Three-Dimensional Arrangement of Lactiferous Ducts in the Human Nipple Visualized by X-Ray Dark-Field Computed Tomography

Nipple-sparing mastectomy, one of the surgical treatments for breast cancer, has spread rapidly in recent years. However, the three-dimensional (3D) structure of the human nipple, the target of conservation, is not fully understood. In this study, we visualized and analyzed the three-dimensional anatomical structure of the human nipple in detail with X-ray dark-field computed tomography (XDFI-CT), which is a powerful tool for reconstructing the 3D distribution pattern of human lactiferous ducts non-destructively, without contrast agent, and with high tissue contrast.

Nipple-sparing mastectomy (NSM) is a surgical procedure that removes all cancerous or precancerous breast tissue, leaving the nipple, areola, and skin. NSM simultaneously reconstructs the breast, aiming to preserve its preoperative appearance as closely as possible. Many patients desire NSM, but it is known that there is a risk of cancer recurrence in the nipple [1]. In order to improve the treatment results of NSM, interventional techniques such as ductoscopy, ductal lavage, and intraoperative frozen section biopsy for the nipple have been developed. These techniques require three-dimensional anatomical knowledge of the human nipple in detail, but there have been only a few such researches to date.

In this study, to explore the 3D microanatomy of the human nipple, the X-ray dark-field computed tomography (XDFI-CT) technique was used to visualize the internal structure of the nipple. XDFI-CT is a phase-contrast X-ray imaging technique that reconstructs the refractive index distribution proportional to the electron density distribution of an object. XDFI-CT allows the non-destructive visualization of internal structures of soft tissue three-dimensionally with high contrast and a spatial resolution of ten or more μm [2]. XDFI-CT is being intensively studied as an innovative complementary technology that could provide pathologists with 3D information regarding the 2D microscopic images that they observe.

In this study, we examined 51 human nipples by XDFI-CT and visualized the 3D arrangement of the nipple ducts. The XDFI-CT measurement system incorporating a synchrotron radiation X-ray source was constructed at beamline BL-14B. First, we compared CT slice images with conventional hematoxylin-eosin (HE)-stained tissue sections. Next, the number of ducts in the nipple and the number of ducts sharing an ostium near the tip of the nipple were determined by observation of the CT volume. Finally, from 3D rendering of the ducts, we recognized three distinct patterns of ductal arrangement in the nipple.

Figure 1 shows a representative HE-stained tissue section and the corresponding CT slice for one of the samples. In the tissue section, lactiferous ducts with a fold-like structure were identified in the fibrous connective tissue. Each convoluted duct was lined by characteristic mammary epithelium, which was also clearly visualized in the CT images, as well as fluid and protein in the duct lumens and fibromuscular connective tissue. Although some positional deviations caused by subtle gaps in the sampling levels were present between the stained tissue sections and the CT slices, the stained tissue sections and CT slices were mostly structurally compatible. Therefore, we were able to use CT to analyze the tissue structure at the same structural level that is possible by pathological observation.

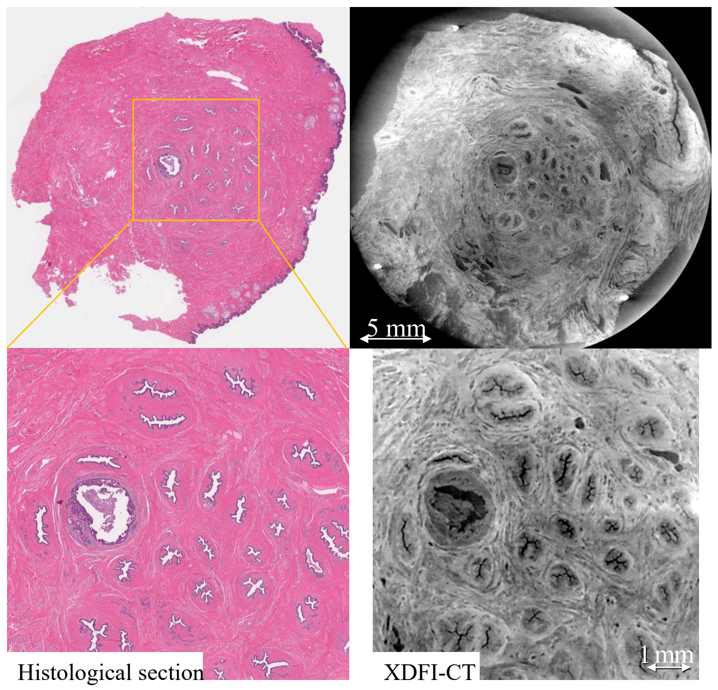

Figure 1: Visualization of the lactiferous ducts in the nipple. Histological section (left), XDFI-CT (right).

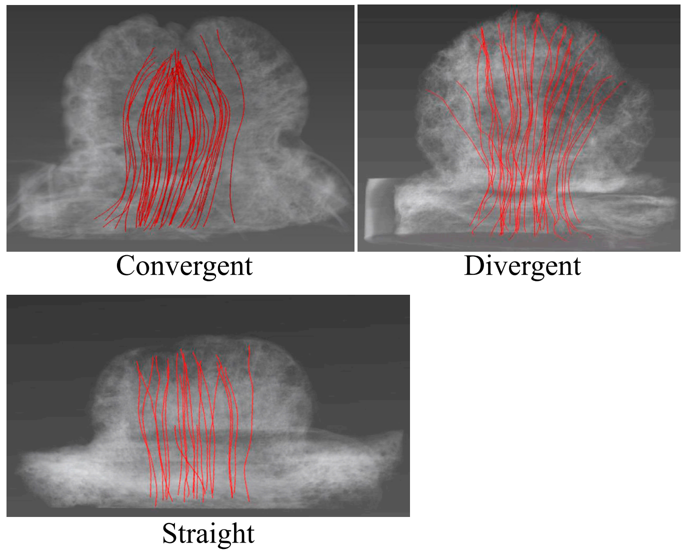

Figure 2: Three types of 3D arrangement of the lactiferous ducts within the nipple.

The number of ducts was counted using CT. In total, 1428 ducts were identified across all 51 samples. The mean, median, and standard deviation of the number of ducts were 28, 27, and 9.14, respectively. The interquartile range and the maximum and minimum range were 21–33 and 14–51, respectively. The total number of ducts sharing an ostium near the tip of the nipple was 525 of 1428 (36.8%). The average number of ostia at which two or more ducts merged in all cases was 3.6.

By observing the structure of the ducts using 3D volume rendering of the 51 samples, we discovered three different types of duct arrangement. **Figure 2** shows typical 3D volume-rendered images of each type selected from among the 51 cases. The three types were: (1) convergent, in which each duct gathered in a bowl shape at the tip; (2) straight, in which each duct extended straight from the areola to the tip; and (3) divergent, in which each duct diverged toward the tip. Based on subjective observation, the 51 cases were classified into 13 (25%) of the convergent type, 19 (37%) of the straight type, and 19 (37%) of the divergent type, indicating that the distribution of ducts near the nipple tip showed marked variation.

According to "sick lobe theory" [3], non-invasive ductal carcinoma (DCIS) begins and spreads within a single mammary lobe. We tested whether the findings of the present study support this theory or not. In one particular sample, three seemingly separate ducts with DCIS converged into a single opening near the tip of the nipple, implying that the three DCIS-ridden ducts were derived from the same cancerous mammary lobe. See reference [4] for more information.

XDFI-CT is a promising non-destructive virtual histology technique not only for analyzing the structure of the nipple but also for scanning other soft tissues or organs. Though there are still some technical limitations to implementing XDFI-CT for diagnostic or exploratory purposes, the approach employed in the present study will become highly relevant once these hurdles are overcome.

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