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CLINICIAN'S PERSPECTIVE

Tumour Shrinkage during Proton-based Chemoradiation for Non–small-cell Lung Cancer May Necessitate Adaptive Replanning during Treatment

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ABSTRACT

This study aimed to evaluate the dosimetric impact of tumour shrinkage during proton-based chemoradiotherapy. This dosimetric study describes a patient who presented with synchronous bilateral T2 non–small-cell lung cancers with no clinical or radiographical evidence of nodal or haematogenous dissemination. The patient was treated with three-dimensional conformal proton radiotherapy to an internal target volume dose of 75.6 Cobalt Gray Equivalent with concomitant weekly chemotherapy (paclitaxel 50 mg/m² and carboplatin AUC 2). Computed tomographic scans were performed weekly to evaluate tumour shrinkage and density changes. Composite plans were generated with and without weekly adaptive replanning. During the course of proton radiation, tumour shrinkage of up to 80% was noted. With replanning, the initial target-volume coverage was maintained, while the spinal cord, oesophagus, and lung doses remained equal to or below initially planned levels. Although the target dose coverage was not compromised, without replanning, the actual doses to certain normal tissues would have exceeded the initial planned estimates by 250%. Tumour regression and density change during a course of proton-based chemoradiotherapy can substantially impact dosimetry. Close monitoring of tumour regression during the treatment course is crucial. Physicians and physicists treating lung cancer patients with protons should be open to adaptive replanning during treatment so as to maintain target volume coverage and minimise the risk of normal-tissue overexposure.

Key Words: *Carcinoma, non-small-cell lung; Lung neoplasms; Protons; Radiotherapy planning, computed-assisted*

中文摘要

質子放化療治療非小細胞肺癌過程中因腫瘤萎縮而需重新規劃劑量

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本研究評估質子放化療治療過程中，腫瘤萎縮對於放化療劑量的影響。本文報告一宗雙側同時患有T2期非小細胞肺癌的病例。病人病發時並無臨床或放射性淋巴結或血原性散播，遂接受三維質子適形放射治療。起初內靶體積劑量為75.6 CGE，同時配合每週化療（paclitaxel 50 mg/m²及carboplatin

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AUC 2）。每星期為病人進行CT掃瞄評估腫瘤的萎縮情況及密度改變，並可能按可規劃劑量重新為病人計劃。質子放化療過程中顯示腫瘤已萎縮八成。經重新規劃後，起初的標靶體積維持不變，脊髓、食道及肺的劑量則調較至原先或較低的水平。雖然目標劑量未受影響，可是如果沒有重新規劃，一些正常組織所接受的劑量會遠超於原本計劃的2.5倍。進行質子放化療的過程中，腫瘤的萎縮情況及密度改變可以大大影響放射劑量測定。所以在治療過程中密切監察腫瘤的萎縮情況相當重要。醫生與物理師為肺癌病人進行質子放化療的過程中對於規劃劑量應採取開放的態度，以使達至目標劑量的同時，亦可令正常組織接受的劑量減至最低。

INTRODUCTION

Radiation therapy plays a critical role in the treatment of non–small-cell lung cancer (NSCLC), either as definitive treatment or part of a multimodality approach. Regrettably, conventional photon radiation therapy for advanced disease is associated with unsatisfactory local control rates (usually <50%).[1] Dose escalation to the target volume may improve the likelihood of local control but is limited by the dose to normal tissues, while the lung itself is often the dose-limiting organ.[2]

Proton beam radiation has distinct physical advantages over conventional X-ray beams. Proton beams stop abruptly at a prescribed depth and produce little side scatter. These characteristics make it possible to reduce the dose to the normal tissues. Studies have demonstrated the dosimetric advantages of such radiation over conventional radiation therapy or intensity-modulated radiation therapy (IMRT) for lung cancer.[3-5] Institutional reports have also described successful use of proton radiotherapy for treating NSCLC.[6-8] Proton therapy, however, does have specific physical features that may compromise the advantage over photons, such as its sensitivity to changes in radiological depth and tissue density along the beam path. These changes can result in significant distortion of the proton dose distribution due to changes in tumour contour and density during a course of fractionated treatment. Because of these issues, special care is needed while designing proton beam plans.[1,9]

At the University of Florida Proton Therapy Institute, we treat patients with NSCLC with proton beam therapy under Institutional Review Board–approved protocols, which include weekly computed tomography (CT) evaluation of tumour response and plan modifications as indicated. In this case study, we observed significant tumour shrinkage during the course of proton radiation therapy and evaluated its impact on dose distribution.

METHODS

Patient and Treatment Characteristics

This case study evaluated a patient with histologically confirmed bilateral adenocarcinomas of the lung (both T2N0) who received definitive radiotherapy. An extensive work-up showed no evidence of nodal or extrathoracic disease. Bilateral surgery was not feasible and optimised IMRT photon radiotherapy to the primary tumours would have resulted in an unacceptably high pulmonary V20 and mean lung dose. The patient was treated with three-dimensional (3D) conformal proton radiotherapy to a 75.6 Cobalt Gray Equivalent (CGE) with concomitant weekly chemotherapy (paclitaxel 50 mg/m^2 and carboplatin AUC 2). A weekly CT scan was performed during the course of proton beam radiation.

Imaging for Lung Adaptive Treatment Planning

For the initial treatment planning, the patient was positioned with an active breathing control (ABC) device during the acquisition of three sets of CT images. These CT image sets were then registered in translation and rotation to each other. Image registration was achieved by manipulating the position of the patient's thoracic vertebral bones near the target.

A set of 4D free-breathing images was also captured. For the 4D CT image sets, a 0.1-mm thick plastic sheet was placed over the patient and tightly fitted to the patient's outer contour by removing the air between the patient and the plastic sheet. Reduced breathing amplitude was achieved with this 'shrink wrap' technique. Because the CT image sets for different phases shared the same DICOM (Digital Imaging and Communications in Medicine) coordinates, no image registration was necessary. The curvature and movement of the thoracic vertebral bones varied minimally (<3 mm) among the image sets. Target motion seen in the 4D CT image sets were compared to the motion in the three image sets with ABC devices.

Radiation Therapy Planning

The magnitude of tumour motion from the 4D CT was compared to the three ABC CTs. The ABC setup resulted in less tumour motion and was used for treatment. Gross tumour volume (GTV) was defined as the abnormality seen on contrast-enhanced CT in the lung window. The clinical target volume (CTV) was defined as the GTV with an 8-mm expansion with modifications of normal tissue boundaries, such as the ribs or chest wall. The internal target volume (ITV) was the CTV plus an expansion determined by simulation CT. In the current case, ITV was the CTV plus an expansion of 2 mm laterally, 4 mm superior-inferiorly, and 4 mm anterior-posteriorly. The planning target volume (PTV) was a 5-mm uniform expansion of the ITV, and was used for aperture design. The radiation dose was prescribed to 95% of the volume. Thus at least 95% of the ITV received the prescribed dose. The minimum dose to the ITV was at least 95% of the prescribed dose. The ITV was used for radiation prescription, and PTV was used for target coverage evaluation. This method of prescription is due to the unique feature of range modulation of proton beam. Two proton beams were used for each tumour. Proton therapy plans were generated on the Varian Eclipse (Varian, Inc., Palo Alto [CA], USA) planning system. For the proton plans, the aperture margins covered the PTV plus 1 cm. The spread-out Bragg peak included a 0.5-cm margin distal and proximal to the target. Smearing margins of 0.8 cm were used for each beam. Beam angles were selected to either avoid the treatment table completely or enter it in an en-face or slightly oblique direction. Gantry angles intersecting the table edge were avoided.

Evaluation of the Dosimetric Impact With and Without Adaptive Replanning

To assess the dosimetric impact of tumour shrinkage without replanning, the initial proton beam plan was recalculated based on new weekly CTs as the verification plan. All beam angle, aperture, compensator, and range modification parameters were kept unchanged. A verification plan for each week of treatment and composite plans were generated. To evaluate the benefit of replanning, the initial plan was applied to the new CT. However, all calculations and optimisations were repeated. The only parameters that were not modified were the beam angles. The initial target volume was then used throughout such that, for each replanning, at least 95% of the ITV would get 100% of the prescribed dose, and 100% of the ITV would receive at least 95% of that dose. Composite plans were also generated.

RESULTS

Significant tumour shrinkage was observed during the course of proton beam radiation. At the end of the treatment, the left-side tumour shrunk by 80% and the right-side by 55%. Representative CT slices are shown in Figure 1. The proton beam arrangement used for the treatment is shown in Figure 2.

Verification plans showed that the initial target volume coverage was maintained with or without replanning. However, without replanning, a significant increase in normal-tissue structure dose was noted. Specifically, the pulmonary V20 CGE increased from 25.3% to 31.1% (123% of initial value). The doses received by 1 cc of the spinal cord increased from 12.8 CGE to 34.4 CGE (269% of initial value); and the dose to 5 cc of

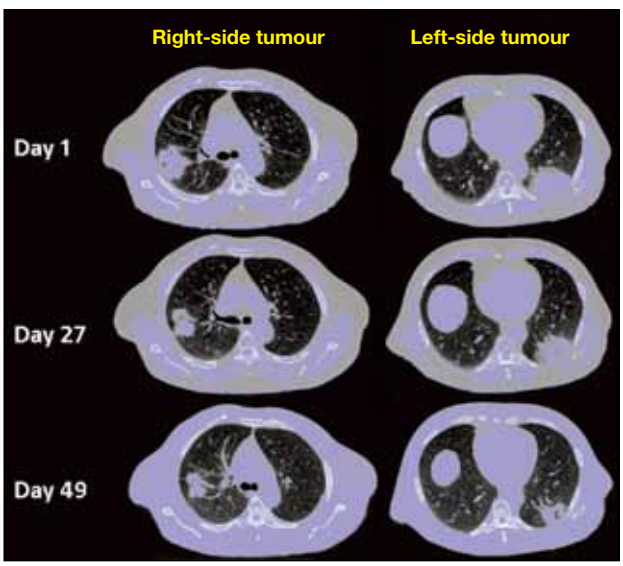

Figure 1. Tumour shrinkage during the course of chemoradiation treatment with proton beams.

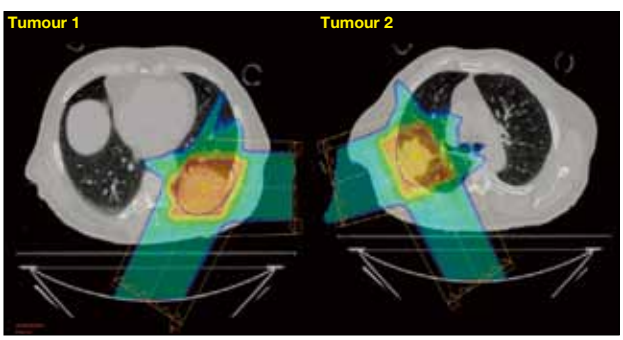

Figure 2. The proton beam arrangement used for the treatment.

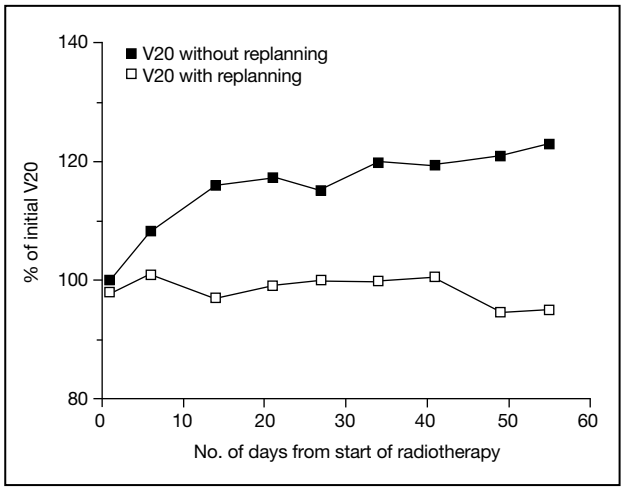

Figure 3. V20 values during the course of radiation with and without replanning.

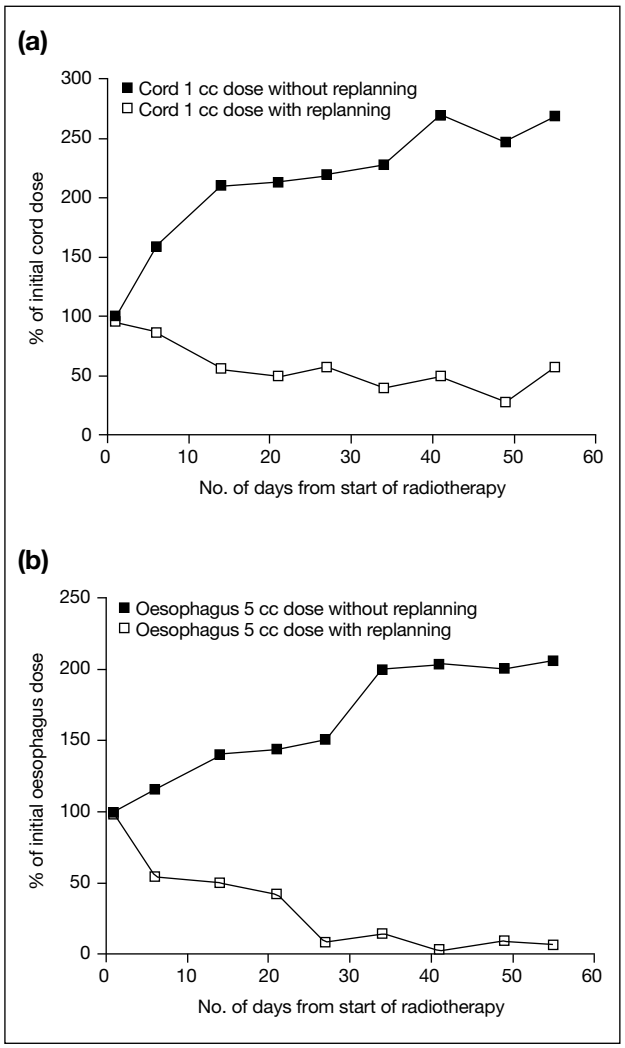

Figure 4. Doses to (a) 1 cc of the spinal cord and (b) 5 cc of the oesophagus during the course of radiation with and without replanning.

the oesophagus increased from 33.5 CGE to 69.0 CGE (206% of initial value). When adaptive replanning was utilised, normal-tissue doses were kept at or below the initially planned dose in all of the normal tissue structures evaluated (Figures 3 and 4).

DISCUSSION

Lung tumour regression during a course of conventional fractionated radiation treatment has been investigated with reported mean daily regression rates of 0.6 to 1.2%.[10-14] Some tumours regress at a rate of 2.3% per day.[10,13,14] While the reported data are based on photon radiation, a similar magnitude of tumour response can probably be expected with low linear energy transfer radiation such as proton beam radiation therapy.[15]

Significant changes in tumour size can affect the radiation dose distribution with protons since changes in tissue density can dramatically affect the proton range. This sensitivity can result in over-treatment of normal tissues distal to the targeted tissues. In the current study, an increase of over 250% in the spinal cord dose and an increase of over 200% in the oesophageal dose were noted. These increases could result in excess normal tissue doses in the clinical setting, especially for locally advanced NSCLC patients with large pretreatment tumour volumes. Efforts were taken to avoid stopping the proton beam in front of critical structures and to pick beams with a shortened path length in normal lung tissue. As a result of this strategy, the lung V20 change was relatively small in our current study.

The current study illustrated the potential of over-dosing normal structures due to tumour shrinkage and density change. Normal tissues distal to the proton beam are at risk of receiving more radiation when the tumour size shrinks. Careful consideration of the beam angles and arrangement may minimise the potential risk. Nonetheless, the finite distal range of the proton beam is its dosimetric advantage for the ever present more distal normal tissue. In our institute, we avoid beam arrangement with distal range stops in front of dose limiting critical structures, so as to avoid potential severe complications due to overdosage related to tumour density change.

Interestingly, proton beam adaptive treatment can be achieved without compromising the coverage of the initial target volume. This is one difference from photon-based adaptive therapy, in which the initially covered target volume is sacrificed when target volumes

and field sizes are reduced.[11,12] The main concern with the latter approach is the uncertainty about histological clearance of microscopic tumour in the setting of a significant radiographic response. This was not a problem with proton planning. With proton therapy, we were able to maintain the initial ITV/PTV coverage through replanning, without increasing doses to normal tissue. This is fundamentally different from photon adaptive treatment, in which the adaptive plan covers a smaller ITV/PTV than the initial ITV/PTV ratio.

Optimal use of proton beam radiation for NSCLC is far from defined. With proton-based adaptive treatment, many important questions have yet to be answered, such as the frequency of replanning and the threshold of tumour response that warrants adaptive changes. These questions are under active investigation at our institution, and the answers will be critical to maintaining a smooth clinical work flow and patient safety.

CONCLUSIONS

Tumour regression and density change during a course of proton-based chemoradiation therapy may have a substantial impact on dosimetry. Close monitoring of tumour regression during the treatment is crucial. Physicians and physicists treating lung cancer patients with protons should be prepared to perform adaptive replanning during treatment, so as to maintain target volume coverage and minimise the risk of normal-tissue overexposure.

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