Breast cancer is a kind of prevalent disease among women in all over the world, especially western and industrialized countries, with an incidence of about 180,000 new diagnoses each year in the United States alone [1]. The mortality rate of breast cancer is currently estimated at about 26 per 100,000 annually [2]. A successful treatment for this disease was determined, in part, by early diagnosis. Thus, some effective screening methods have been performed, including ultrasonography, mammography and magnetic resonance imaging (MRI).

MRI has been increasingly used as a secondary characterizing tool [3]. Recent advances dynamic contrast-enhanced (DCE) MRI of the breast has demonstrated improved sensitivity for detection of breast cancer compared to x-ray mammography, particularly in settings problematic for the latter such as the dense, augmented, irradiated or post-surgical breast [4–7], suggesting the potential of MRI to become both highly sensitive and highly specific in breast cancer diagnosis [8, 9].

In contrast to the structural information provided by MRI, in vivo proton magnetic resonance spectroscopy (1H MRS) provides a qualitative analysis of a number of chemical content within breast lesions, and performs a quantitative analysis if a reference of known concentration is used [10–19]. These metabolites reflect aspects of cell integrity, cell membrane proliferation or degradation, energy metabolism and necrotic transformation of breast or tumour tissue.

Molecular causes of appearance of 1H MRS in breast lesions

The first breast 1H MRS reports focused on the diagnostic utility of the water: fat ratio in the breast lesions [20–22], but subsequent studies did not find this ratio to be a useful diagnostic criterion [15, 19]. However, recent many studies performed with 1H MRS noted that a resonance from choline-containing compounds (tCho) was commonly present in malignant lesions but not in benign or normal tissues [13–16, 18, 19, 21]. Analysis of early pooled clinical experience with in vivo 1H MRS yielded a sensitivity and specificity for detection of breast cancer of 83% and 85%, respectively [23]. However, the precise mechanisms that produce an elevated tCho concentration ([tCho]) have not yet been fully identified.

Choline (Cho), consisting of free, phospho-, glycerophospho- and phospholipid- choline, is a classic in vivo biomarker for cellular proliferation, which participates in cell membrane transportation and diffusion and involves in multiple metabolic pathways. Choline concentration cannot be detected in normal human mammary epithelial cells (HMECs), and becomes higher in lactation than do in the others physical period. Breast cancer cells contain at least 10 times more phosphocholine than do normal mammary epithelial cells [24]. Breast cancer cells exhibited increased phosphocholine, total choline-containing metabolites, and significantly decreased glycerophosphocholine compared with HMECs [25–27]. The study of Glunde et al found that decreased 13C-enrichment was detected in choline and phosphocholine of breast cancer cells.
compared with HMECs, indicating a higher metabolic flux from membrane phosphatidylcholine to choline and phosphocholine in breast cancer cells. Choline kinase and phospholipase C were significantly overexpressed, and lysophospholipase 1, phospholipase A2, and phospholipase D were significantly underexpressed, in breast cancer cells compared with HMECs [25]. In vitro MRS of breast cell lines confirms that Cho levels increase with progression from normal to immortalized to oncogene-transformed to tumor-derived cells [28]. With progression to malignant phenotype, HMECs show an increase in phosphocholine (PC) and total choline-containing compounds, as well as a switch from high glycerophosphocholine (GPC) / low PC to low GPC / high PC. Alterations in choline membrane metabolism in malignant breast cancer cells and nonmalignant are detected by in vivo 1H MRS.

**Application of 1H MRS in breast lesions**

**Differentiated diagnosis between benign and malignant breast lesions**

To date, it is a research focus to distinguish benign from malignant breast lesions before biopsy. Conventional mammography has been the primary screening and diagnostic tool for breast cancer for more than 20 years. Although mammography has high sensitivity for malignancy, it has poor specificity reported in the range of 60%–80%. In recent years, results of many studies have shown that the noninvasive techniques of magnetic resonance (MR) imaging have strong potential to improve sensitivity and specificity in the diagnosis and evaluation of breast cancer. Especially, DCE MR imaging is now an integral part of a proposed standard diagnostic protocol for breast cancer due to its excellent sensitivity (88%–100%). However, specificity of DCE MR imaging has been variable, ranging from 37% to 97%, and there is considerable overlap in response between benign and malignant lesions. For example, fibroadenomas sometimes demonstrate an enhancement pattern similar to that of invasive cancer.

1H MRS by use of the composite choline signal is highly reported as a useful diagnostic tool for distinguishing malignant from benign breast lesions [13–16, 18, 19, 23]. Roebuck and colleagues first proposed the idea that total Cho could be used as a marker of malignancy [15]. Several papers followed consistent results, while performed studies with somewhat different techniques [13-16, 18, 19, 23]. Katz-Brull and colleagues published a pooled analysis and reported an overall sensitivity of 83% and specificity of 85%, with near 100% for both in a subgroup of young women [29]. Whereas, a composite choline signal in 1H MRS was also found in normal breast tissue of lactating women [14]. The state of lactation is associated with increased choline metabolism because of the need to nourish the newborn with large amounts of choline supplied in the milk predominantly as phosphatidylcholine, phosphocholine, glycerophosphocholine, and free choline [30]. Breast 1H MRS, therefore, is not suitable for differentiating malignant from benign breast tumors in lactating women. However, the unique state of lactation is rarely associated with breast malignancy. Some benign lesions, such as fibroadenomas [8, 9, 13, 18], were also found a detectable tCho signal at 1.5 T MRI.

It is a problem how to improve the specificity of diagnostic breast lesions in 1H MRS. Several reports points out that a combined MR protocol can improve diagnostic specificity of breast lesions [13, 24, 31, 32]. Meisamy et al reported that adding quantitative MRS results to a DCE-MRI exam produced improvements in the sensitivity, specificity, and accuracy for all readers, and improved the interobserver agreement between the readers [24]. Huang and colleagues, appending a single-voxel MRS measurement and a single-slice T2*–weighted perfusion measurement to a conventional DCE-MRI exam, found that the addition of MRS increased the specificity of the exam from 62.5% to 87.5%, and the further addition of the perfusion measurement raised the specificity to 100% [32].

**Detecting metastasis in axillary lymph nodes**

Evaluation of axillary lymph nodes in breast cancer should be worth of attaching importance. For many patients with proved breast cancer who would have to undergo complete axillary lymph node dissection, however, the development of noninvasive procedures that enabled reliable detection of axillary lymph node metastases would not only help to reduce the risks of axillary dissection complications [33] but also help to determine the best treatment strategy. Although gadolinium-enhanced MR imaging has a good positive predictive value in the detection of lymph node metastases, it cannot be used to exclude positive nodes [34]. A study of in vitro MRS that assesses breast cancer metastases in axillary nodes revealed the levels of the glycerophosphocholine–phosphocholine (GPC–PC), choline, lactate, alanine and uridine diphosphoglucose were elevated significantly in nodes with metastases. Moreover, the intensity ratio of GPC–PC/threonine (Thr) was higher in nodes with metastases, and using this as marker, MRS detected the axillary metastases with a sensitivity, specificity and accuracy of 80%, 91% and 88%, respectively [35]. The study of Yeung et al first observed that in vivo 1H MRS of axillary lymph nodes to be feasible and that tCho could be reliably detected in metastatic nodes by sensitivity of 82%, specificity of 100%, and accuracy of 90% in patients with breast cancer [36].

**Early assessment of treatment response and prediction of prognosis**

At present, primary systemic therapy (PST), also