9 Medical Imaging

9-1 Attempt at Visualizing Internal Organs Using X-Ray Refraction Based 3-Dimensional Imaging – Is It Possible to Establish an X-Ray Pathology ? –

Mortality statistics have dramatically changed since the early 1980's when the Photon Factory initiated the development of X-ray optics for intravenous coronary angiograms in order to reduce physical and psychological pressure on both patients and medical staff. As the result of great medical effort the current growth rate of mortality due to heart disease and brain disease, two of the three major adult diseases, seems to have reached a plateau, or has even begun to decrease. However mortality due to cancer has increased by a factor of more than two in the past twenty years.

There are several X-ray visualisation techniques that could be potentially used for cancer diagnosis, including absorption, phase-interference, refraction and fluorescence-based techniques. However revealing cancerous parts in the body using absorption-based imaging is not easy. This is due to there being too small a difference in the absorption coefficients between the healthy and sick parts of an individual organ. Thus, other modalities such as MRI and sonography have been introduced, both of which have high sensitivities to soft tissue.

These techniques are unlikely, however, to be useful in the early diagnosis of cancer due to their poor spatial resolution. There remains a great wish to be able to clinically discover cancer in its early stages using an X-ray visual technique.

Both the phase-interference contrast technique and the refraction-contrast technique have a potentially high contrast enhancement, with δ/β factors of approximately 1000, where δ is the real part of the refraction coefficient and β the imaginary one. In 2000 we commenced participation in refraction-based X-ray imaging studies, which have the potential of being able to visualize soft tissues including cancer.

In 2002 we began to investigate the possibilities offered by X-ray dark-field imaging (XDFI), afforded basically by a double-crystal arrangement [1]. A thickness-controlled Laue-type angular analyzer (Laa) allows only the refraction signal produced from an illuminated cancer part to pass through the Laa in the forward diffraction direction, with all other signals being diffracted in the diffraction direction. Using this scheme enabled us to obtain a very clear image of an articular in a shoulder [2] amputated from a cadaver. This can be regarded as a nearly clinical condition.

In addition, by reducing the thickness of the Laa one can achieve an even better spatial resolution of ~ 23 μm [3], calculated based on X-ray dynamical theory. Applying this technique to a micropapillary carcinoma clearly discerns cancer nests, isolated cancer cells, and stroma, as shown in Fig. 1. Furthermore, we have developed a refraction-based algorithm for CT [4]. This was applied to DCIS (ductal carcinoma *in-situ*) to successfully visualize a 3-dimensional figure (see Fig. 2) of not only the calcification but also the ductus lactiferi (milk duct) and necrosis [5], which have never been observed previously with X-rays.

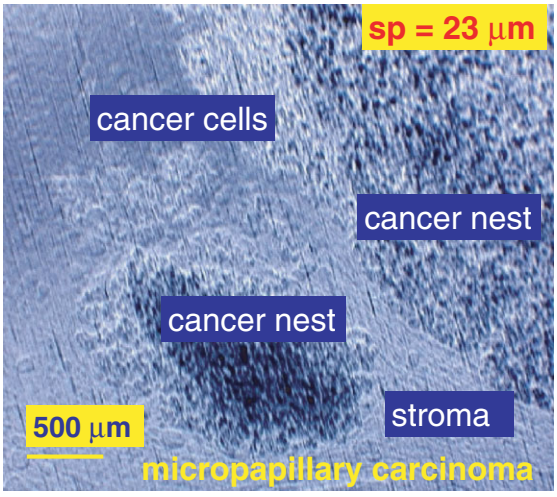

Figure 1
X-ray dark-field imaging of a sliced micropapillary carcinoma with a thickness of 2.8 mm. One can clearly observe cancer nests, independent cancer cells and stroma. The spatial resolution is approximately 23 μm as calculated by X-ray dynamical diffraction theory applied to Laa with a thickness of 125.6 μm and 220 diffraction at 13.7 keV.

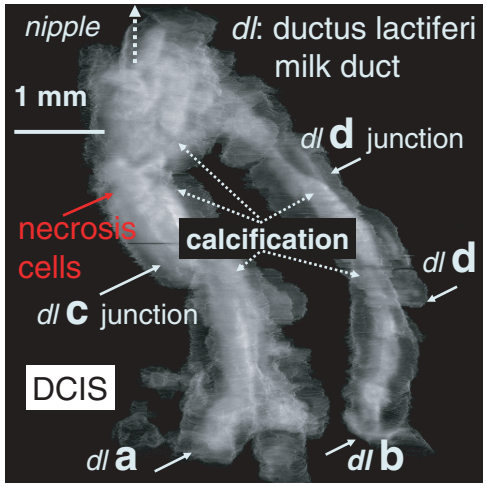

Figure 2
3-dimensional CT due to refraction of DCIS (ductal carcinoma in-situ) with a diameter of 3. 5 mm and length of 3.6 mm. The X-ray energy used was 11.7 keV. The image clearly shows calcification, the ductal lactiferi (milk duct) and necrosis.

M. Ando[1], A. Maksimenko[2], T. Yuasa[3] H. Sugiyama[2], K. Hyodo[2], E. Hashimoto[2] S. Ichihara[4] and T. Endo[4]
([1]Tokyo Univ. of Sci., [2]KEK-PF, [3]Yamagata Univ. [4]Natl. Hospital Or. Nagoya Medical Center)

Reference

[1] M. Ando, A. Maksimenko, H. Sugiyama, W. Pattanasiriwisawa, K. Hyodo and C. Uyama, *Jpn. J. Appl. Phys.*, **41** (2002) L1016.
[2] M. Ando, H. Sugiyama, T. Kunisada, D. Shimao, K. Takeda, H. Hashizume and H. Inoue, *Jpn. J. Appl. Phys.*, **43** (2004) L1175.
[3] M. Ando, H. Sugiyama, S. Ichihara, T. Endo, H. Bando, K. Yamasaki, C. Ohbayashi, Y. Chikaura, H. Esumi, A. Maksimenko and G. Li, *Jpn. J. Appl. Phys.*, **45** (2006) L740.
[4] A. Maksimenko, M. Ando, H. Sugiyama and T. Yuasa, *Appl. Phys. Lett.*, **86** (2005) 124105.
[5] E. Hashimoto, A. Maksimenko, T. Yuasa, H. Sugiyama, K. Hyodo, D. Shimao and M. Ando, *Phys. Rev. Lett.*, submitted

9-2 An Intravenous Coronary Angiography System

We are currently developing a two-dimensional imaging system for intravenous coronary angiography (IVCAG) using monochromatized synchrotron radiation in the X-ray energy region at AR-NE1A2. The purpose of the development is to pursue the possibility of evaluating coronary arteries in screening or follow-up examinations for ischemic heart disease with simple intravenous injection of a contrast medium, a technique safer and simpler than conventional coronary angiographies.

The new system has the advantage of producing two-dimensional dynamic images of cardiovascular systems using asymmetric reflection from a silicon crystal and a two-dimensional imaging system. Twelve patients were examined using imaging system I. The imaging system was improved and the experimental hutch at NE1A2 was rearranged and dedicated to clinical examinations. Subsequently, system II for IVCAG has been employed for clinical examinations since 2000 in a collaboration *between* the University of Tsukuba and the Institute of Materials Structure Science.

A schematic diagram of imaging system II is shown in Fig 3. A monochromatic X-ray beam is obtained using an asymmetrically cut silicon crystal with 311 reflecting planes, yielding a view size of 120 mm (vertically) by 93 mm (horizontally). The horizontal beam size was increased from 75 to 93 mm in 2003 by rearranging the beamline to find the optimal patient position for more effective examinations [1]. Images were recorded at and above the K-edge energy of iodine at 35 keV using an image intensifier/television (II-TV) system and a flat panel detector (FPD) for the most recent eight patients. The PF-AR is usually operated in single-bunch mode at an energy of 6.5 GeV. However, the ring is operated at an energy of 5.0 GeV to reduce the third harmonic X-rays from a silicon crystal. Further, two-bunch-mode operation is made to increase the initial current for clinical examinations [2].

The photon flux density of monochromatic X-rays transmitting the lung region is much higher than that at the mediastinum, and the limited dynamic range of the II-TV system caused degradation of the image of the vascular diacrisis in the mediastinal region where the coronary arteries overlapped other organs. The FPD employed has more than ten times the dynamic range of the II-TV system as a two-dimensional imaging detector for visualizing the coronary arteries, in particular for the circumflex artery which overlaps the left ventricle.

In the most recent studies contrast materials were injected a total of three times into each patient at the left anterior oblique (LAO) position and the right anterior oblique (RAO) position to evaluate the right and left coronary arteries. Contrast material with a total amount of 40 ml was injected into the jugular vein or the vein of upper extremity at a rate of 17-20 ml/sec. An X-ray exposure time of 3.5 msec was used, with an exposure rate of 10 images/sec. The main branches of the right and left coronary arteries for each patient could be clearly detected [3]. The advantage of the two-dimensional imaging system for IVCAG was verified by these examinations. It was possible to obtain not only morphological information on the coronary artery, but also functional information from moving images.

Figures 4 and 5 show typical images from the examinations. The ability to evaluate the circumflex artery was improved by using the FPD, and the spatial resolution of the detector is more than two line-pairs/mm. We plan to continue this project, aiming at more detailed clinical evaluations.

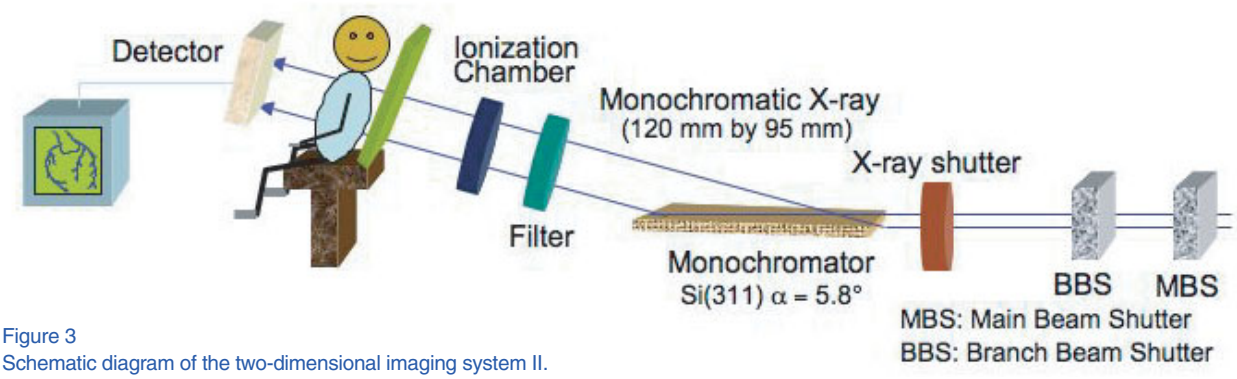

Figure 3
Schematic diagram of the two-dimensional imaging system II.

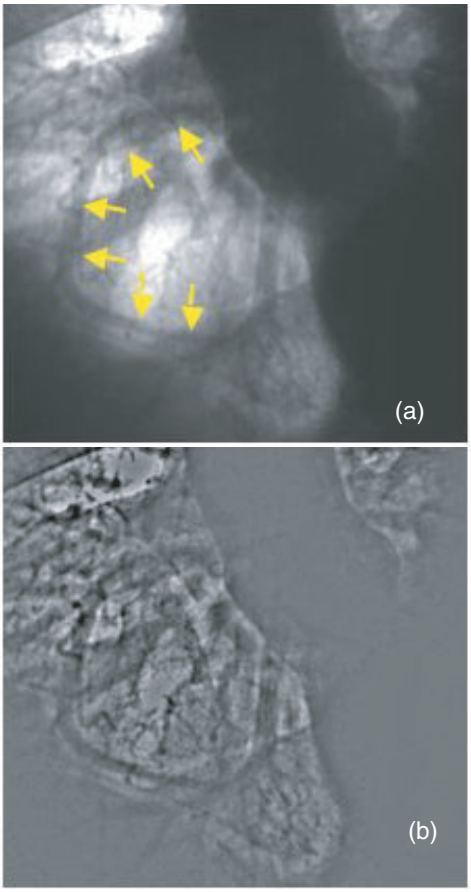

Figure 4
Images of the right coronary artery (arrows). (a) Original image. (b) Digitally filtered image (Univ. of Tsukuba).

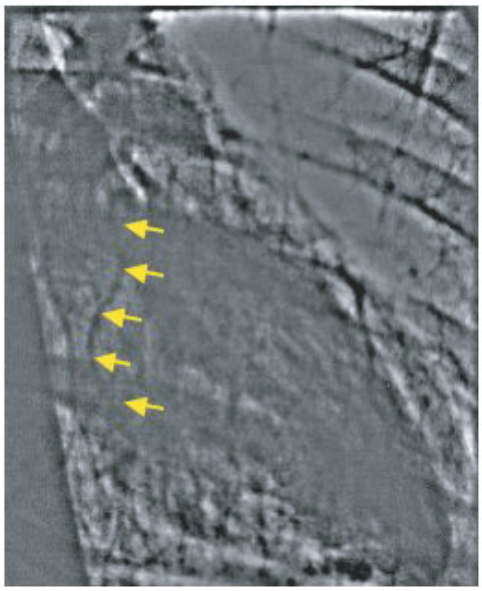

Figure 5
Image of the left coronary artery (arrows) following digital image processing to improve the image quality (Univ. of Tsukuba).

K. Hyodo[1], M. Ando[1], S. Ohtsuka[2], J. Wu[2], T. Takeda[2] and I. Yamaguchi[2] ([1]KEK-PF, [2]Univ. of Tsukuba)

References

[1] *Photon Factory Activity Report* **21A** (2003) 64.
[2] *Photon Factory Activity Report* **21A** (2003) 109.
[3] S. Ohtsuka, K. Hyodo, J. Wu, T. Takeda, A. Maruhashi, I. Yamaguchi and M. Ando, *Nucl. Instrum. Meth. Phys. Res. A*, **548** (2005)73.

9-3 Quantitative Analysis of Amyloid Plaques in a Mouse Model of Alzheimer's Disease by Phase-Contrast X-Ray Computed Tomography

Alzheimer's disease (AD) is the most common cause of dementia and is pathologically characterized by the presence of amyloid plaques. These are composed of densely aggregated β-amyloid (Aβ) peptides which are believed to play a key role in the pathogenesis of AD. Thus, amyloid plaques are a potential target for molecular imaging to determine the clinical status of AD. Phase-contrast X-ray imaging combined with computed tomography (phase-contrast X-ray CT) is a promising technique that allows one to visualize the physical density of structures in biological tissues non-invasively without the use of imaging agents. A cancerous region in rabbit liver has been successfully visualized using this technique [1,2]. It is still unknown, however, whether phase-contrast X-ray CT is capable of detecting and quantifying fine pathological structures such as amyloid plaques. In this study [3], we used brain tissues removed from PSAPP mice, which provide suitable AD models for examining amyloid deposition [4]. We studied whether amyloid plaques could be detected by using a phase-contrast X-ray imaging system fitted with a two-crystal X-ray interferometer [5] at BL-14C1. All experiments were made with the approval of the Animal Ethical Committee of Astellas Pharma Inc. and the special auspice of KEK.

Numerous bright white spots, known as high-density spots, were observed in the PSAPP mouse brain at the age of 12 months (Fig. 6A). To confirm the identity of these bright spots, histological sections of the brain (Fig.

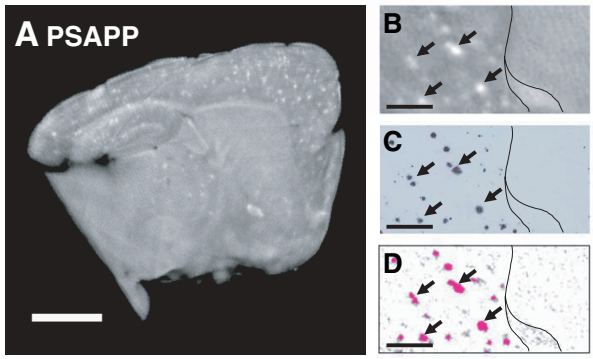

Figure 6
Identification of bright spots observed in phase-contrast X-ray CT. (A) The bright spots observed in the brain of a PSAPP mouse at the age of 12 months using phase-contrast X-ray imaging. Scale bars = 2 mm. (B) Magnified image of bright spots observed in phase-contrast X-ray CT. Black lines indicate the borders of brain subregions. (C) Histological sections corresponding to the area shown in (B), immunostained with Aβ40. The bright spots (arrows; B) correspond to the Aβ40-positive amyloid plaques (arrows; C). (D) Processed image of Aβ spots observed in phase-contrast X-ray CT. Aβ spots are shown in magenta. Scale bars = 0.5 mm (B-D).

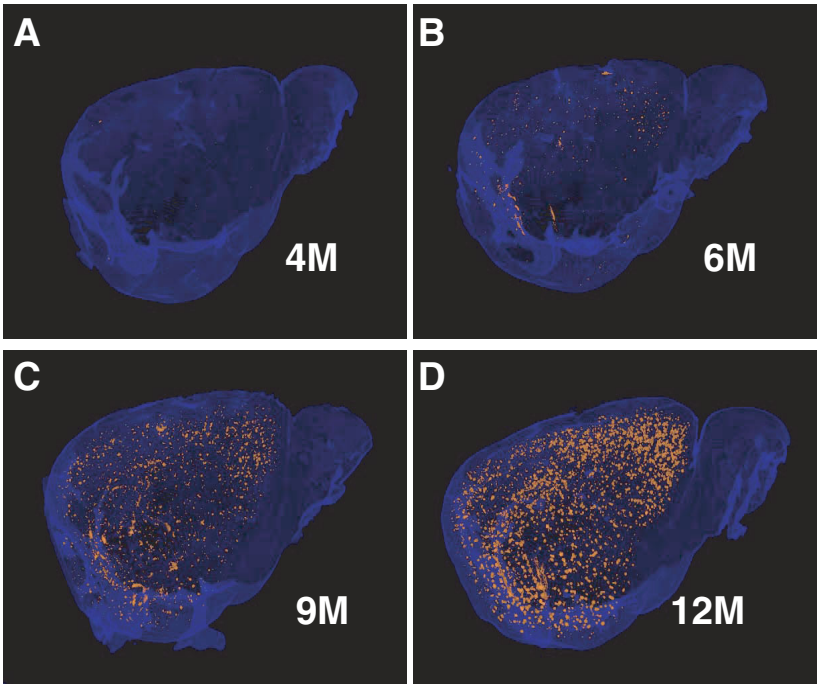

Figure 7
Representative three-dimensional images of Aβ spots (orange) in the brains (cerebral cortex and hippocampus) of PSAPP mice at 4 (A), 6 (B), 9 (C), and 12 (D) months (M) of age.

6B) were prepared after analysis with phase-contrast X-ray CT. A comparison of the phase-contrast X-ray CT images and the corresponding histological sections demonstrated that the bright spots correspond to amyloid plaques (Figs. 6B and 6C). In order to isolate the bright spots from the adjacent background, we determined a threshold based on the density difference between the bright spots and the background ($\Delta\rho$ value). The appropriate threshold value was found to be $\Delta\rho = 2.7$ mg/cm^3. This enabled us to detect the bright spots with a sensitivity comparable to that of histological analyses (Figs. 6C and 6D). The spots above threshold were defined as "Aβ spots".

Finally, we performed a quantitative analysis of Aβ spots in the brains of PSAPP mice at 4, 6, 9, and 12 months of age. The total volume of Aβ spots clearly increases with age (Figs. 7A-D), reaching 0.56 ± 0.04% at 12 months of age.

Our results show that phase-contrast X-ray CT can be used to detect and quantify amyloid plaques with an extremely high spatial resolution comparable to histological analysis, without using any specific probe or contrast agent. This technique has the potential to become valuable for future biomedical research and clinical evaluation especially in the field of AD.

Y. Shitaka[1], K. Noda-Saita[1], A. Yoneyama[2], Y. Hirai[2], K. Hyodo[3] and T. Takeda[4] ([1]Astellas Pharma Inc., [2]Hitachi Ltd., [3]KEK-PF, [4]Univ. of Tsukuba)

References

[1] A. Momose, T. Takeda, Y. Itai and K. Hirano, *Nat. Med.*, **2** (1996) 473.
[2] T. Takeda, A. Momose, K. Hirano, S. Haraoka, T. Watanabe and Y. Itai, *Radiology,* **214** (2000) 298.
[3] K. Noda-Saita, A. Yoneyama, Y. Shitaka, Y. Hirai, K. Terai, J. Wu, T. Takeda, K. Hyodo, N. Osakabe, T. Yamaguchi and M. Okada, *Neuroscience,* **138** (2006) 1205.
[4] L. Holcomb, MN. Gordon, E. McGowan, X. Yu, S. Benkovic, P. Jantzen, K. Wright, I. Saad, R. Mueller, D. Morgan, S. Sanders, C. Zehr, K. O'Campo, J. Hardy, CM. Prada, C. Eckman, S. Younkin, K. Hsiao and K. Duff, *Nature Medicine*, **4** (1998) 97.
[5] A. Yoneyama, T. Takeda, Y. Tsuchiya, J. Wu, T. T. Lwin, A. Koizumi, K. Hyodo and Y. Itai, *Nucl. Instrum. Meth. Phys. Res. A,* **523** (2004) 217.