A Case of a Secretory Carcinoma of the Breast: Radio-Pathological Correlation

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1. Introduction

Secretory carcinoma of the breast is a rare variant (the frequency is below 0.15 %) of breast tumor[1, 2]. It was first described by McDivitt and Stewart in 1966, as a juvenile breast carcinoma as it was thought to occur only in childhood[3]. Subsequently, in 1970 Norris et al.[2] and in 1980 Tavassoli et al.[4] advocated "secretory carcinoma" based on histopathological feature. It is now well known to occur in all age groups. As review of available literature, about 100 cases of secretory carcinoma of the breast has been reported at histopathology[5]. However, its gene expression profiling and the imaging appearances of this carcinoma are not well described. We report the gene expression profiling and the imaging characteristics of the secretory carcinoma of the breast.

2. Case report

The patient had no palpable mass or nipple discharge or axillary lymph node swelling but she was pointed out abnormality in her left breast for the screening of mammography and ultrasonography. She visited our hospital for further examination and medical treatment. Mammography showed multiple iso-density masses with unclear and partly spiculated margin on the mid portion of left Mediolateral-oblique view and inner portion of left Cranio-caudal view (Figure1A, 1B). Ultrasonography revealed multiple nodular hypo-echoic masses measured 67 × 14 mm with high Depth/Width ratio, which suggested a malignant nature (Figure 2). Then HR-MRI on a 1.5-T system using a surface breast coil was performed. Diffusion weighted HR-MR image showed multiple mass-like high signal intensities. Contrast enhanced T1 weighted HR-MR image of early phase showed segmental distribution of multiple nodular mass-like enhancements measured by 60 × 40 mm (Figure 3A, 3B). Thus malignancy was suspected. Non-contrast enhanced T1 weighted image of HR-MRI revealed multiple dot-like high signal intensities in the mass (Figure 3C). Therefore this tumor was thought to contain rich protein or hemorrhage. Fat-saturated T2 weighted image of HR-MRI revealed nodular high signal intensities in the mass (Figure 3D).
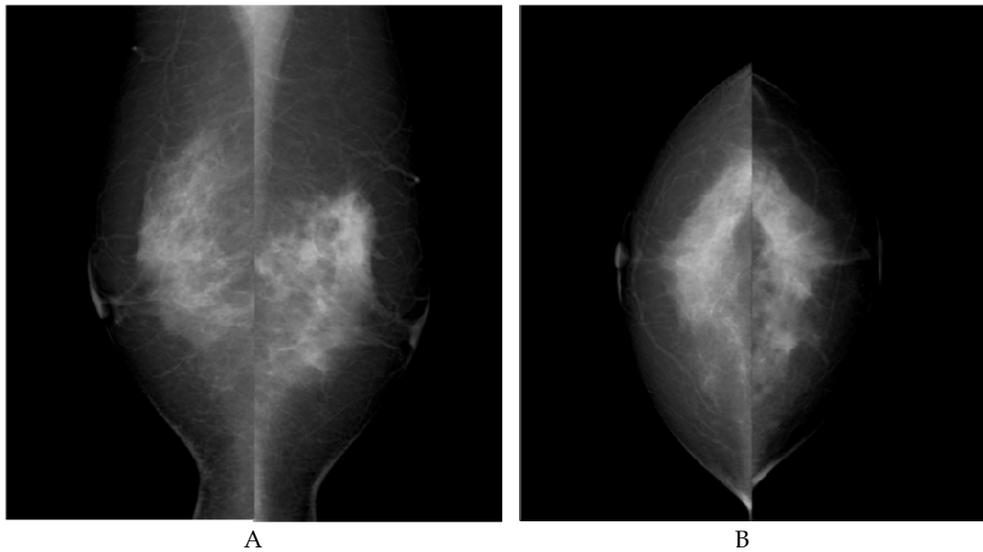
Fig. 1. A. MLO view of mammography, B: CC view of mammography; Multiple iso-density masses with unclear and partly spiculated margin are seen on the mid portion of left MLO view (A) and inner portion of left CCview (B).
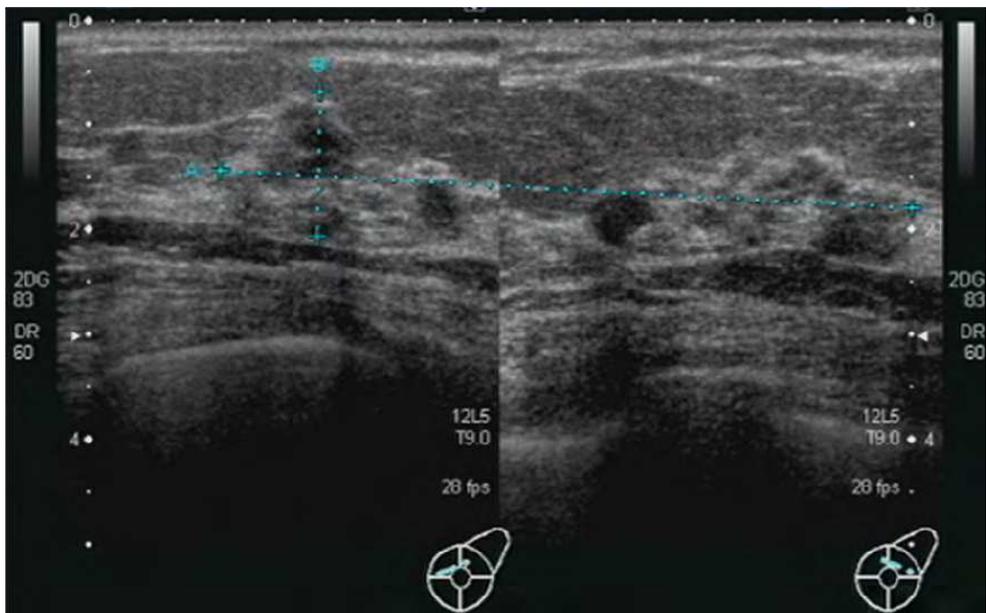
Fig. 2. Ultrasonography of the left breast; Multiple nodular hypo-echoic masses with high Depth/Width ratio are seen and which suggested a malignant nature.
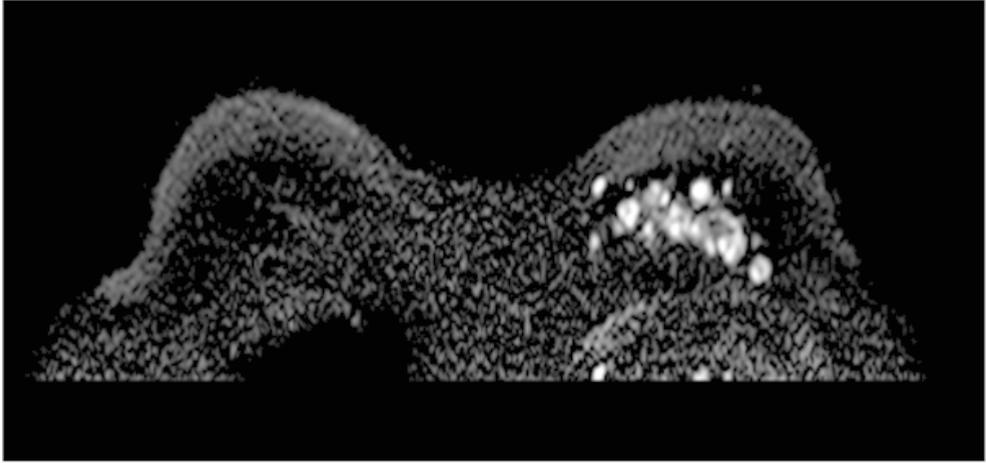
Fig. 3A. Diffusion weighted image of HR-MRI; Multiple mass-like high signal intensities are seen in the left breast.
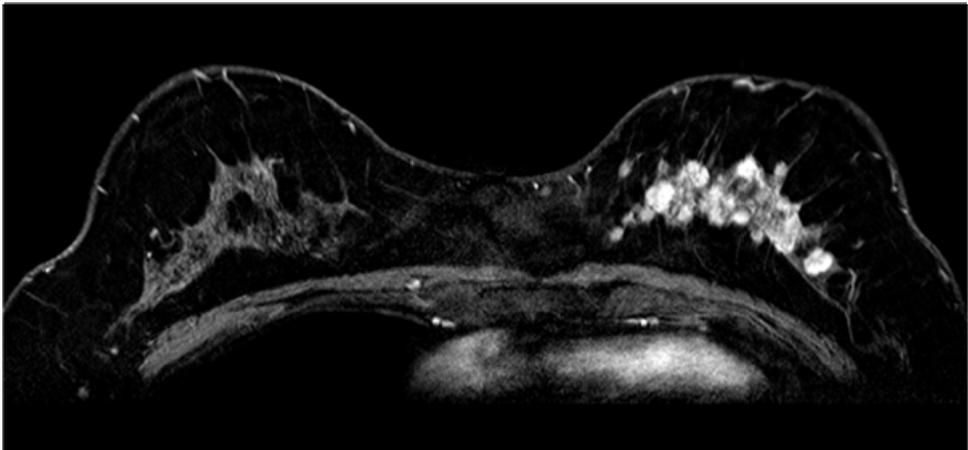
Fig. 3B. Contrast enhanced T1 weighted image on early phase of HR-MRI; Segmental distribution of multiple nodular mass-like enhancements are seen in the left breast. These mass-like enhancements might reflect the nodular growth of the secretory carcinoma.
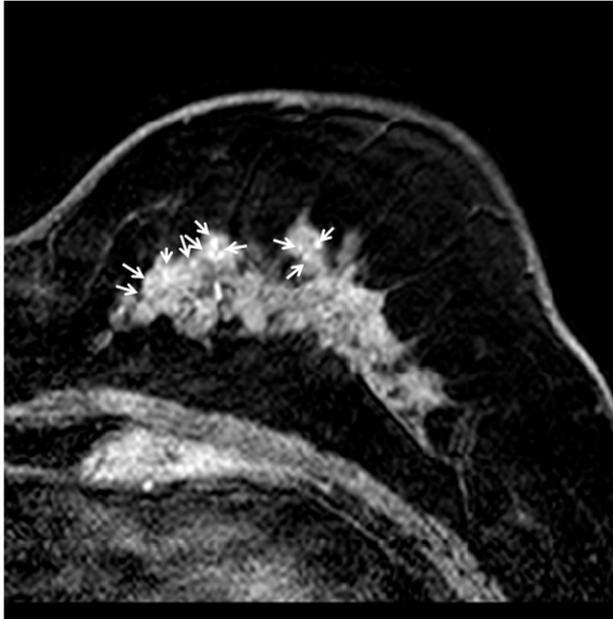
Fig. 3C. Non-contrast enhanced T1 weighted image of HR-MRI; Multiple dot-like high signal intensities are seen on the mass (arrows). These high signal intensities might reflect the secretory material of the secretory carcinoma.
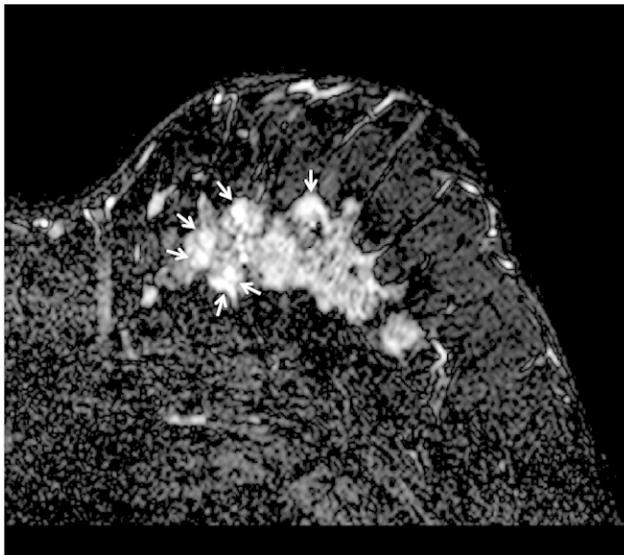
Fig. 3D. Fat-saturated T2 weighted image of HR-MRI; Multiple nodular high signal intensities are seen on the mass (arrows). These high signal intensities might reflect the secretory material of the secretory carcinoma.

Cytology showed typical aggregated forms of tumor cells like bunches of grapes and the cytologic smears revealed grapelike clusters of mucous globular structures (MGSs) and speculated as a secretory carcinoma (Figure 4). Then left mastectomy was performed as a curative operation. Grossly, the tumor measured 6.8 x 4.5 x 2.0 cm and was gray-whitish circumscribed multiple nodular firm mass. And the tumor size was concordant with HR-MR imaging findings. The resected specimen of histopathological feature was microcystic or glandular architecture and composed of cells that produce abundant intracellular and extracellular secretory material, and immunohistochemically the tumor was positive for periodic acid-Schiff (PAS) as well as S-100 protein. The tumor consisted cells of pale-to-clear or eosinophilic cytoplasm, and small, round, low-grade nuclei with inconspicuous nucleoli. The tumor cells showed nodular growth and invasion of the adipose tissue was seen part of the tumor. Hence that was diagnosed a secretory carcinoma (Figure 5A, 5B, 5C, 5D). Secretory carcinoma is associated with a genetic ETV-6-NTRK3 gene fusion leading to a chimeric protein tyrosinase kinase expression, however it was not experimented in the present case.

ER, PgR, and HER2 were all negative and triple negative cancer is suggested in our case. Immunohistochemically, the tumor cells are CK5/6, CK8/18, EGFR, vimentin, and c-kit all positive and our case of secretory carcinoma was considered to have the spectrum of basal-like type in gene expression profiling.
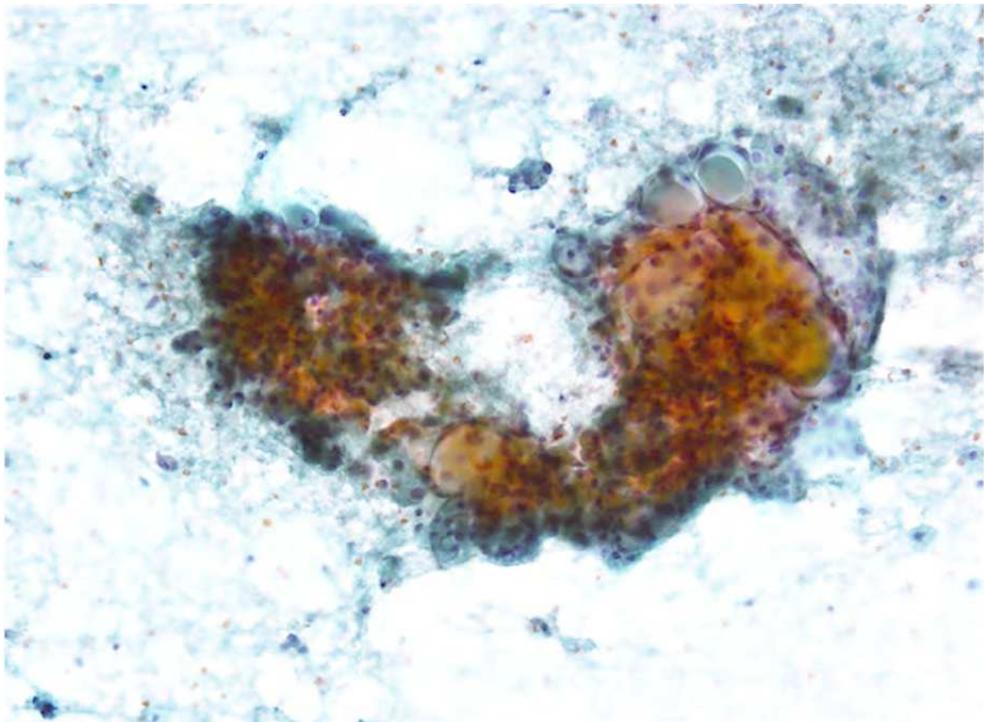
Fig. 4. Cytology of the secretory carcinoma (Papanicolaou stain, x400); Aggregated forms of tumor cells like "bunches of grapes" are seen.
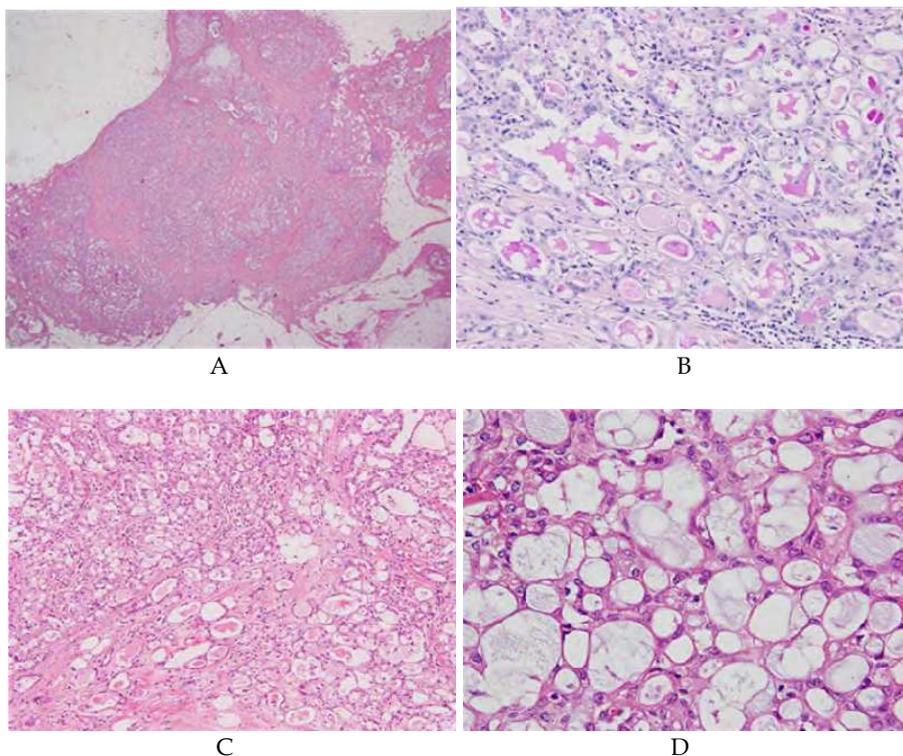
Fig. 5. A: Histology of the secretory carcinoma (Haematoxylin and Eosin stain, ×2); Low magnification view of the secretory carcinoma. The secretory carcinoma of the nodular growth is seen. B: Histology of the secretory carcinoma (Periodic acid-Schiff stain, ×200); Higher magnification view of the secretory carcinoma. The secretory material of the secretory carcinoma is positive for Periodic acid-Schiff stain. C, D: Histology of the secretory carcinoma (Figure 5C; Haematoxylin and Eosin stain ×100, Figure 5D; Haematoxylin and Eosin stain, ×400); Higher and high magnification view of the secretory carcinoma. The carcinoma cells arranged microcystic or glandular architecture and abundant intracellular and extracellular secretory material is seen.

3. Discussion

Secretory carcinoma of the breast is a rare but histopathologically distinct variant of invasive ductal carcinoma that thought to be indolent growth pattern and a more favorable prognosis than that of typical ductal carcinoma[6]. The frequency is thought to be below 0.15 % of all breast tumors[1, 2]. In our hospital, the frequency was 0.05 %.

By using DNA microarray techniques, it has been shown that breast cancers can be classified into biologically distinct groups based on their gene expression profiles. These groups comprise luminal A (ER positive and HER2 negative), luminal B (ER and HER2 positive), ERBB2 (ER negative and HER2 positive), and triple negative (ER and HER2 negative) subtypes[7]. Our case was ER, PgR and HER2 negative, hence the triple negative cancer is

suggested. The triple negative cancer is a heterogeneous group and is further categorized into the basal-like and the normal breast subtypes, which are positive and negative, respectively, for myoepithelial/basal markers such as basal CKs. The consensus criteria for the basal-like subtype which has been reported is as follows. Nielsen et al. suggested four representative surrogate markers for the basal-like subtype: ER, HER2, EGFR, and CK5/6[8]. Other additional criteria used for the basal-like subtype comprise (1) ER negativity and HER2 negativity, and vimentin, EGFR, CK8/18, and/or CK5/6 positivity, and (2) triple negativity, and CK5/6 and/or EGFR positivity[7]. Other markers that have been included in the myoepithelial/basal biomarkers are laminin[9, 10], c-kit[11], p63[12], nestin[13], osteonectin[14], caveolin 1[15]. In the present case, the tumor cells were CK5/6, CK8/18, EGFR, vimentin, and c-kit all positive and our case of secretory carcinoma was considered to have the spectrum of basal-like type in gene expression profiling. Lae et al reported that secretory carcinomas in woman were ER negative, PgR negative and HER2 negative, so called triple negative[16]. The tumors were also reactive for S100 and E-cadherin and focally for CK8/18 and CK5/6[16]. Our case was compatible with the report of Lae et al.. Secretory carcinoma has been reported as low-grade carcinoma, however our case suggests that not always a secretory carcinoma is low-grade carcinoma. Triple negative cancer is considered to be a clinicopathological entity with aggressive behaviors and poor prognosis. Our case suggests that the secretory carcinoma of the breast should need careful therapeutic follow up.

Here we will discuss about the imaging features of the secretory carcinoma. Mammography of a secretory carcinoma usually reveals a discrete tumor with smooth or irregular borders[17]. Also, our case of mammography showed multiple iso-density masses with unclear and partly spiculated margin and this finding was not specific for the entity of a secretory carcinoma. On ultrasonography, secretory carcinoma of the breast is frequently shown as a small benign-looking nodule or group of nodules with low clinical stage[18]. And secretory carcinoma of ultrasonographic appearance is a solid, well-circumscribed mass and is not specific for this entity and mimics benign entities such as fibroadenoma, as well as other well-differentiated breast carcinomas[19]. Ultrasonography of the present case revealed multiple nodular hypo-echoic masses measured 67×14 mm with high Depth/Width ratio, which suggested a malignant nature, however was not specific for a secretory carcinoma. It is not well known that the HR-MR imaging feature of secretory carcinoma of the breast. However, in our case, dot-like high signal intensities within the mass were observed on T1 and high signal intensities on T2 weighted images on HR-MRI and additionally nodular multiple mass-like early enhancements were seen on contrast enhanced HR-MR imaging. Therefore this tumor was thought to contain rich protein or hemorrhage. The rich protein lesions reveal high signal intensity not only T1 weighted image but also T2 weighted image on HR-MR imaging by the concentration of protein[20, 21, 22]. Dot-like high signal intensities on T1 weighted image and nodular high signal intensities on fat-saturated T2 weighted image of HR-MRI might correspond to the groups of intracellular and extracellular secretory milk-like material of the secretory carcinoma (Figure 3C, 3D, 5C, 5D). And mass-like early enhancements on contrast enhanced T1 weighted HR-MR image might correspond to the nodular growth of the secretory carcinoma (Figure 3B, 5A). Moreover, these findings of dot-like high signal intensities on T1 weighted image with the distribution of scattered within the mass and high signal intensities on T2 weighted image of HR-MRI besides mass-like early enhancement on contrast enhanced T1 weighted HR-MR images are thought to be one of the imaging features of secretory carcinoma of the breast. Differential diagnoses of the

secretory carcinoma on imaging characteristics including HR-MRI might theoretically be mucinous carcinoma of pure and mixed forms, sarcomas (angiosarcoma, myxofibrosarcoma and so on), and matrix-producing carcinoma as concerning about mucinous or rich protein lesion, and invasive ductal carcinoma with hemorrhage and angiosarcoma as concerning about hemorrhage on HR-MR images. Mucinous carcinoma of pure and mixed forms might typically reveal lobulated shape and very high signal intensity on T2 weighted images, and a pattern of gradual enhancement or heterogenous enhancement on dynamic HR-MR images[23]. And the most common appearance of mucinous carcinoma is a hypo-echoic lesion with heterogenous internal echo on ultrasonography[24]. Matrix-producing carcinoma might typically reveal hypo- or high-echoic zone in the tumor on ultrasonography and ring-shaped enhancement on contrast enhanced HR-MRI with high signal intensity in the central area of the tumor on T2 weighted imaging[25]. Angiosarcoma might typically reveal both a high- and hypo-echoic lesion without acoustic shadow on ultrasonography[26], and HR-MRI of angiosarcoma might reveal low intensity tumor on T1 weighted images, markedly high intensity on T2 weighted images and prolongation of enhancement on the dynamic study and the presence of multiple regions without enhancement in the tumor[27]. Sarcomas might contain mucinous lesion, however the distribution of mucin might not be typically dot-like and scattered in the mass on T1 weighted image of HR-MRI. Invasive ductal carcinoma with hemorrhage and angiosarcoma might have hemorrhagic lesion and sometimes reveal high signal intensity on T1 weighted image of HR-MRI, however their distribution might rarely be scattered in the mass on T1 weighted image of HR-MRI.

In conclusion, these findings of dot-like high signal intensities on T1 weighted image with their distribution of scattered within the mass and high signal intensities on T2 weighted image of HR-MRI besides mass-like early enhancement on the dynamic HR-MR image are thought to be one of the imaging features of secretory carcinoma of the breast. And our findings of HR-MR images might be helpful to diagnose the secretory carcinoma of the breast on HR-MR imaging.

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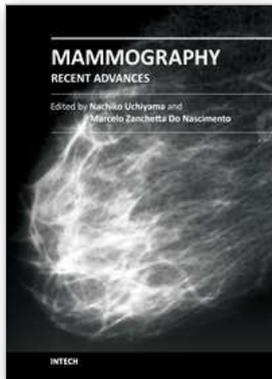
Mammography - Recent Advances

Edited by Dr. Nachiko Uchiyama

In this volume, the topics are constructed from a variety of contents: the bases of mammography systems, optimization of screening mammography with reference to evidence-based research, new technologies of image acquisition and its surrounding systems, and case reports with reference to up-to-date multimodality images of breast cancer. Mammography has been lagged in the transition to digital imaging systems because of the necessity of high resolution for diagnosis. However, in the past ten years, technical improvement has resolved the difficulties and boosted new diagnostic systems. We hope that the reader will learn the essentials of mammography and will be forward-looking for the new technologies. We want to express our sincere gratitude and appreciation?to all the co-authors who have contributed their work to this volume.

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