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Treatment planning study comparing proton therapy, RapidArc and IMRT for a synchronous bilateral lung cancer case

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Original Article

Abstract

Purpose: The main purpose of this study is to perform a treatment planning study on a synchronous bilateral non-small cell lung cancer case using three treatment modalities: uniform scanning proton therapy, RapidArc, and intensity modulated radiation therapy (IMRT). **Methods**: The maximum intensity projection (MIP) images obtained from the 4 dimensional-computed tomography (4DCT) scans were used for delineation of tumor volumes in the left and right lungs. The average 4D-CT was used for the treatment planning among all three modalities with identical patient contouring and treatment planning goal. A proton therapy plan was generated in XiO treatment planning system (TPS) using 2 fields for each target. For a comparative purpose, IMRT and RapidArc plans were generated in Eclipse TPS. Treatment plans were generated for a total dose of 74 CGE or Gy prescribed to each planning target volume (PTV) (left and right) with 2 CGE or Gy per fraction. In IMRT and RapidArc plans, normalization was done based on PTV coverage values in proton plans. **Results:** The mean PTV dose deviation from the prescription dose was lower in proton plan (within 3.4%), but higher in IMRT (6.5% to 11.3%) and RapidArc (3.8% to 11.5%) plans. Proton therapy produced lower mean dose to the total lung, heart, and esophagus when compared to IMRT and RapidArc. The relative volume of the total lung receiving 20, 10, and 5 CGE or Gy (V20, V10, and V5, respectively) were lower using proton therapy than using IMRT, with absolute differences of 9.71%, 22.88%, and 39.04%, respectively. The absolute differences in the V20, V10, and V5 between proton and RapidArc plans were 4.84%, 19.16%, and 36.8%, respectively, with proton therapy producing lower dosimetric values. **Conclusion**: Based on the results presented in this case study, uniform scanning proton therapy has a dosimetric advantage over both IMRT and RapidArc for a synchronous bi-lateral NSCLC, especially for the normal lung tissue, heart, and esophagus sparing. Further studies on a large group of patients with bi-lateral lung cancer are required to validate the dosimetric superiority of proton therapy over the IMRT and RapidArc.

Keywords: Synchronous Bilateral; Lung Cancer; Proton Therapy; IMRT; RapidArc; Treatment Planning

Introduction

Lung cancer is the second most commonly diagnosed cancer in the US. Non-small cell lung cancer (NSCLC) is considered as the leading killer among different types of lung cancer.[1] Medically inoperable NSCLC patients are typically treated with a combination of external beam radiation therapy (EBRT) and chemotherapy. It has been reported that the DNA damage can be induced by an ionizing radiation [2], but the radiation dose to the tumor is often limited by the critical structures adjacent to the tumor. For instance, treatment of lung cancer using higher radiation dose can cause pneumonitis and esophagitis.[3] Due to the advancements in treatment delivery techniques in EBRT, it is now possible to minimize the dose to the organs at risk (OAR), and this could reduce acute and late normal tissue toxicities.

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Several authors [4-7] have performed the treatment planning studies on inoperable NSCLC cases comparing the dosimetric quality of different treatment techniques such as 3-dimensional conformal radiation therapy (3CDRT), intensity modulated radiation therapy (IMRT), and proton therapy. Dosimetric studies on NSCLC have demonstrated that proton therapy is superior in terms of sparing uninvolved lung tissue when compared to the 3DCRT and IMRT.[4-7] Furthermore, few other studies have reported that proton therapy has dosimetric advantages over photon based stereotactic body radiation therapy (SBRT) when a smaller size of lung tumor is involved.[7-10] However, Zhang *et al.* [11] suggested that IMRT may be better than the passive-scatter proton therapy, especially when a tumor has an irregular shape and involves the mediastinum. Recently, a number of studies have reported the clinical results of NSCLC patients treated with proton therapy. Specifically, Nakayama *et al.* [12] reported an overall survival rate of 97.8% and local control rate of 97.0% at 2 years. Bush *et al.* [13] reported an overall survival rate and local control rate of 44% and 74%, respectively, at 3 years, and Nihei *et al.*[14] reported an 84% survival rate and 80% local control rate at 2 years.

The majority of literature on the treatment of NSCLC using radiation therapy involves a single tumor in a patient, and the literature on synchronous bi-lateral NSCLC cases, especially for proton therapy, is very limited. Sinha *et al.*[15] reported that SBRT could be a safe and an effective treatment modality for inoperable bilateral lung cases. Loo *et al.*[16] presented a case study on synchronous bilateral squamous cell carcinoma and compared the dosimetric results of the IMRT plan with that of the 3DCRT plan. Both of these studies [15, 16] used the mega-voltage (MV) photons to generate the lung treatment plans. Recently, Shi *et al.* [17] presented a case study on proton-based chemoradiation for synchronous bilateral NSCLC, and compared the dosimetric results of the proton plan with that of 3DCRT and IMRT plans. However, the study of Shi *et al.* [17] utilized double-scatter proton therapy, and the use of uniform scanning proton therapy (USPT) for a synchronous bi-lateral NSCLC remains to be addressed. The USPT is relatively a new treatment modality, which scans the degraded proton beam laterally with a constant frequency in order to deliver a uniform dose for a near rectangular scanning area. Furthermore, to our knowledge, no dosimetric study has been published investigating the feasibility of RapidArc (Varian Medical Systems, Palo Alto, CA), an example of volumetric modulated radiation therapy (VMAT), for the treatment of synchronous bi-lateral lung cancers. RapidArc is also a new treatment modality, which delivers radiation (MV X-ray beams) by a simultaneous adjustment of dose rate, gantry rotation speed, and multi-leaf collimator (MLC) leaf positions. In this study, we compared the dosimetric quality of the USPT with that of the RapidArc and IMRT for a synchronous bilateral NSCLC case treated with USPT at our proton therapy center.

Methods and Materials

Clinical History

The patient is a 72-year old male with multiple co-morbidities. He was presented with L sided shoulder and chest wall pain in April of 2012 (lvl 7/10). He also has H/O tobacco use and significant COPD (FEV1 37% predicted and DLCO 45 % of predicted) resulting in use of NC O2 on an as needed basis and 2 -3 L at night. Work up ensued and a chest CT showed left lower lobe (LLL) lesion (5.6 × 3.6 cm) invading chest wall and right upper lobe (RUL) lesion (3.7 × 3.2 cm) invading parietal pleura. Biopsy revealed poorly differentiated squamous cell carcinoma with extensive necrosis. The PET CT confirmed these lesions with SUV of 12.9 on the left and 8.9 on the right, no lymphadenopathy, and no metastatic disease. Both the lung lesions were therefore presumed to be synchronous primaries: one being T3 N0 M0, stage IIB and the other being T3 NO M0, stage IIb. The results from the magnetic resonance imaging (MRI) on the brain showed no sign of metastasis.

The patient went on to receive 2 cycles of Carboplatin and Taxotere. The PET scan showed little radiographic response, but his chest wall pain did decrease, so the patient was referred for radiation. The patient has consented to participation in the Proton Collaborative Group (PCG) REG001-09, WIRB Protocol # 20091082. He did well throughout the proton therapy, which was given with concomitant weekly Carboplatin AUC 2 and Taxol 75 mg/m^2 3 weeks on 1 week off as a radiation sensitizer with resolution of his chest wall pain and improvement in his perceived respiratory status. The patient has developed Grade 2 radiation dermatitis during treatment.

Simulation and contouring

4-dimensional (4D) computed tomography (CT) simulation was performed in a head first supine position using immobilization devices wing board, knee roll, and Vac-lok system (CIVCO Medical Solutions, Kalona, Iowa).

The CT images were acquired with a 1.25 mm spacing using General Electric CT Scanner. The digital imaging and communication in medicine (DICOM) CT data set was imported into Velocity, version 2.8.0 (Velocity Medical Solutions, Atlanta, GA) and fused with patient's positron emission tomography (PET) scan for contouring purpose. For both the left and right lung lesions, delineation of the internal gross tumor volume (IGTV) was done by a radiation oncologist based on the maximum intensity projection (MIP) images. The clinical target volume (CTV) was generated by a 7 mm uniform expansion around the IGTV, whereas the planning target volume (PTV) was obtained by expanding 2.5 mm from the CTV. Other normal tissues contoured were the right lung (excluding right CTV), left lung (excluding left CTV), heart, esophagus, and spinal cord.

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Treatment Planning

Proton therapy plans were generated in the XiO treatment planning system (CMS Inc., St. Louis, MO). The beam arrangement in the proton planning was chosen with an objective of maximizing dose to the target volume and minimizing dose to the normal tissues. The feasibility of delivering the proton plans at our proton therapy center was also one of the factors taken into consideration for the beam arrangement. The details on proton beam arrangement are provided in **Table 1**. For each tumor site, an aperture of 1 cm margin around the PTV was manufactured. Additionally, a range compensator (materials type: blue wax) of with a smearing radius of 1 cm was generated for each tumor site. The pencil beam algorithm [18] was used for the dose computation in the treatment plans, and dose calculation grid size was set to 3 mm × 3 mm × 3 mm. Proton treatment plans (left lung plan and right lung plan) were generated for the total dose of 74 CGE prescribed to each PTV (left and right) with 2 CGE/fraction. The isocenter in each plan was selected at the center of the PTV. Dose in proton treatment plans was calculated using relative biologic effectiveness of 1.1. Dose constraints used for the proton planning are provided in **Table 2**.

For a comparative purpose, IMRT and RapidArc plans were generated using the Digital Imaging and Communications in Medicine (DICOM) CT and structure set, which were used for the proton planning. The IMRT and RapidArc planning was done in the Eclipse treatment planning system, version 11 (Varian Medical Systems, Palo Alto, CA) using 6 MV photon beam (Machine type: TrueBeam). First, the de-identified DICOM data were transferred from our proton center to "institution". Second, both the IMRT and RapidArc treatment were generated by a clinical physicist at "institution" based on the dose constraints (**Table 2**) for the prescription dose of 74.0 Gy to each PTV with 2 Gy/fraction. Specifically, a 5-field technique was used for both the right and left IMRT plans such that the beam entrance through the contra-lateral lung was avoided. For example, the left IMRT plan setup did not include the beam entering through the contra-lateral lung (i.e., right lung in this case). RapidArc plans were generated for each site using one arc with an avoidance sector for the contra-lateral lung. Treatment plan optimization for the IMRT and RapidArc planning was done using progressive resolution optimizer, version 11.0. Anisotropic Analytical Algorithm (AAA), version 11.0, was used for dose computations in both the IMRT and RapidArc plans, and dose calculation grid size was set to 2.5 mm.

TABLE 1: Beam parameters for proton, IMRT and RapidArc planning. The unit for gantry, couch, collimator, and avoidance sector angle is in degree. The isocenter of beam arrangement was placed at the center of the planning target volume (PTV).

	Proton planning				
	Beam #	Gantry	Couch	Collimator	Avoidance Sector
Left PTV	1	90	0	--	--
	2	180	0	--	--
	Beam #	Gantry	Couch	Collimator	Avoidance Sector
Right PTV	1	30	0	--	--
	2	180	0	--	--
	IMRT planning				
	Beam #	Gantry	Couch	Collimator	Avoidance Sector
	1	230	0	0	--
	2	180	0	0	--
Left PTV	3	130	0	0	--
	4	80	0	0	--
	5	20	0	0	--
	Beam #	Gantry	Couch	Collimator	Avoidance Sector
	1	130	0	0	--
	2	210	0	0	--
Right PTV	3	260	0	0	--
	4	310	0	0	--
	5	0	0	0	--
	RapidArc planning				
	Arc #	Gantry	Couch	Collimator	Avoidance Sector
Left PTV	1	179 to 181	0	0	351 to 247
	Arc #	Gantry	Couch	Collimator	Avoidance Sector
Right PTV	1	181 to 179	0	0	359 to 103

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TABLE 2: Dose constraints used for the treatment planning (Total prescribed dose to each PTV (left and right) was 74.0 CGE or Gy with a daily dose of 2 CGE or Gy per fraction)

Normal structure	Dosimetric parameter	Dose-volume constraint
Total lung	V20	< 35%
	V10	< 45%
	V5	< 65%
Spinal cord	Maximum Dose	< 50.5 CGE or Gy
Esophagus	V60	< 50%
	Mean Dose	< 34 CGE or Gy
Heart	V60	< 33%
	V45	< 67%
	V40	< 100%

Abbreviations: V_x = relative volume of the structure receiving x Gy or CGE; Total lung = left lung - left CTV + right lung - right CTV

The beams parameters used for the IMRT and RapidArc planning are listed in **Table 1**. After the final dose calculation in the IMRT and RapidArc plans, normalization of treatment plans was carried out using the PTV coverage values, which were obtained from the proton plans. Specifically, both the IMRT and RapidArc plans were normalized such that 95% of the left PTV volume received at least 73.64 Gy and 95% of the right PTV volume received at least 74.13 Gy.

Evaluation

The treatment plans evaluation was done by comparing the dosimetric results obtained from the cumulative dose-volume histograms (DVH) of the IMRT, RapidArc, and proton plans. The PTVs were evaluated for the minimum, maximum, and mean doses, whereas the heart and esophagus were evaluated for the mean dose. The total lung (i.e., left lung -left CTV + right lung - right CTV) was evaluated for the mean dose and the relative volume receiving 20, 10, and 5 CGE or Gy (V20, V10, and V5, respectively). The maximum dose to the spinal cord was compared too.

Results

PTV

Among three planning techniques, proton therapy produced the highest minimum PTV dose and the lowest maximum PTV dose, whereas the IMRT produced the lowest minimum PTV dose and the highest maximum PTV dose. Proton therapy produced the mean PTV dose closest to the prescription dose (within 2.2% for the left PTV and 3.4% for the right PTV), whereas the mean PTV doses in the IMRT and RapidArc plans were higher from the prescription dose by 6.5% to 11.3% in the IMRT plans and by 3.8% to 11.5% in the RapidArc plans.

Normal tissues

Proton therapy produced lower values for the mean dose to the total lung, heart, and esophagus when compared to the IMRT and RapidArc. The mean dose evaluation between the IMRT and RapidArc plans showed that IMRT produced lower mean dose to the heart (5.32 Gy vs. 6.82 Gy) but higher mean dose to the total lung (15.46 Gy vs. 13.62 Gy) and esophagus (10.25 Gy vs. 9.21 Gy). The V20, V10, and V5 were lower using proton therapy and higher using IMRT. Specifically, in comparison to the IMRT, the V20, V10, and V5 were lower in the proton plans by absolute differences of 9.71%, 22.88%, and 39.04%, respectively. The absolute differences in the V20, V10, and V5 between proton and RapidArc plans were 4.84%, 19.16%, and 36.8%, respectively, with proton therapy producing lower dosimetric values. The absolute differences in the V20, V10, and V5 between the IMRT and RapidArc plans were 4.87%, 3.72%, and 2.24%, respectively. The maximum dose to the spinal cord was the highest using the IMRT (47.34 Gy) and the lowest using the RapidArc (37.57 Gy), which had a value slightly lower (difference of 0.77%) than that of proton therapy (37.86 CGE).

Discussion

A dosimetric case on a synchronous bi-lateral NSCLC was presented in this study, and the dosimetric quality of the IMRT, RapidArc, and proton therapy was compared. Our results demonstrated that the proton therapy provides dosimetric advantage over both the IMRT and RapidArc for the treatment of bi-lateral synchronous NSCLC. Specifically, proton therapy produced more homogenous plans, with PTV doses in the proton plans being closest to the prescription dose when compared to the PTV doses in the IMRT and RapidArc plans. Additionally, the proton therapy is superior in sparing the normal lung tissue, with lower mean dose and smaller V20, V10, and V5 values. This could potentially decrease the probability of occurring pneumonitis and esophagitis for the synchronous bi-lateral NSCLC patients treated with radiation therapy.

The dosimetric results in our case study showed an agreement with Shi *et al.* [17], who reported better dosimetric results using proton therapy than using the IMRT. Furthermore, our study and Shi *et al.* [17] showed that the proton therapy could be used for radiation dose escalation and concurrent chemotherapy without violating normal tissue dose

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constraints. The proton therapy, however, has several limitations such as the uncertainty in the proton beam. Our study included the geometry-based PTVs, which were generated using a uniform expansion from the CTV. Recently, the study by Park *et al.* [19] suggested the use of beam-specific PTV in proton therapy accounting setup and range uncertainties. At present, there is no common agreement among all proton centers on the use of range uncertainty in proton therapy.[20] At our proton center, the recommended range certainty is 2.5% + 2 mm. This value, however, may not always be applicable for all the tumor sites. Furthermore, dependency of range uncertainty on the beam direction, treatment planning system, treatment delivery unit, and tumor site remains to be addressed for the proton therapy. Another issue with scanning proton therapy for lung cancer is the interplay effect, which may degrade the dose distributions.[21]

Dosimetric findings from treatment planning studies are also dependent on the accuracy of dose calculation algorithm employed in treatment planning system. For instance, Rana *et al.* [22] showed that the pencil beam algorithm/XiO treatment planning system can overestimate the lateral penumbra in proton therapy by up to 2.5 mm for a large air gap. The findings from Rana *et al.* [22] were based on the water-equivalent homogeneous medium. The real clinical situation such as the one for lung cancer treatment, however, will include the tissue heterogeneities, which may have an impact on the accuracy of proton beam range and lateral penumbra predicted by the pencil beam algorithm/XiO treatment planning system. In the near future, we aim to investigate the accuracy of XiO treatment planning system in predicting proton beam range and lateral and distal penumbra in the presence of different tissue heterogeneities. In the case of Eclipse TPS, it has been reported that the AAA has some limitations in dose computations when low-density medium is involved along photon beam path.[23] Since the AAA was the only available photon dose calculation algorithm in the Eclipse used for this study, we were not able to compute the dose with more accurate photon dose calculation algorithms such as collapsed cone convolution superposition and Acuros XB.[23-25]

TABLE 3: Comparison of the dosimetric parameters of the PTVs (left and right) in the IMRT, RapidArc, and proton plans for a synchronous bi-lateral lung cancer case. For all three modalities (IMRT, RapidArc, and Proton), the D95 of the left PTV was 73.64 CGE or Gy, whereas the D95 of the right PTV was 74.13 CGE or Gy.

		Proton	RapidArc	IMRT
Left PTV	Minimum Dose	67.97 CGE	67.75 Gy	66.95 Gy
	Maximum Dose	82.27 CGE	82.70 Gy	83.30 Gy
	Mean Dose	75.61 CGE	76.84 Gy	78.84 Gy
Right PTV	Minimum Dose	68.93 CGE	69.53 Gy	67.22 Gy
	Maximum Dose	82.52 CGE	88.56 Gy	90.40 Gy
	Mean Dose	76.78 CGE	82.52 Gy	82.37 Gy
Total Lung	Mean Dose	0.09 CGE	13.62 Gy	15.46 Gy
	V20	17.59 %	22.43 %	27.30 %
	V10	21.22 %	40.38 %	44.10 %
	V5	24.06 %	60.86 %	63.10 %
Heart	Mean Dose	0.03 CGE	7.03 Gy	6.01 Gy
Esophagus	Mean Dose	0.05 CGE	9.21 Gy	10.25 Gy
Cord	Maximum Dose	37.86 CGE	37.57 Gy	47.34 Gy

Abbreviations: D95 = Dose delivered to the 95% of the planning target volume (PTV); V_x = relative volume of the structure (total lung in **Table 3**) receiving x Gy or CGE; Total lung = Left lung - left CTV + right lung - right CTV

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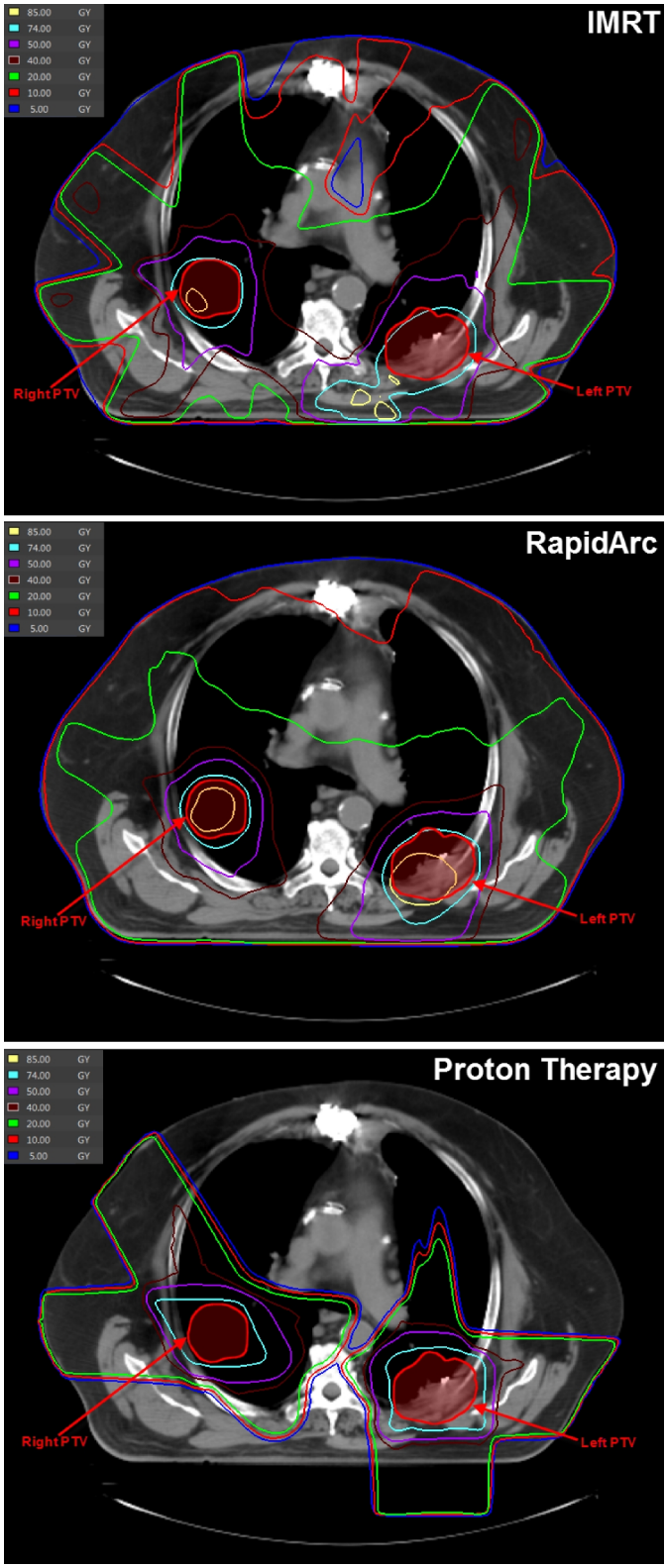

FIG. 1: Isodose lines generated by three different planning techniques for a synchronous bi-lateral lung cancer case. For a comparative purpose, this figure was generated in the Velocity based on the RT dose information from the original treatment plans (IMRT, RapidArc, and Proton).

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Conclusion

Based on the results presented in our study, uniform scanning proton therapy has a dosimetric advantage over both IMRT and RapidArc for a synchronous bi-lateral NSCLC, especially for the normal lung tissue, heart, and esophagus sparing. Further studies on a large group of patients with bi-lateral lung cancer are required to validate the dosimetric superiority of proton therapy over the IMRT and RapidArc.

Conflict of interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. American Cancer Society. Cancer Facts & Figures 2013. Atlanta: American Cancer Society; 2013.
2. Grosse N, Fontana AO, Hug EB, *et al*. Deficiency in homologous recombination renders Mammalian cells more sensitive to proton versus photon irradiation. *Int J Radiat Oncol Biol Phys* 2014; **88**:175-81.
3. O'Rourke N, Roqué I Figuls M, *et al*. Concurrent chemoradiotherapy in non-small cell lung cancer. *Cochrane Database Syst Rev* 2010; (6):CD002140.
4. Skinner HD, Komaki R. Proton radiotherapy in the treatment of lung cancer. *Transl Cancer Res* 2012; **1**:264-70.
5. Nichols RC, Huh SN, Henderson RH, *et al*. Proton radiation therapy offers reduced normal lung and bone marrow exposure for patients receiving dose-escalated radiation therapy for unresectable stage iii non-small-cell lung cancer: a dosimetric study. *Clin Lung Cancer* 2011; **12**:252-7.
6. Lee CH, Tait D, Nahum AE, *et a*l. Comparison of proton therapy and conformal X-ray therapy in non-small cell lung cancer (NSCLC). *Br J Radiol* 1999; **72**:1078-84.
7. Chang JY, Zhang X, Wang X, *et al*. Significant reduction of normal tissue dose by proton radiotherapy compared with three-dimensional conformal or intensity-modulated radiation therapy in Stage I or Stage III non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2006; **65**:1087-96.
8. Hoppe BS, Huh S, Flampouri S, *et al*. Double-scattered proton-based stereotactic body radiotherapy for stage I lung cancer: a dosimetric comparison with photon-based stereotactic body radiotherapy. *Radiother Oncol* 2010; **97**:425-30.
9. Wang C, Nakayama H, Sugahara S, *et al*. Comparisons of dose-volume histograms for proton-beam versus 3-D conformal x-ray therapy in patients with stage I non-small cell lung cancer. *Strahlenther Onkol* 2009; **185**:231-4.
10. Macdonald OK, Kruse JJ, Miller JM, *et al*. Proton beam radiotherapy versus three-dimensional conformal stereotactic body radiotherapy in primary peripheral, early-stage non-small-cell lung carcinoma: a comparative dosimetric analysis. *Int J Radiat Oncol Biol Phys* 2009; **75**:950-8.
11. Zhang X, Li Y, Pan X, *et al*. Intensity-modulated proton therapy reduces the dose to normal tissue compared with intensity-modulated radiation therapy or passive scattering proton therapy and enables individualized radical radiotherapy for extensive stage IIIB non-small-cell lung cancer: a virtual clinical study. *Int J Radiat Oncol Biol Phys* 2010; **77**:357-66.
12. Nakayama H, Sugahara S, Tokita M, *et al*. Proton beam therapy for patients with medically inoperable stage I non-small-cell lung cancer at the university of tsukuba. *Int J Radiat Oncol Biol Phys* 2010; **78**:467-71.
13. Bush DA, Slater JD, Shin BB, *et al*. Hypofractionated proton beam radiotherapy for stage I lung cancer. *Chest* 2004; **126**:1198-203.
14. Nihei K, Ogino T, Ishikura S, Nishimura H. High-dose proton beam therapy for Stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2006; **65**:107-11.
15. Sinha B, McGarry RC. Stereotactic body radiotherapy for bilateral primary lung cancers: the Indiana University experience. *Int J Radiat Oncol Biol Phys* 2006; **66**:1120-4.
16. Loo SW, Smith S, Promnitz DA, Van Tornout F. Synchronous bilateral squamous cell carcinoma of the lung successfully treated using intensity-modulated radiotherapy. *Br J Radiol* 2012; **85**:77-80.
17. Shi W, Nichols RC, Flampouri S, *et al*. Proton-based chemoradiation for synchronous bilateral non-small-cell lung cancers: A case report. *Thoracic Cancer* 2013; **4**: 198–202.
18. Hong L, Goitein M, Bucciolini M, *et al*. A pencil beam algorithm for proton dose calculations. *Phys Med Biol* 1996; **41**:1305-30.
19. Park PC, Zhu XR, Lee AK, *et al*. A beam-specific planning target volume (PTV) design for proton therapy to account for setup and range uncertainties. *Int J Radiat Oncol Biol Phys* 2012; **82**:e329-36.
20. Paganetti H. Range uncertainties in proton therapy and the role of Monte Carlo simulations. *Phys Med Biol* 2012; **57**:R99-117.
21. Dowdell S, Grassberger C, Sharp GC, Paganetti H. Interplay effects in proton scanning for lung: a 4D Monte Carlo study assessing the impact of tumor and beam delivery parameters. *Phys Med Biol* 2013; **58**:4137-56.

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22. Rana S, Zeidan O, Ramirez E, *et al*. Measurements of lateral penumbra for uniform scanning proton beams under various beam delivery conditions and comparison to the XiO treatment planning system. *Med Phys* 2013; **40**:091708.
23. Lu L. Dose calculation algorithms in external beam photon radiation therapy. *Int J Cancer Ther Oncol* 2013; **1**:01025.
24. Kroon PS, Hol S, Essers M. Dosimetric accuracy and clinical quality of Acuros XB and AAA dose calculation algorithm for stereotactic and conventional lung volumetric modulated arc therapy plans. *Radiat Oncol* 2013; **8**:149.
25. Rana S. Clinical dosimetric impact of Acuros XB and analytical anisotropic algorithm (AAA) on real lung cancer treatment plans: review. *Int J Cancer Ther Oncol* 2014; **2**:02019.

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