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Original paper

Lung tumors on multimodal radiographs derived from grating-based X-ray imaging – A feasibility study

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ABSTRACT

Purpose: The purpose of this study was to assess whether grating-based X-ray imaging may have a role in imaging of pulmonary nodules on radiographs.
Materials and methods: A mouse lung containing multiple lung tumors was imaged using a small-animal scanner with a conventional X-ray source and a grating interferometer for phase-contrast imaging. We qualitatively compared the signal characteristics of lung nodules on transmission, dark-field and phase-contrast images. Furthermore, we quantitatively compared signal characteristics of lung tumors and the adjacent lung tissue and calculated the corresponding contrast-to-noise ratios.
Results: Of the 5 tumors visualized on the transmission image, 3/5 tumors were clearly visualized and 1 tumor was faintly visualized in the dark-field image as areas of decreased small angle scattering. In the phase-contrast images, 3/5 tumors were clearly visualized, while the remaining 2 tumors were faintly visualized by the phase-shift occurring at their edges. No additional tumors were visualized in either the dark-field or phase-contrast images. Compared to the adjacent lung tissue, lung tumors were characterized by a significant decrease in transmission signal (median 0.86 vs. 0.91, $p = 0.04$) and increase in dark-field signal (median 0.71 vs. 0.65, $p = 0.04$). Median contrast-to-noise ratios for the visualization of lung nodules were 4.4 for transmission images and 1.7 for dark-field images ($p = 0.04$).
Conclusion: Lung nodules can be visualized on all three radiograph modalities derived from grating-based X-ray imaging. However, our initial data suggest that grating-based multimodal X-ray imaging does not increase the sensitivity of chest radiographs for the detection of lung nodules.

Introduction

Lung cancer is the leading cause of cancer death worldwide accounting for more than 1.3 million deaths annually [1]. Lung cancer can be detected as single or multiple lung nodules on chest radiographs. However, the sensitivity of conventional chest X-rays for lung nodules is rather poor, especially for smaller lung nodules. In one recent study, the sensitivity of radiologists to detect lung cancers with a mean size of 19 mm on chest X-ray was just under 50% [2]. Several studies have found that the average size of lung nodules missed on chest radiographs exceeds 15 mm [3]. This limited sensitivity likely explains why lung cancer screening trials using chest radiographs have consistently failed to show a mortality reduction. By contrast, computed tomography (CT) is far more sensitive for pulmonary nodules. One recent large trial has demonstrated a reduction in lung cancer specific and overall mortality for lung cancer screening with low dose CT in high-risk individuals [4]. However, the rate of false-positive results in CT lung cancer screening exceeds 95% [4] causing repeated imaging tests and potentially harmful invasive procedures. Furthermore, there are serious concerns regarding the radiation exposure and socio-economic costs associated with CT screening. Therefore, increasing the accuracy of chest radiographs in the detection of pulmonary

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nodules may improve detection of lung cancer while avoiding the low specificity and the much higher costs and radiation exposure associated with CT.

In grating-based X-ray imaging, a grating interferometer is introduced into a projection setup and allows to extract three different X-ray-based image modalities [5]: in addition to the transmission signal (equivalent to a conventional X-ray image), grating based X-ray imaging generates a phase-contrast signal as well as a dark-field signal [5]. The phase-contrast signal represents the first derivative of the phase shift while the dark-field signal measures the local small angle scattering of X-rays in the sample [5–7]. Theoretical considerations and experimental data have shown that both phase-contrast and dark-field signals reveal additional information about the specimen, complementary to the information provided by the transmission signal [8–10]. In dark-field imaging, the signal strength is determined by small-angle scattering from microstructures on a scale below the spatial resolution of the imaging system [5,10] thus revealing structural information that is inaccessible for transmission and phase-contrast images [8]. This makes X-ray dark-field imaging a promising technology for lung imaging, since the alveoli that constitute most of the pulmonary parenchyma have a diameter well below the resolution of clinical X-ray projection images. A recent study demonstrated that diagnosing and mapping pulmonary emphysema is feasible by combining transmission and dark-field signal in grating-based X-ray imaging [11]. It has also been shown that X-ray dark-field imaging increases the contrast-to-noise ratio of lung radiographs [12].

The purpose of the present study was to evaluate the feasibility of grating-based X-ray imaging combining transmission, dark-field and phase-contrast images for the depiction of pulmonary nodules on radiographs.

Materials and methods

Ethics and animal welfare

This study does not involve human participants or human samples. Animal experiments were performed with permission of the Institutional Animal Care and Use Committee of the Regierungspräsidium Gießen, Hessen, Germany. Experiments were performed according to national (GV-SOLAS) and international (FELASA) animal welfare guidelines.

Murine model of lung tumors

KRasLA1 mice are a well characterized model for lung cancer development [13]. These mice carry an oncogenic K-RasG12D allele which becomes activated upon spontaneous recombination. Within a few months, these mice develop multiple tumors in the lung, ranging from adenomatous hyperplasia and adenoma to invasive adenocarcinoma [13]. For this study, we used an excised lung from a 6 month old KRasLA1 mouse. The heart was retained in the specimen to achieve an image resembling an *in vivo* chest radiograph.

Histopathology

After washing to remove paraformaldehyde, the specimen was decalcified in 10% EDTA for 5 days. Subsequently, the specimen was dehydrated and embedded in paraffin. Multiple 10 μm thin sections were prepared in the coronal plane at intervals of 0.5 mm to obtain representative sections covering the entire organ. Sections were deparaffinized, hydrated, stained using a routine Mayer's hematoxylin and eosin (H&E) staining protocol, and dehydrated. Sections were scanned at various magnifications to create digital images.

Imaging protocol

To minimize the risk of formalin leaking into airspaces and thus changing the signal characteristics of the specimen, imaging was performed within 3 days after fixating the air-filled lungs in formalin. The *ex vivo* murine lung was imaged in a cylindrical container using a small-animal phase-contrast, dark-field scatter-contrast CT scanner [14,15]. The scanner consists of a rotating gantry built into a housing suitable for preclinical small-animal *in vivo* imaging. The scanner has a tungsten-target 50 W source (RTW, MCBM 65B) built in with a focal spot size approximately of 50 μm in diameter. The X-rays are detected with a flat-panel GOS scintillator (Hamamatsu, C9312SK-06). The detector pixel size is 50 μm. For imaging a three grating Talbot-Lau interferometer has been introduced into the beam. The source grating G0 (period 10 μm, gold height 35 μm), the phase grating G1 (period 3.24 μm, nickel height 4.0 μm, phase shift $\pi/2$ for 23 keV) and absorption grating G2 (period 4.8 μm, gold height 45 μm) are 300 and 145 mm apart, respectively. Thus, the interferometer is operated at the first fractional Talbot distance. The scanner is operated in the source grating stepping mode, acquiring absorption, phase-contrast and dark-field images simultaneously [5].

For imaging the X-ray source was operated at 35 kV peak voltage and 500 μA current. No additional filters were used. However, all gratings are mounted on 500 μm thick silicon wafers. Taking this filtering into account, the beam mean energy is estimated to be 27 keV. Eight stepping positions were acquired and for acquisition of reference images the sample was removed from the beam. The acquired images were processed using Fourier signal analysis approach to retrieve the three imaging modalities [5]. The lung was placed in a container, filled with saturated formalin vapor to prevent the lung from drying out during the scan. To study the influence of overlying structures of the thorax wall on imaging of lung parenchyma, we additionally acquired chest radiographs of a healthy mouse immediately *post mortem*.

Dose calculation

The animal dose was estimated using a patient skin dosimeter (Unfors PSD, Unfors Instruments AB, Billdal, Sweden) placed in the center of a polymer cylinder with a 3 cm diameter. The polymer material resembles carbon in density and is a good approximation for a mouse phantom. To avoid statistical errors the dosimeter was placed in the beam for 10 min. The mouse scan dose was subsequently calculated from the measured value [16]. The radiation dose was approximately 2.3 mGy for the entire acquisition.

Image reading

Image reading was performed by an experienced radiologist. The transmission image was chosen as standard of reference as it is equivalent to a conventional X-ray image. All lung lesions which could be clearly identified as areas of opacification on the transmission images and which finally corresponded to lung tumors in the histopathologic evaluation were included in the analysis. The maximum diameter of these lesions was measured on the histopathologic sections. We then determined whether these lesions could also be identified on the dark-field or phase-contrast images by using a three-point scale: "not conclusively visualized", "faintly but conclusively visualized", "clearly and conclusively visualized". We additionally assessed whether additional lesions could be visualized on the dark-field or phase-contrast images, which corresponded to lung tumors in the histopathologic section and had not been visualized in the transmission image.

Data processing and statistical analysis

Data processing and statistical analysis were performed using Microsoft Excel for Mac 2011 (version 14.1.3) and IBM SPSS