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LEVERAGING 3-D SURFACE GUIDANCE AND DEEP INSPIRATION BREATH HOLD PROTOCOL TO OPTIMIZE SIMULATIONS OF INHALABLE NANOPARTICLE THERAPY FOR RADIO-ENHANCED LUNG CANCER TREATMENTS

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INTRODUCTION

Nanoparticles (NPs) made of high electron density materials are known to provide imaging contrast and have the potential to enhance radiation therapy. One material of particular interest has been gold. When targeted with an external beam of sufficient energy, gold nanoparticles (GNPs) will produce secondary electrons, causing radio-sensitization of the immediate surrounding area[1,2]. Administration of these nanoparticles, however, requires further investigation. Traditional routes of entry typically include systemic delivery and direct injection. When delivered throughout the whole body, there runs the risk for systemic toxicities. When directly injected, the payload leaks out from the target, reducing its effectiveness. In an effort to avoid these complications, inhalation has been investigated as a feasible route of entry for GNPs. However, due to the complexities of lung morphology and the impact it has on air travel throughout the lung, this approach is not without complication.

Previous work has investigated the behavior of inhaled nanoparticles for representative lung volumes with the goal of treating lung cancer. This previous work validated the use of the computer code SAEROSA to simulate the coagulation and deposition of inhaled, aerosolized nanoparticles based on boundary layer theory as a component for future treatment planning approaches[3,4,5]. Through this work, it was found that at therapeutically relevant concentrations of GNP (~1.5E8 NPs/cc air), significant coagulation occurs over a 10 second breathing cycle of inhale, breath hold and exhale. Importantly, coagulation dynamics impact where and in what quantity deposition occurs. The longer the particle-laden air remains within the lung, the higher the likelihood for coagulation and deposition to occur. This behavior also impacts the level of dose enhancement once inside the tumor because self-shielding can occur in large enough particle cluster sizes.

To advance the previous work towards clinical application, the current work focuses on leveraging the newly installed LAP Luna 3-D Surface Guidance (3D SGRT) technology in combination with the deep inspiration breath holding (DIBH) technique[6]. Patients undergoing DIBH treatments have two CT simulations performed: one during free breathing and one under DIBH, with the surface of their chest captured by the SGRT system. The parameters of the patient's surface that are monitored throughout treatment include latitude, longitude, altitude, yaw, pitch and roll. These captured parameters can be exported at the end of each treatment session. This exported data also includes the timing of each breath hold, allowing investigators to determine how long each step of the breathing cycle takes for each patient. Using the CT images, the lungs and early airways are contoured to measure their volumes, diameters and lengths. Collected data will be analyzed to determine the relationship between lung volumes and monitored surface area to be applied to new simulations of inhaled GNP dynamics to optimize treatment payload and increase the simulation's personalization.

MATERIALS AND METHODS

Previous simulations have demonstrated the dependence of inhaled NP behavior on lung volume, breath hold length, NP size and initial number density. Until now, parameters used have been average lung volumes and breath hold lengths dictated by previously published experiments. For two test patients, each lung and bronchus were contoured and measured for volume, length and diameter. This was done both on a free breathing scan and a deep inspiration breath hold scan. After their first treatments, the surface guidance measurement output was exported as a .CSV file. Using this .CSV file, the change in mapped surface area was measured again for free breathing and deep inspiration breath hold. From this data, the length of time each were able to hold their breath was obtained as well. Preliminarily, patients were assumed to be cylindrical with lateral surface areas determined via the equation $2\pi rh$ where the radius was assumed to be ½ the longitude measured by the SGRT and h assumed to be the latitude. Since the SGRT system is only tracking the exposed surface, these lateral surface areas were then divided in half (Table 2).

RESULTS

Preliminary data were analyzed for changes in lung volumes (right, left and total), bronchus length, monitored surface area and breathing cycle lengths. Table 1 shows bronchial expansion between free breathing and DIBH conditions with a lengthening of ~0.5cm and ~0.8cm and widening of almost 0.2cm for both patients. The total lung volume measured for DIBH differs greatly between the two patients (~5300cc vs ~3000cc) but both are smaller than the tidal volume used for previous simulations (5600cc) (Table 1). Shown in Table 2, the lengths of breathing cycles over two fields for each patient are displayed. Patient A's breathing cycle averaged ~37s while patient B's breathing cycle averaged just under 15s. Both patients' breath holding ability are longer than the 10s used in the previous work. In sum, this preliminary data demonstrates the high variability from patient to patient, highlighting the need for a higher level of personalization.

Table 1:Lung parameters measured from CT in free breathing and deep inspiration breath hold conditions for two preliminary patients. The difference between free breathing parameters and DIBH are also included.

		Bronchus Length (cm)	Bronchus Diameter (cm)	Left Lung Volume (cc)	Right Lung Volume (cc)	Total Lung Volume (cc)
PT A	Free Breathing	11.88	1.3	1594.61	1756.31	3350.92
	DIBH	12.32	1.47	2468.46	2820.17	5288.63
	Difference	0.44	0.17	873.85	1063.86	1937.71
PT B	Free Breathing	13.23	1.53	861.91	1058.04	1919.95
	DIBH	14.05	1.65	1369.99	1626.8	2996.79
	Difference	0.82	0.12	508.08	568.76	1076.84

		Lateral Surface Area (cm2)		Breathing Cycle Length (s)	
		Field 1	Field 2	Field 1	Field 2
PT A	Free Breathing	-0.1639	-0.1296	41.234	31.984
	DIBH	0.1333	0.1762		
	Difference	0.2972	0.3058		
PT B	Free Breathing	0.0860	-0.1090	15.44	13.02
	DIBH	1.8663	1.0189		
	Difference	1.7803	1.1279		

Table 2: Lateral surface areas in free breathing and DIBH conditions calculated from SGRT captured parameters for two treatment fields. The breathing cycle lengths (inhale, breath hold and exhale) for the same treatment fields.

DISCUSSION

Since the ultimate goal of inhalable gold nanoparticle therapy is for them to accumulate within the tumor and be used both as fiducials and radio-enhancement, it would be ideal for NP administration to occur before the patient has their CT simulation. This is so treatment planning can focus the treatment on the accumulated NPs to elicit the secondary radiations discussed in the introduction. For proper selection of initial airborne concentration and number of breathing cycles required to attain proper accumulation within the tumor, personalized NP deposition simulations would need to be run. Therefore, there is a necessity for individual lung dimension estimates prior to imaging procedures.

Using surface guidance technology, the relationship between change in lung dimensions and change in external surface contour is sought to provide these individual estimates. Interestingly, the preliminary test data indicates larger lung volume changes corresponding with a smaller change in surface area. However, a larger sample size is necessary to actually establish this relationship.

CONCLUSIONS

Inter patient variability of lung volumes, breath holding ability and breathing cycle lengths deviate significantly from parameters used during previous simulations, demonstrating the need for increased personalization. The ability to monitor the patient's surface while undergoing treatment provides a further avenue for simulation personalization, so long that the relationship between lung volume and patient surface area can be elucidated.

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