Clinical development of photoacoustic mammography for the diagnosis of breast cancer

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Purpose

Breast cancer is one of the most common malignant diseases in women. Early detection and diagnosis are essential to decrease the mortality. In addition, as the number of cases of primary systemic therapy (PST) increases, efforts have been made to develop a sensitive method for monitoring the treatment effect. Conventional diagnostic modalities, including X-ray mammography (MMG), ultrasonography (US), and magnetic resonance imaging (MRI), are useful for these purposes, but each has some drawbacks. Optical detection of breast cancer using near-infrared (NIR) light has drawn much attention because it can measure hemoglobin distribution and oxygenation state inside the tissue noninvasively [1]. Angiogenesis is essential for breast cancer growth and also correlated with the malignant potential of precursor lesion [2]. It is known that microvessel density in the cancer tissue significantly decreases in the responders for PST from the early period [3]. Several studies have reported promising results for diffuse optical tomography (DOT) used for differential diagnosis and therapeutic monitoring of breast cancer [4-6]. However, at present, its clinical usefulness seems to be limited due to poor spatial resolution. Photoacoustic tomography is another modality of optical imaging based on photoacoustic technology, which can make an image of hemoglobin distribution and oxygenation state inside tissue with higher spatial resolution than DOT [7, 8]. In this paper, we report early results for the clinical application of PAM and investigate its usefulness for the diagnosis of breast cancer.
Methods and Materials

Instruments

A prototype machine of a dual illuminated mode photoacoustic tomography system (Canon Inc., Tokyo, Japan) was used. Figure 1 shows a photograph of the machine and Figure 2 shows a schematic description of the measurement. The patient-instrument interface was a sliding bed with a hole of 17 cm by 18 cm, which was mounted on the frame housing laser-emitting and ultrasound detection units. The patient lay in a prone position on the bed with her breast placed in the hole. The breast was mildly compressed in a cranio-caudal direction between holding plates. Acoustic coupling gel was used between the breast and the holding plate that carried the scanning system. Pulsed laser beams were irradiated to the breast from both sides and the photoacoustic signals were detected on the caudal side by an array transducer. The lasers were mounted at the bottom of the bed and coupled to the scanning system. A Ti:Sa laser optically pumped with a Q-switched Nd:YAG laser, having a tunable wavelength of 700 to 900 nm. The measurable area was 30 mm by 46 mm for one scan, and the scanning system was automatically moved in an area of 120 mm by 46 mm.
**Fig. 1:** A photograph of the prototype machine: The patient-instrument interface was a sliding bed with a hole of 17 cm by 18 cm. The lasers were mounted at the bottom of the bed and coupled to the ultrasound scanning system.

**References:** Breast Surgery, Kyoto University, Kyoto University Hospital - Kyoto/JP

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**Fig. 2:** A schematic description of PAM measurement: Near-infrared laser pulse was irradiated to the breast and thermoelastic waves produced by absorbers in the breast were detected by ultrasound detectors.

**References:** Breast Surgery, Kyoto University, Kyoto University Hospital - Kyoto/JP

Photoacoustic image reconstruction was carried out using a modified universal backprojection algorithm. Light fluence distribution inside the breast was estimated using the published data of absorption and scattering coefficients (ma and ms') of the breast [9].

Specific parameters of the PAM are as follows:

Laser Wavelength 1064, 825, 797, 756 nm
Pulse width 7 ns
Repetition rate 10 Hz
Detector Matrix shape Rectangular
Number of elements 15 by 23
Element size 2 by 2 mm
Central frequency 1 MHz

The distribution of ma in the breast was calculated from the initial pressure distribution at each wavelength. Oxygen saturation of hemoglobin (SO₂) and total hemoglobin concentration (THC) of the lesions were calculated using ma values at 797 nm and 756 nm. Extinction coefficients of oxyhemoglobin and deoxyhemoglobin were used as 0.231 and 0.259 at 797 nm, and 0.163 and 0.511 at 756 nm, respectively.

Patients

Twenty seven breast lesions of twenty-six cases were studied at Kyoto University Hospital from August 2010 to July 2011. All patients underwent breast surgeries following PAM measurements, and no anti-cancer treatment was given during the interval. The excised specimens were pathologically examined. For assignment of the pathological effect of PST, Histopathological Criteria for Assessment of Therapeutic Response of Japanese Breast Cancer Society were used [10], which assigned the pathological effect as grade 0 (no response) to grade 3 (complete response). Visibility assignment for PAM images was made by a radiologist who specialized in the diagnosis of breast cancer. The study protocol was approved by the Medical Ethical Committee of Kyoto University.
Results

The average age was 58.0 years (36 ~ 83 years), and the tumor size measured by MRI was 20.1 mm (11 ~ 70 mm). Preoperative diagnosis was invasive breast cancer (IBC) in twenty one breasts, including twenty invasive ductal carcinomas (IDC), one invasive lobular carcinoma (ILC), ductal carcinoma in situ (DCIS) in five cases, and phyllodes tumor in one case. Biological subtype of IBC was ER+/HER2- in eighteen lesions, ER-/HER2+ in two, and ER-/HER2- in one. PST was given in 9 out of 21 IBC patients. The tumor was assigned as visible by PAM in 20 out of 27 breasts (74 %), as shown in Table 1.

Table 1. Tumor visibility by PAM images

<table>
<thead>
<tr>
<th>diagnosis</th>
<th>Tumor visibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBC without PST</td>
<td>8 / 12</td>
</tr>
<tr>
<td>IBC after PST</td>
<td>7 / 9</td>
</tr>
<tr>
<td>DCIS</td>
<td>5 / 5</td>
</tr>
<tr>
<td>Phyllodes tumor</td>
<td>0 / 1</td>
</tr>
<tr>
<td>All</td>
<td>20 / 27</td>
</tr>
</tbody>
</table>

IBC: invasive breast cancer, PST: preoperative systemic treatment, DCIS: ductal carcinoma in situ

Table 2 shows the results of IBC cases without PST. Eight out of twelve IBC were visible. Table 3 shows the results with PST. Five out of seven cases showed clinical partial response and pathological therapeutic effect better than grade 2 (marked response). Six cases were assigned as visible in spite of decreased size of tumor after PST.

Table 2. Results in cases of IBC without PST

<table>
<thead>
<tr>
<th>Case</th>
<th>Diameter (MRI)</th>
<th>Diameter (specimen)</th>
<th>Pathological diagnosis</th>
<th>Subtype</th>
<th>Histological grade</th>
<th>PAM visibility</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>15 mm</td>
<td>17 mm</td>
<td>ILC</td>
<td>ER+/HER2-</td>
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<tr>
<td>2</td>
<td>28</td>
<td>21</td>
<td>IDC</td>
<td>ER+/HER2-</td>
<td>2</td>
<td>No</td>
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<tr>
<td>Case</td>
<td>Subtype</td>
<td>Regimen</td>
<td>Clinical Response</td>
<td>Pathological Response</td>
<td>Diam.</td>
<td>PAM visibility</td>
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<td>------</td>
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<td>-----------------------</td>
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<td>----------------</td>
</tr>
<tr>
<td>1</td>
<td>ER+/HER2-</td>
<td>Let</td>
<td>SD</td>
<td>Grade 1a</td>
<td>10 mm</td>
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<tr>
<td>2</td>
<td>ER+/HER2-</td>
<td>Let + CPA</td>
<td>PR</td>
<td>Grade 1b~2a</td>
<td>8, 13</td>
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<td>Let + CPA</td>
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<td>4</td>
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<td>Let + CPA</td>
<td>SD</td>
<td>Grade 2a</td>
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<tr>
<td>Case</td>
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<td>Diameter (specimen)</td>
<td>Pathological diagnosis</td>
<td>PAM visibility</td>
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<td>------------------------</td>
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<tr>
<td>1</td>
<td>30 mm</td>
<td>30 mm</td>
<td>DCIS, intermediate~high grade</td>
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<td>DCIS, high grade</td>
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<td></td>
<td></td>
<td>DCIS, grade</td>
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<td>Phyllodes</td>
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<td></td>
<td></td>
<td>tumor, border line</td>
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</table>

A mean value of SO$_2$ in the visible lesions was 78.6 % (53.7 ~ 100%), and THC was 207 mM (87 ~ 309 mM).

Two particular cases of IBC with or without PST are now presented in detail.

1) IBC without PST (Figure 3, 4)

The patient was a 75-year-old woman with left breast cancer. MRI showed a tumor with ring enhancement with a diameter of 22 mm. Pathological diagnosis was IDC (ER+/HER2+). At PAM measurement, the breast was compressed to a thickness of 58 mm. Figure 3 shows subcutaneous blood vessels by PAM. The value of SO$_2$ ranged from 92.1% to 98.6%. Figure 4 shows a maximum intensity projection (MIP) image of PAM at a depth between 7.75 and 11.5 mm, indicating clustered signals aligned in a ring shape and a linear-shaped signal. These signals were comparable with the MRI findings and considered to represent the tumor and the feeding vessel, respectively. Mean values of SO$_2$ and THC in the areas with these signals were 87.1% and 112 mM, respectively.

![Subcutaneous blood vessels](image)

**Fig. 3:** Subcutaneous blood vessels were clearly shown (depth: 1.5~2.25 mm). The SO$_2$ values ranged from 92.1 % to 98.6 %
Fig. 4: IBC without PST
Upper panel: PAM image showed clustered signals aligned in a ring (dotted circle) and a linear signal (arrow) (depth: 7.75~11.5 mm, breast thickness: 58 mm). These signals were considered to represent the tumor and the feeding vessel, respectively. Mean values of SO2 and THC of the tumor were 87.1% and 112 #M, respectively. Lower panel: MRI showed a tumor with ring enhancement. The dotted square corresponds to the area of the PAM image.

References: Breast Surgery, Kyoto University, Kyoto University Hospital - Kyoto/JP

2) IBC after PST (Figure 5)

The patient was a 41-year-old woman with left breast cancer. The tumor was reduced in size from 34 mm to 22 mm in diameter after six-month treatment with endocrine therapy. Signals in PAM image at a depth of 28.25 mm were comparable with those of MRI image.
Pathological diagnosis was IDC (ER+/HER2-) and the therapeutic effect was assigned as grade 1b (moderate response). Mean values of $\text{SO}_2$ and THC of the two assigned lesions were 74.5 % and 385 mM, and 53.8 % and 307 mM, respectively.

**Fig. 5:** IBC after PST

Upper panel: PAM image showed clustered signals (squared areas A and B). (depth: 28.25 mm, breast thickness: 68 mm). Mean values of $\text{SO}_2$ and THC of the assigned lesions were (A) 74.5 % and 385 #M, and (B) 53.8 % and 307 #M, respectively. Lower panel: MRI showed an enhanced tumor of 22 mm in size. The dotted square corresponds to the area of the PAM image.

**References:** Breast Surgery, Kyoto University, Kyoto University Hospital - Kyoto/JP
Conclusion

PAM could detect 20 out of 26 cases of breast cancer. Notably, the lesions were visible in the cases which showed significant reduction in size after PST or in the cases of DCIS. The tumor images by PAM were comparable with those by MRI or excised specimen. PAM also could provide functional images of tumor vasculature and oxygenation, which cannot be obtained by MMG or US. It was suggested that PAM can be useful for the diagnosis and characterization of breast cancer and its further clinical exploration is promising.
References


