically evaluated for each 4D CT scan and used to determine the strategies in motion management. Depending on facility and beam delivery system, a limit of motion magnitude is set, beyond which the patient will need additional motion management or be excluded from proton treatment. For example, at our center, we generally treat patients using USPT with a maximum motion of 10–15 mm, while at the MD Anderson Proton Therapy Center, 5 mm maximum motion was used for patients under PBS proton treatment [6]. While respiratory gating or breath holding could reduce the tumor motion, currently, it is only used clinically in a very few proton centers due to challenges such as relatively low proton dose rate that leads to long treatment time for gated treatment, lack of connection between the respiratory device and the proton beam delivery machine, and difficulty of holding breath for lung cancer patients.
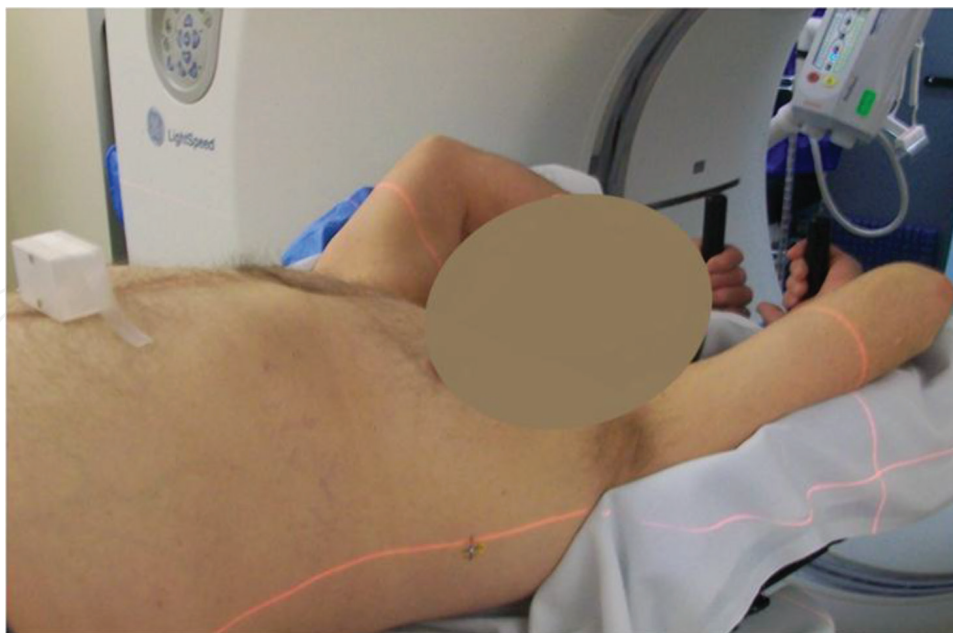
Figure 2. Typical CT simulation and immobilization technique for lung cancer treatment using uniform scanning proton therapy.

3.2. Treatment planning

Treatment planning can be performed on the average CT based on the 4D CT scan, or at a certain respiratory phase when gating or breast holding is used. At our center, we use the average CT and an Internal target volume (ITV) approach to account for motion effect during treatment, which is similar to what used at MD Anderson Cancer Center for lung treatment using passive scattering proton beams [7]. The internal gross target volume (IGTV) is contoured on the maximum intensity pixel (MIP) images and expanded 7–10 mm to generate the clinical target volume (CTV), which is expanded further by 5 mm to obtain the planning target volume (PTV). The average CT will be used for treatment planning and dose calculation. The magnitude of motion will be evaluated by a physicist, and the treatment of lung patient with uniform scanning proton beams is often limited to those who have a motion magnitude of 10 mm or less. To be conservative, a smearing of 10 mm is used in compensator calculation for all lung cancer treatment planning. To ensure adequate coverage of the target at the presence of tumor motion, the stopping power ratio of IGTV is overridden with the average stopping power ratio of the tumor tissue, which is about 1.01 based on sampling of over 10 lung patients treated at our center. Each patient is treated with uniform scanning proton beams typically using 2–4 fields. The prescription is typically 74 Cobalt Gray-equivalent (CGE) at 2 CGE per fraction for 37 fractions.

3.3. Dosimetric advantages

Proton beams provide a superior dose distribution for lung cancer treatment compared to photon beams. Chang *et al.* reported that PSPT significantly reduced dose to normal tissues

and the integral dose to patients with non-small cell lung cancer (NSCLC) compared to three-dimensional conformal radiation therapy (3D-CRT) and intensity modulated radiation therapy (IMRT) [2]. Kadoya *et al.* reported that using proton beam significantly reduced Lung dose compared to stereotactic body radiation therapy (SBRT) for Stage I non-small-cell lung cancer [8]. The mean dose, V5, V10, V15, and V20 were 4.6 Gy, 13.2%, 11.4%, 10.1%, and 9.1% for proton therapy compared to 7.8 Gy, 32%, 21.8%, 15.3%, and 11.4%, respectively, for SBRT with a prescribed dose for 66 Gy. In a similar study, Hoppe *et al.* reported that in addition to better dose sparing to the lung, PSPT delivered less dose ($D_{0.1cm}{}^{3}$ and $D_{5cm}{}^{3}$) to the heart, esophagus and bronchus compared to SBRT [9]. For locally advanced Stage III NSCLC patients, Wu *et al.* found that proton beam therapy was feasible and superior to three-dimensional conformal radiotherapy for several dosimetric parameters such as the mean dose for lung, heart, and spinal cord [3]. Using IMPT, doses to normal tissues, such as the lung, spinal cord, heart, and esophagus, can be further reduced compared to passive scattering proton therapy and IMRT for extensive Stage IIIB NSCLC, as reported by Zhang *et al.* [10]. The dosimetric advantage of IMPT would allow further dose escalation from 74 to 84.4 Gy while keeping normal tissue sparing at a lower or similar lever. IMPT proved also advantageous in terms of lung sparing compared to both Tomotherapy and IMRT in a study by Stuschke *et al.* [11]. A brief summary of literature on plan comparison between proton and photon therapy discussed here is listed in **Table 1**.

When uniform scanning proton therapy is used, similar normal tissue sparing to passive scattering proton therapy can be achieved. **Figure 3** shows the dose comparison of USPT versus IMRT for a lung case. The patient was a 72-year-old female with severe chronic obstructive pulmonary disease (COPD) and Stage IIIA (cT1aN2MpG2) squamous cell carcinoma of the right upper lung.

References	Year	Institution	Tumor stage (patient no)	Proton vs. photon	Normal tissues receiving less dose from proton therapy
Chang *et al.* [2]	2006	MDACC	Stage I (10) and III (15)	PSPT vs. 3DCRT	Lung, spinal cord, heart, esophagus, integral dose
Kadoya *et al.* [8]	2011	STPTC	Stage I (21)	PSPT vs. SBRT	Lung
Hoppe *et al.* [9]	2010	UFPTI	Stage I (8)	PSPT vs. SBRT	Lung, heart, esophagus, bronchus
Zhang *et al.* [10]	2010	MDACC	Stage IIIB (10)	IMPT vs. IMRT	Lung, spinal cord, heart, esophagus
Stuschke *et al.* [11]	2012	UHE	NA (6)	IMPT vs. IMRT/ tomotherapy	Lung
Wu *et al.* [12]	2016	NCCHE	Stage III (33)	PSPT vs. 3DCRT	Lung, heart, cord

Abbreviations: MDACC: M. D. Anderson Cancer Center; STPTC: Southern Tohoku Proton Therapy Center; UFTPI: University of Florida Proton Therapy Institute; NCCHE: National Cancer Center Hospital East; UHE: University Hospital Essen. Others see above.

Note: Reports from the literature.

Table 1. Comparison studies between proton and photon therapy for NSCLC patients.

a) Proton plan   b) IMRT plan
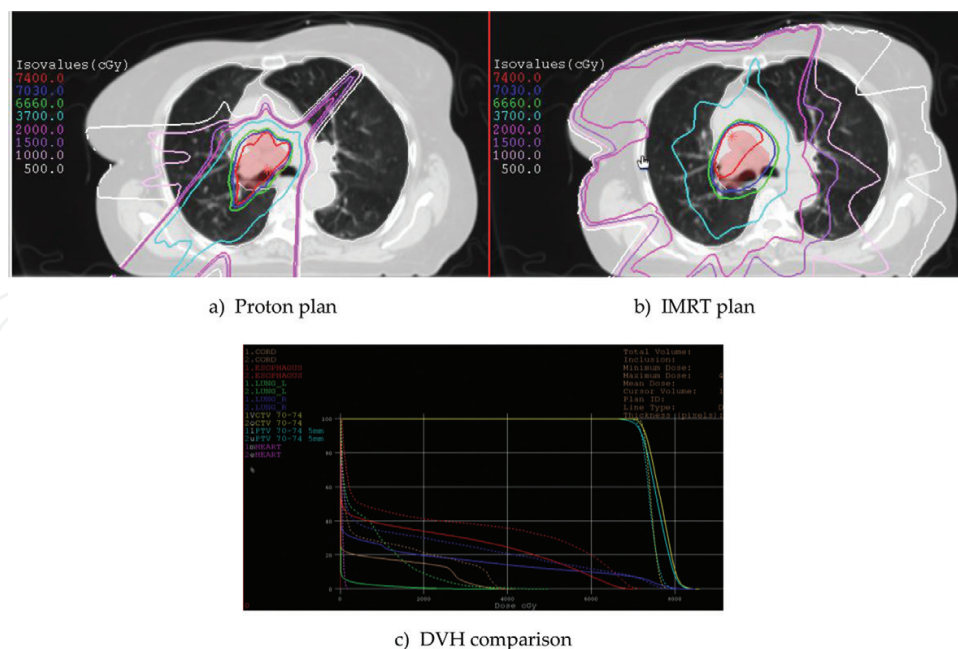
c) DVH comparison

Figure 3. Dose comparison of Uniform Scanning proton plan and IMRT plan. (a) Proton plan, (b) IMRT plan, and (c) DVH comparison (solid line—proton, dashed line—IMRT). The prescribed dose was 74 cobalt gray equivalent (CGE) at 2 CGE per fraction for 37 fractions.

4. Adaptive proton therapy of lung cancers

4.1. Rationale

Adaptive radiation therapy (ART) is a closed-loop process where the treatment plan will be re-optimized for treatment variations such as patient anatomy change using a systematic feedback of measurements. [13]. Thanks to the advancement of imaging modalities available for treatment planning and delivery, such as 4D CT and onboard imaging, ART has been feasible and clinically implemented at many cancer centers. The main goal of plan adaptation is to adjust the treatment plan to the change of patient anatomy, tumor motion, or setup, so that the target coverage and normal tissue sparing remain optimal for each individual patient during the whole course of treatment. For lung cancer patients, anatomy change is often inevitable due to tumor regression, pleural and pericardial effusions, or atelectasis. Adaptive photon therapy has been shown to be beneficial in lung cancer treatment, resulted in a mean reduction of 21% for the volume of ipsilateral lung receiving 20 Gy (V20) [14], and an average of 65 cGy reduction in mean lung dose and reductions in cord max dose, mean esophageal dose, and heart dose [15]. It was reported that ART has the potential to improve the accuracy of radiation treatments, thus reducing the exposure of organs at risk and facilitating safe dose escalation, leading to potentially better local control and overall survival [16–19].

Because a proton beam has a finite range and sharp distal dose fall off, the dose distribution of a proton plan is very sensitive to anatomy change; therefore, the need for lung cancer treatment adaption in proton therapy is even greater than photon therapy. Hui *et al.* found that the effects

of inter-fractional motion and anatomic change could lead to a result of up to 8% reduction of the CTV coverage, a mean 4% dose increase of the volume of the contralateral lung receiving at least 5 CGE, and a mean 4.4 CGE increase in spinal cord maximum dose [20]. Koey *et al.* reported that without adaptive planning, target coverage could be dropped to below 60% compared with adaptive planning for some lung cancer case undergoing proton therapy [21]. The potential considerable dose change in proton therapy due to anatomy variation indicates that plan adaptation is essential in proton therapy of lung cancer.

4.2. Process for adaptive proton planning

A typical adaptive planning process includes measuring the treatment variations such as anatomic change, evaluating their dosimetric and clinical impact, and adapting the radiation treatment to the updated information as necessary. In proton therapy of lung cancer, anatomic change is of main concern. Repeated CT scans are commonly used to measure the anatomic change during the treatment course. Ideally, the repeated CT scans should be performed frequently with a 4D CT scan so that patient anatomy and motion can be accurately evaluated. However, depending on facility resources and patient compliance, in room CBCT or slow CT scans can also be used. The repeated CT will be registered to the initial CT, and a QA plan will be generated by applying the same beam configuration from the initial plan to the registered repeated CT data, which will be evaluated on dosimetric change and potential clinical impact. The physicist and physician will then determine whether and how the plan will be adapted. If plan adaptation is determined necessary, plan change will be made according to the physician/physicist instruction, and the new plan will be changed and go through the process of plan review, QA, and approval before beam delivery similar to the initial plan. In addition to deciding whether a plan adaptation is needed, one should also decide whether any other change is needed for the patient. For example, if the patient anatomy is likely to change significantly before the next scheduled CT scan, we may want to increase the imaging frequency for the patient.

A clinical workflow of the adaptive planning for lung cancer treatment at our center is shown in **Figure 4**. After initial 4D CT imaging, treat planning, and beam delivery, QA CT (i.e., repetitive CT) will be performed after a patient receives 14, 30, and 50 CGE of proton dose, that is, after the 7th, 15th, and 25th fraction for most patients treated with 2 CGE per fraction. The repeated average CT was fused to the original average CT based on bony anatomy by a dosimetrist using the VelocityAI software system (Version 3.1.0, Varian Medical Systems, Palo Alto, CA). A quality assurance (QA) plan was generated after each CT scan by applying the same proton beams and hardware (apertures and compensators) in the original plan to the registered new CT dataset using the XiO TPS (Version 5.0, Elekta Inc., St. Louis, MO). A physicist will first review the CT fusion to evaluate the anatomic change and check the correctness of the fusion. The physicist will then review the QA plan to evaluate the dosimetric change and the correlation between the dosimetric change and the anatomy variation. Together with the attending physician, the physicist will make a recommendation on whether plan adaption is needed. If plan adaptation is determined to be necessary, a dosimetrist will make the plan change, and treatment with the new plan will start as soon as possible. The process of treatment, QA CT, QA planning, and plan adaptation will be repeated until the patient complete the treatment course.
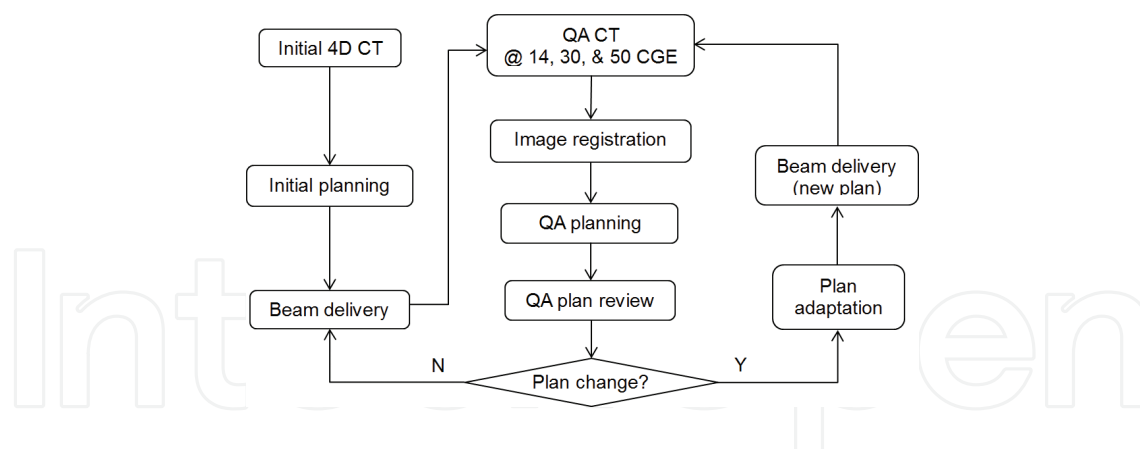
Figure 4. A clinical workflow of adaptive planning for lung cancer treatment using uniform scanning proton therapy.

4.3. Strategies for plan adaptation

One straightforward way of plan adaptation is to re-plan based on the newly obtained CT, repeating the same process as how the initial plan is created. Re-planning has been used for most adaptive treatment in both photon therapy and proton therapy and generally includes target contouring, beam placement, dose optimization, plan review and approval, documentation and billing, calendar adjustment, QA, and so on. For adaptive proton therapy where PSPT and USPT are used, new patient specific devices such as apertures and compensators are also needed during re-planning, which can lead to added cost and long turnaround time due to the manufacturing process. Substantial effort is needed from the dosimetrists, physicist, and machinists, and it can take several days to make the new plan available for treatment. Before the new plan becomes available, the patient can either continue to be treated with the initial plan or have a treatment break, depending on the extent of anatomy change and its impact on dose distribution and potential clinical effect. On the other hand, re-planning can fully adapt a plan and achieve the best optimization of dose distribution based on the new CT data set. **Figure 5** shows an example of re-planning with new patient specific hardware. Substantial tumor shrinkage was observed on the repeated CT scan, which led to a large increase in lung and cord dose (**Figure 5b**). A new plan was created based on the new 4D CT (**Figure 5c**), with an improved normal tissue sparing while maintaining target coverage similar to the initial plan.

Another way of plan adaptation is to make some simple changes in beam parameters, such as range, modulation, or beam weight of any combination. Because a uniform scanning or passive scattering proton beam delivers a uniform dose to patients, it is possible to adjust the range and/or modulation for a proton beam to shift the depth of the spread out Bragg peak (SOBP) region so that the adjusted beam would conform to the target after the water equivalent thickness (WET) changes due to anatomy change. For uniform scanning proton beams, such parameter change is very easy and can be made for the TPS and R&V in minutes plus some additional work on documentation. **Figure 6** shows an example of such case that patient developed pleural effusion at the 25th fraction. After simply increasing the proton

a) Original plan   b) QA plan
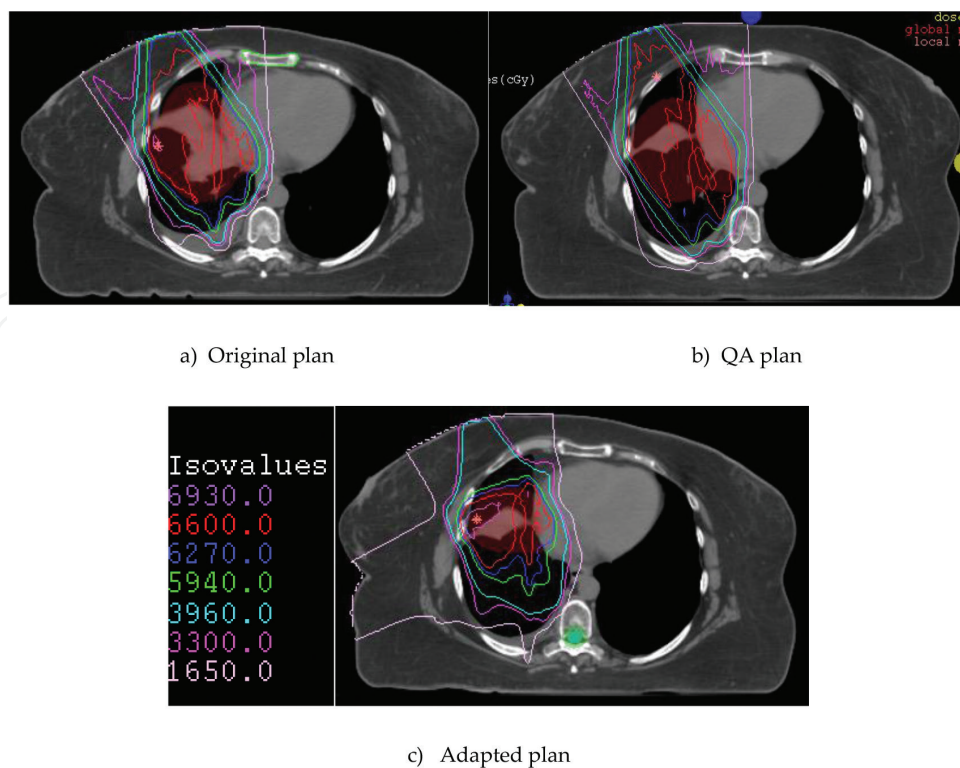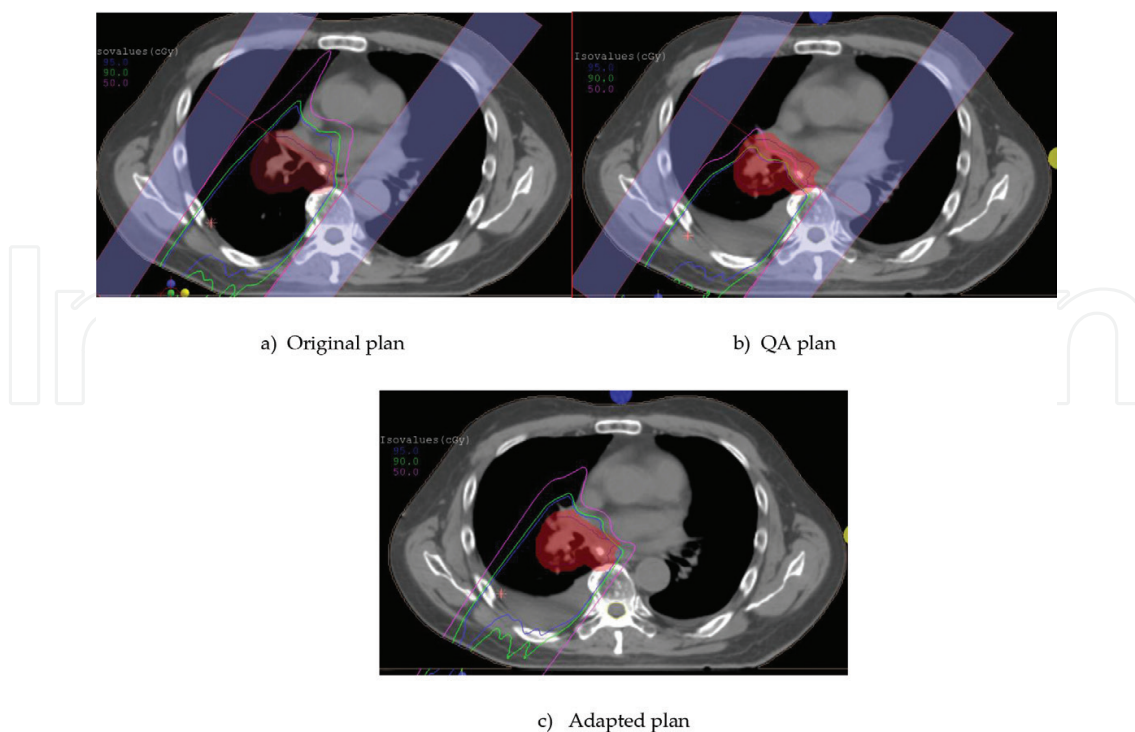

c) Adapted plan

Figure 5. An example case of re-planning with new patient specific device. The patient has small cell Stage IIIA lung cancer with COPD. A 66 CGE was delivered at 33 fractions using uniform scanning proton beams. (a) Original plan; (b) QA plan; (c) adapted plan based on the new CT data.

range by 2.2 cm, the target became fully covered while the normal tissues of lung and heart were still well protected. This simple approach can be highly desirable for certain anatomy changes such as patient weight change which pulls back or increase the range relatively uniform, and/or a quick plan adaptation is needed due to concern on treatment breaks. Please note that such approach is unique in uniform scanning and may not be available in PBS or passive scattering PT.

Other strategies of plan change for USPT could be beam weight change, for example, decrease the weight of beam(s) that is adversely affected by the anatomy change, and increase the weight of beam(s) that is least affected. In addition, a hybrid approach, such as re-planning for one beam and range adjustment for another, can also be used as appropriate.

The strategy used for plan adaptation depends largely on the institutional practice and the beam delivery technique used for lung cancer treatment. For lung cancer treatment with PSPT, Koay *et al.* reported that 20.5% of patients underwent adaptive planning using re-planning with new patient-specific hardware [21]. For USPT, Zheng *et al.* reported that 18.8% of lung cancer patients underwent adaptive planning, using various strategies including range change only (10.9%), range and modulation change (1.8%), range, modulation, and beam weight change (1.2%), and re-planning with new hardware (5.5%) [22]. For PBS or IMPT, Chang *et al.* reported that 26.5% patients were re-planed [6]. A brief summary of adaptive proton therapy literature discussed here is listed in **Table 2**.

a) Original plan   b) QA plan

c) Adapted plan

Figure 6. The dose distribution from the right posterior oblique beam normalized at the isocenter for a lung cancer patient undergoing adaptive proton therapy using parameter adjustment. (a) Initial plan; (b) QA plan; (c) adapted plan with a 2.2 cm range increase. The patient had a right hilar mass and was treated with three proton beams for a total dose of 74 CGE. Fluid buildup was observed on a repeated CT scan after the 25th fraction.

References	Year	Institution	Treatment technique	No. of patients	Adaptation percentage	Repeated CT scanning	Median time for plan change
Koay *et al.* [21]	2012	MDACC	PSPT	44	20.5%	At week 3 or 4	At 24 fractions
Chang *et al.* [6]	2014	MDACC	PBS/IMPT	34	26.5%	Every 2 weeks	After 10 fractions
Zheng *et al.* [22]	2015	ProCure	USPT	165	18.8%	After 7, 15, and 25 fractions	After 18 fractions

Abbreviations: MDACC: M. D. Anderson Cancer Center; STPTC: Southern Tohoku Proton Therapy Center; UFTPI: University of Florida Proton Therapy Institute; NCCHE: National Cancer Center Hospital East; UHE: University Hospital Essen.
Note: Reports from the literature.

Table 2. Adaptive proton therapy.

5. Practical considerations

While adaptive planning can potentially improve the dose distribution and clinical outcome, there are also many pitfalls and limitations in the current adaptive planning process. An optimal adaptive planning process should be developed based on both practical considerations and theoretical dosimetric and clinical gains.

5.1. Frequency of repeated CT scanning and QA planning

The frequency of repeated CT scans depends on facility-specific protocol or individual patient need. Chang reported that 4D CT scans were repeated during week 3 or 4 of treatment or as clinically indicated by the treating physician for lung cancer patients undergoing PSPT [23], and weekly or every 2 to 3 weeks for those receiving intensity modulated proton therapy at MD Anderson Cancer Center [6]. At our center, 4D CT is generally repeated after 7, 15, and 25 fractions of treatment. However, for special cases, more repeated CT scans may be needed such as when patients have a pleural effusion or large weight change. In addition, if hypo-fraction-ated or hyper-fractionated treatment is used, more frequent monitoring should be considered. Daily imaging has becoming available with the introduction of in room CT like CBCT into proton therapy; however, its clinical implementation may be limited due to the extra treatment time and human effort as well as concerns on the increased imaging dose to patients.

5.2. Limitations of image registration and QA planning

One key component of adaptive planning is the image registration. Accurate imaging regis-tration can be challenging, especially for lung adaptive planning where considerable anatomy change may be observed due to disease progression, tumor response to therapy and respira-tory motion [24, 25]. It is important to setup and immobilize the patient for repeated CT as close as possible to the initial CT scan that is used for the treatment planning as large patient setup variation could lead to difficulty on image registration and anatomy change evaluation. The accuracy of image registration needs to be carefully evaluated. In addition, there can be limitation on how a QA plan is generated. For example, our treatment plan system does not account for the patient pitch and roll when a QA plan is applied to the new CT data, although our image registration software does. Another issue is that there could be human errors asso-ciated with the image registration and QA plan process, such as beams may be placed with an incorrect isocenter in a QA plan. Limitations or errors in the image registration and QA plan process could result in artificial dose deviation unrelated to anatomy change and poten-tial errors in decision-making of plan adaptation. Therefore, it is critical to understand these limitations and evaluate the accuracy of image registration and QA planning to avoid errors in decision-making that may lead to unnecessary plan change and potential mistreatment. Our guideline is, in addition to review the QA plan and dose distribution beam by beam, we also analyze the anatomy change and the correlation between the dose change and anatomy change. Any noticeable dose change in the QA plan should be correlated to either patient anatomy/motion change or setup variation; otherwise, the dose change may be artificial as a result of software limitations or human errors, and further investigation should be warranted.

5.3. Correlation between dose change and anatomy variation

The penetration depth of a proton beam is a function of the proton energy and the WET of the materials it passes through. Therefore, for a proton beam of given energy, the depth of the dose falloff is directly correlated to the WET associated with the anatomy in the beam path. Common changes in anatomy that could lead to plan adaptation include patient weight gain or loss, tumor shrinkage or growth, pleural effusion, atelectasis, and so on. For example, when

a patient gains weight, the WET in beam path will increase, leading to a range pull back. The effect of patient weight change typically is more noticeable for anterior proton beams, and may be addressed by simply adjusting the range and/or modulation as the WET change is relatively uniform within the field. Similarly, tumor shrinkage will result in a decrease in WET and beam overshoot, which could lead to more dose to normal tissues such as lung and cord. Target coverage is generally not an issue when a tumor shrinks but can be severely compromised when a tumor progresses and increases in volume. Tumor shrinkage or progression will have an effect on the dose distribution from all beams and is likely to lead a re-planning if the tumor volume change is considerable. About half of cancer patients develop a plural effusion, which is a buildup of extra fluid in space between lung and chest cavity. Clearly, any change in pleural effusion would lead to change in WET and dose deviation from the beam passing through the fluid buildup. If the tumor is far away from the fluid buildup and no beam passes through it, the effect of pleural effusion could be negligible on the dose distribution and no plan adaptation is needed. In most cases, one would only need to make adjustments for the beam(s) that passes the fluid, by either changing the range and/or modulation or re-planning the beam with a new compensator.

Please note that for the composite dose distribution from several proton beams, the correlation to the anatomy may not be straightforward. Anatomy and WET changes will lead to visible dose change for one beam; their effect may not show up well on the overall dose distribution and the DVH. For example, the volume of the target receiving at least 95% of the prescription dose (V95) may show minimal change, while there is a clear under coverage due to a range pullback from a certain beam and plan adaptation should be used. Therefore, beam-by-beam analysis is strongly recommended to evaluate the dose correlation due to the anatomy change.

5.4. Patient motion and motion management

Given the sensitivity of proton beam to anatomy variation, accurate evaluation and appropriate management of motion are very important in lung cancer therapy. For PSPT and USPT, the patient motion is typically accounted for during the initial treatment planning using techniques such as target expansion (ITV), range smearing, and stopping power ratio override [7, 26]. In addition, motion can be managed using respiratory gated system [27]. From our experience, the effect of motion variation in the QA plan based on repeated 4D CT scan seems to be relatively low, and the original plan is typically robust enough to adequately cover the target as long as no anatomy change is present. For PBS, the interplay of patient motion and dynamic beam delivery could result in dose heterogeneity in target and potential under coverage. To mitigate the interplay effect, the motion magnitude for patients treated with PBS is often restricted, such as at a maximum of 5 mm. In addition, several techniques have been used or proposed to mitigate the interplay effect, such as layer repainting, large beam spot, respiratory gated beam delivery, robust planning optimization accounting for the motion, and tumor tracking [6, 12, 28–31]. It has also been reported that the interplay effect may be averaged out during fractionated treatment [32]. However, to fully achieve the potential of IMPT, it may be necessary to routinely evaluate motion change and adapt treatment accordingly.

5.5. Resource constraints and potential risk associated with plan change

When re-planning is used in plan adaptation, new patient specific apertures and compensators may need to be manufactured for both PSPT and USPT. The manufacturing process usually takes hours or more to complete, depending on field size and shape as well as the queuing status of other hardware. If no machine shop is available onsite, the hardware needs to be manufactured by other contracting companies which may take 1–2 days to become available. Furthermore, additional time is needed for the following QA process for the hardware and output measurement. While no hardware is needed for PBS, the robust treatment planning and optimization and the consequent QA process can be very time and effort consuming. In addition, the plan change can lead to unexpected consequences and increased risk of treatment errors, especially when it is not communicated well. Therefore, we have to take the associated cost and risk into account in addition to the dosimetric and clinical gain when deciding whether plan change is necessary.

5.6. Treatment volume with tumor shrinkage

It is still unclear on whether the clinical target volume should be reduced accordingly when a tumor shrinks during the treatment course. Siker *et al.* cautioned field reductions for tumor shrinkage during radiotherapy, questioning the significance of tumor regression because histologic tumor clearance was hard to document [33]. However, Guckenberger *et al.* believed that adaptation of radiotherapy to the shrinking GTV did not compromise the dose coverage of volumes of subclinical microscopic disease [34]. In adaptive proton therapy for both USPT and PSPT, the treatment target volume is commonly kept the same as the initial plan and the same apertures are used, while the beam penetration is adjusted, that is, the range is adjusted or the compensator is recalculated, to account for the WET change associated with the tumor shrinkage. Exceptions can be made per physicians' discretion for cases that normal tissue sparing is critical, such as for patients with a very large initial tumor volume and normal dose can be close or exceed the tolerance with the initial plan. One proposal is to treat the initial target volume for at least 50 Gy, the standard dose for microscopic disease, and then treat the reduced volume to the full dose with a boost [35].

5.7. Dose accumulation

Accurate accounting doses at the presence of anatomy change and plan adaptation is important to make informed decision on whether and how to adapt a plan. However, this can be challenging due to limitation of image registration when large anatomic change or setup variation exist. In addition, CT scans are often repeated on a non-daily basis, and the exact patient anatomy between CT scans is unknown. To estimate the actual dose delivered between two image scans when daily patient anatomy information is not available, one may use a weighted summation of the doses calculated on the two CT data sets, or interpolate patient anatomy between the two scans and calculate doses based on the interpolated data sets. The latter can be more realistic, but a good software tool for interpolation is needed.

5.8. Criteria on plan change

The criteria on when and how to adapt a plan can differ from institution to institution and depend on the attending physician and/or individual patient. There are several considerations during QA plan evaluations including: (1) Is there noticeable anatomic change? How will the anatomy change affect the dose? (2) How much does the PTV coverage change compared to the initial plan? Is the target coverage still acceptable? (3) How much does the normal tissue dose change? Is the normal tissue dose within tolerance? (4) How much is the dose deviation from the original plan? Will a re-planning improve the dose distribution significantly? (5) How long does it take to have the revised plan ready for treatment? Will a treatment break be needed before the new plan becomes available? (6) How much are the cost and effort for a plan adaptation (e.g., whether new hardware fabrication was involved, or just some parameter change)? How many fractions are left? Is it worthwhile to make a plan change for the remainder of treatment? (8) Are there any special consideration for the patients, for example, does the patient need more sparing in lung due to pre-existing lung function such as COPD?

Change *et al.* reported that the main criteria for plan adaptation was whether CTV or GTV receives <95% of dose and whether doses for normal tissues such as heart and cord dose were out of tolerance [6]. At our center, in addition to looking into dosimetric effect such as the target coverage and normal tissue dose, we take into account the potential clinical gain as well as the cost and time associated with plan adaptation to decide on whether and how to adapt a plan. For example, if the patient is close to the end of treatment and the clinical impact of plan adaptation is low, we may use a simple adaptation strategy like range adjustment or no adaptation at all for the rest of treatment.

6. Future directions

The technology of proton therapy is evolving very quickly, and many progresses are being made toward more accurate and efficient adaptive planning. Currently, only offline adaption has been reported in proton therapy due to the lack of accurate in-room imaging system and long turnaround of manufacturing patient specific hardware for both PSPT and USPT. However, PBS has been increasingly used for lung cancer treatment, and CBCT and other in-room CT have become available. The advancement of both PBS and in-room CT makes online adaptive planning possible in proton therapy in the future. Before online proton adaptive planning becomes a reality, many challenges need to be addressed. Better tools are needed for automatic image registration and dose accumulation, the dose calculation accuracy of in-room CT such as CBCT needs to be improved, and automatic and fast robust re-planning and QA with IMPT should be developed. In addition, criteria on plan adaptation based on both dosimetric parameters and clinic outcome should be developed for quick and accurate decision-making.

While adaptive planning is needed for proton therapy of lung cancer, it is time and effort consuming, and not every patient can benefit from this process. It would be helpful to be able to predict when adaptive planning is needed and for which patients. This would allow

personalized adaptive planning process for patients, improve treatment efficiency, save costs, reduce risks of treatment errors from the plan adaptation process, and eliminate unnecessary imaging dose to patients with the repeated CT scanning. Berkovic *et al.* used volume and dosimetric data to construct lookup tables in attempt to predict whether and when ART could be useful based on the timing of the radiation treatment, the tumor volume, and whether it was a concurrent or sequential chemo-radiotherapy [36]. Based on our experience with USPT, it is found that patients with noticeable weight change (e.g., 3% or more), pleural effusion, and pneumonitis in addition to the tumor volume change are indicatives of plan adaptation.

7. Summary

Adaptive planning is necessary for proton therapy treatment of lung cancer to maintain optimal dosimetric distribution when patient anatomy changes. To achieve optimal adaptive planning process and clinical outcome, we need to consider not only the benefits from the improved dosimetric distribution and potential clinical outcome with plan adaptation but also its cost and limitations, available resources, and potential risks associated with plan change. Better tools for image registration, dose accumulation, and plan automation are desired to make the plan adaption process more efficient and accurate. The plan adaptation process, for instances, the frequency of repeated CT scanning and the criteria for plan adaptation, needs to be adapted with institutional resource and experience. Online adaption in proton therapy can be feasible with the advancement of pencil beam scanning and in-room CT, but many challenges, such as the limitation of the in room CT image quality, efficient robust proton re-planning and quality assurance, need to be addressed before its clinical use.

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