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PHYSICS CONTRIBUTION

A RABBIT IRRADIATION PLATFORM FOR OUTCOME ASSESSMENT OF LUNG STEREOTACTIC RADIOSURGERY

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Purpose: To evaluate a helical tomotherapy–based rodent radiosurgery platform that reproduces human image-guided radiosurgery treatment to study radiobiologic effects of stereotactic radiosurgery on lung tissues using functional magnetic resonance imaging (MRI).

Methods and Materials: Hypofractionated radisourgery (20 Gy × 3) was delivered to the right lung of three New Zealand rabbits using Helical TomoTherapy with MVCT image guidance. Contrast-enhanced MR perfusion, hyperpolarized helium-3 MR ventilation, and CT were obtained before radiation and monthly for 4 months after radiation. All MRI was performed on a 1.5-T whole-body scanner with broad-band capabilities.

Results: Precise dose delivery to 1.6 cc of the lower right lung was achieved without additional immobilization. No deficits were detected at baseline with respect to perfusion and ventilation. Lung perfusion deficits in the irradiated lung regions began at 2 months after radiation and worsened with time. No ventilation deficits were observed after radiation. Decrease in lung CT density in irradiated regions was observed after radiation, but the changes were less significant than those in perfusion MRI.

Conclusions: We demonstrated that highly conformal radiation can be reproducibly delivered to a small volume of rodent lung on a widely available clinical unit. The radiation-induced lung injury can be detected as early as 2 months after radiation with perfusion MRI. The primary pattern of injury agrees with previously reported endothelial damage to radiosurgical radiation doses. This experimental design provides a cost-effective methodology for producing radiosurgical injuries in rodents that reproduces current human treatments for studying radiation injury and agents that might affect it. © 2009 Elsevier Inc.

Stereotactic body radiation therapy, Radiation-induced lung injury, Perfusion MRI, Hyperpolarized helium-3, Functional MRI.

INTRODUCTION

Stereotactic radiosurgery of lung cancer is gaining wider application and acceptance. Investigators have reported remarkably good results, including high local control rates and low normal tissue toxicities except for centrally located tumors (1–11). Nevertheless, the radiobiology of lung radiosurgery is poorly understood because of relatively few cases, the heterogeneity of the patient population, and short follow-up time. It has been reported that the classic linear quadratic model may not apply to very high dose per fraction treatments (12–14). Despite the conformal nature of lung radiosurgery, a substantial volume of normal lung tissue still receives doses in the range of 20 to 25 Gy, depending on lesion location and size (15), resulting in normal lung radiation injury. The biologic effective dose (BED) based on the α/β ratio of normal lung tissue results in numbers of little practical use because of the questionable application of the linear-quadratic model for these fractional doses. In addition, the radiation injury pattern of lung tissue from radiosurgical doses is not completely understood and is at least partially related to local anatomy, with severe injury of the bronchial and vascular structures resulting in impaired function of distal lung because of the linear nature of their organ structure (16, 17). The three most accepted mechanisms of radiation-mediated lung injury include the following: first, that radiation leads to necrosis of the alveolar wall, which then leads to loss of ventilatory function; second, that radiation induces inflammation and the inflammatory process results in fibrosis of the lung; and third, that radiation damages the microvascular structure of the lung (17–19). Early studies showed that endothelial cell destruction may have played a more dominant role in the tissue damage with fractional radiation doses of 10 Gy or higher (20–22),

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but the dose delivery technique used in these early studies was crude, with the animal positioning being performed without any image guidance, high skin dose from using the ortho-voltage X-ray, the lack of 3D dose calculation with heterogeneity correction, and the radiation delivery generally being hemithorax or thorax fields and therefore not conformal. Therefore, results from these experiments may not reflect those for lung radiosurgery. Although larger mammals such as pigs can be studied using therapeutic machines designed for human use, the cost of running such experiments can be prohibitively high. A system to study the radiobiology of radiosurgery on smaller animals makes higher throughput of animal experiments cost effective. Systems based on the Gamma Knife (23) and a high dose rate 192-Ir (24) system have been suggested by previous investigators. However both systems were limited by the lack of image guidance, 3D dose calculation, and intensity modulation. The 192-Ir system is further impaired by the limited penetration of 192-Ir beams. Using a 50 to 225-kVp X-ray source, a collimation system, cone-beam computed tomography (CT) for localization, and a dedicated treatment planning system, Wong *et al.* (25) built a platform that mimics state-of-the-art human radiation therapy treatment. The innovative system computes and delivers dose with submillimeter resolution. As a result, it is feasible to deliver proportionally miniaturized radiation to an organ or a part of an organ in the mouse. Nonetheless, this dedicated system is limited to a small number of institutions because of cost. A method to conduct small-animal conformal irradiation studies based on available clinical infrastructure is highly desired.

In this work, we study the feasibility of an image-guided small-animal irradiation system based on Helical TomoTherapy technology and evaluate the lung injury from radiosurgical doses using a rabbit model.

METHODS AND MATERIALS

Three New Zealand rabbits were used in this feasibility study. All animal experiments were performed according to a protocol approved by the Animal Care and Use Committee and the Infection Control Committee at the University of Virginia. Radiation injury to the rabbit lung was induced via stereotactic lung radiosurgery delivered on a Hi-Art Helical TomoTherapy unit (TomoTherapy, Middleton, WI). Magnetic resonance (MR) perfusion and ventilation scans were performed at baseline and monthly for 4 months postradiation on a 1.5-T whole-body clinical research MR scanner (Sonata, Siemens Medical Solutions, Malvern, PA). Chest CT scans were performed at baseline and at 2 and 4 months postradiation on a single-detector CT scanner (Picker PQ5000; Philips, Bothell, WA) with slice thickness of 1.5 mm. The rabbits were anesthetized with an intramuscular injection of ketamine (50 mg/kg) and xylazine (5 mg/kg) before the stereotactic radiosurgery and for each imaging scan.

Stereotactic lung radiosurgery model

Stereotactic lung radiosurgery to the right rabbit lung was prescribed similar to human protocols with 60 Gy (20 Gy × three fractions in 1 week) (7, 8). A cylindrical treatment volume of 1.6 cm^3 in the lower right lung was contoured. Inverse treatment planning was performed on TomoTherapy to minimize the dose to the heart and large pulmonary and mediastinal vessels using a 1-cm field width. A MVCT scan was performed before each dose delivery and registered to the treatment planning kilovoltage computed tomography (kVCT) to position the rabbit correctly. Large discrepancies (if any), caused by yaw, pitch, or body flex, were corrected manually by adjusting the rabbit position and rescanning with megavoltage computed tomography (MVCT). Isodose distributions and dose–volume histograms (DVHs) of the dosimetry with low-dose spillage to adjacent lung volumes are shown in Fig. 1. The dose was verified by film and ion chamber measurements before treatment.

Perfusion MRI

Contrast-enhanced perfusion MRI was used to measure pulmonary parenchyma perfusion. A peripheral intravenous line was placed in an ear vein for contrast injection before each perfusion MRI study. A 1-ml bolus of gadopentetate dimeglumine (Magnevist, Berlex Laboratories, Wayne, NJ) was administered over 1 s immediately at the start of the imaging procedure. The rabbits breathed normally during the imaging period. Dynamic MR images were acquired with a quadrature knee coil using a three-dimensional (3D) radio-frequency (RF) spoiled gradient-echo sequence. The following acquisition parameters were used: field of view (FOV), 200 × 133 mm^2; matrix, 192 × 128; slice thickness, 12 to 24 mm; repetition time (TR)/echo time (TE), 3.00/1.05 ms; slice per slab, three to six; flip angle, 25°; and bandwidth, 590 Hz/pixel. The temporal resolution was 0.3 to 0.6 s for each 3D data set, but only the reconstructed coronal images were used for analysis. From 50 to 100 3D data sets were obtained continuously during an imaging period of approximately 30 s.

HP He-3 MR ventilation imaging

Helium-3 (He-3) gas was hyperpolarized (HP) to 30% to 40% in a commercial system (model IGI 9600, MITI, Durham, NC) using the spin exchange method (26). The rabbits were anesthetized and ventilated with 50 cc of HP He-3 gas through an endotracheal tube, and the endotracheal tube was clamped during the 4 s of MR acquisition (27). The MR ventilation studies were acquired using fast, low, flip-angle shot (FLASH)–based sequences with a specially designed flexible RF coil (IGC Medical Advances, Milwaukee, WI) tuned to the He-3 frequency. Three contiguous coronal images covering the entire lung volume were acquired with the following parameters: FOV, 282 × 141 mm^2; matrix, 128 × 64; in-plane resolution, 2.2 × 2.2 mm^2; TR/TE, 12.0/6.8 ms; and slice thickness, 20 mm.

Histopathology study

Rabbits were sacrificed 4 months after radiation, and the lungs were removed and fixed. The lungs were inflated with air at a constant pressure of 30 cm H_2O for 2 days. Once the tissue was fully dried, samples from the irradiated right lung regions and control left lung were excised for microscopic study. The size of the visibly injured lung volume was measured and compared with the radiation isodoses to determine the injury threshold.

Data analysis

Perfusion MRI and CT images were analyzed quantitatively at each time point. The HP He-3 MR ventilation images were evaluated qualitatively to determine ventilation deficits. For perfusion MR images, time–intensity curves were determined for regions of interest (ROIs) and fitted to a Gamma function, where $S(t)$ is the signal intensity and a, b, and c are the fitting parameters (28). Maximum enhancement ratio (MER) and slope of enhancement (SLE) were subsequently calculated for each ROI using the equation $MER = (SI_{max} - SI_0)/SI_0$