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(54) **MAGNETIC RESONANCE SPECTROSCOPY OF BREAST BIOPSY TO DETERMINE PATHOLOGY, VASCULARIZATION AND NODAL INVOLVEMENT**

MAGNETISCHE RESONANZ-SPEKTROSKOPIE EINER BRUST-BIOPSIE ZUR BESTIMMUNG EINER PATHOLOGIE, DES FALLES EINER VASKULARISIERUNG ODER DES FALLES EINER NODALEN BETROFFENHEIT

SPECTROSCOPIE PAR RESONANCE MAGNETIQUE DE BIOPSIE DU SEIN POUR UNE EVALUATION DE LA PATHOLOGIE, DE LA VASCULARISATION ET DE L'ATTEINTE GANGLIONNAIRE

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• **SOMORJAI, Rajmund, L.**
Headingly, Manitoba R0H 0J0 (CA)

(30) Priority: **18.10.1999 US 160029 P**

(74) Representative: **Lawrence, John et al**
Barker Brettell,
138 Hagley Road,
Edgbaston
Birmingham B16 9PW (GB)

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(73) Proprietors:
• **NATIONAL RESEARCH COUNCIL OF CANADA**
Ottawa,
Ontario K1A 0R6 (CA)
• **Institute for Magnetic Resonance Research**
St. Leonards NSW 1590 (AU)

(72) Inventors:
• **MOUNTFORD, Carolyn**
East Ryde, NSW 2113 (AU)
• **RUSSELL, Peter**
Pymble, NSW 2073 (AU)
• **SMITH, Ian, C., P.**
Winnipeg, Manitoba R3R 2H2 (CA)

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Description

BACKGROUND OF THE INVENTION

5 1. Technical Field of the Invention

[0001] The present invention relates to the use of magnetic resonance spectroscopy, and more particularly to such use for determining pathology, vascularization and nodel involvement of a biopsy of breast tissue.

10 2. Description of the Related Art

[0002] Within this application several publications are referenced by arabic numerals within parentheses. Full citations for these and other references may be found at the end of the specification immediately preceding the claims.

15 **[0003]** Clinical evaluation, mammography and aspiration cytology or core biopsy (triple assessment) is undertaken on women presenting with breast lesions in most Western countries. Clinical assessment of palpable breast lumps is unreliable (1, 2). Impalpable lesions are usually discovered by screening or diagnostic mammography, which has a reported sensitivity of 77-94% and a specificity of 92-95% (3). Cytological assessment of fine needle aspiration biopsies (FNAB) has sensitivities ranging from 65-98% and specificities ranging from 34-100% (4) depending on the skill of the person performing the aspiration and the expertise of the cytopathologist.

20 **[0004]** Following surgical excision of the lesion a time consuming process of preparation and pathological assessment of the specimen determines the nature of the tumour and the prognostic features associated with it.

SUMMARY OF THE INVENTION

25 **[0005]** Magnetic resonance spectroscopy (MRS) is a modality with a proven record in the diagnosis of minimally invasive malignant lesions (5-11). MR spectra of small samples of tissue or even cell suspensions enable the reliable determination of whether the tissue of origin is malignant or benign. Often MRS is able to detect malignancy before morphological manifestations are visible by light microscopy (8).

30 **[0006]** The potential of proton MRS from FNAB specimens to distinguish benign from malignant breast lesions has been demonstrated previously (12). At that time the MRS method relied on visual reading to process spectra and calculate the ratio of the diagnostic metabolites choline and creatine. This spectral ratio allowed tissue to be identified as either benign or malignant. In a small cohort of 20 patients within that study is also distinguished high grade ductal carcinoma *in situ* (DCIS) with comedonecrosis or microinvasion from low grade DCIS. Despite the limitation of visual inspection which could only access those spectra with a signal to noise ratio (SNR) of greater 10, the visual method resulted in a diagnosis of malignant or benign with a sensitivity and specificity of 95 and 96%. Figure 1 shows malignant and benign spectra with good SNR while Figure 2 shows spectra with poor SNR.

35 **[0007]** Twenty percent of the spectra were discarded because low aspirate cellularity yielded inadequate SNR. In the initial study visual analysis used only two of fifty or more available resonances (6). Thus, potentially diagnostic and prognostic information in the remaining spectrum may have been ignored.

40 **[0008]** A 3-stage robust statistical classification strategy (SCS) has been developed to classify biomedical data and to assess the full MR spectrum obtained from biological samples. The robustness of the method has been demonstrated previously with the analysis of proton MR spectra of thyroid tumours (13), ovarian (14), prostate (9), and brain tissues (15). The present invention applies SCS with enhancements to assess proton MR spectra of breast aspirates against pathological criteria in order to determine the correct pathology on samples with sub-optimal cellularity and: SNR and to determine if other diagnostic and prognostic information is available in the spectra.

45 **[0009]** In reference (14) to Wallace et al., an earlier version of SCS was used to analyze the spectra of ovarian tissues to detect cancer from normal tissue. Even though this reference describes use of an SCS step, it did not employ a cross-validation step which selected a first portion of the spectra from each class, and also repeating the cross-validation step a plurality of times to obtain optimized LDA coefficient for each of said plurality of times using different portions of the spectra for each of said "first portions", and then obtaining a weighted average of the LDA coefficients from the results of the repeating step to obtain final classifier spectra.

50 **[0010]** The inventors have determined that SCS on MRS from breast FNAB is more reliable than visual inspection to determine whether a lesion is benign or malignant, and that a greater proportion of spectra is useful for analysis. Furthermore, spectral information obtained from MRS on FNAB of breast cancer specimens predicted lymph node metastases (overall accuracy of 96%) and vascular invasion (overall accuracy of 92%).

55 **[0011]** According to a first aspect of the invention, there is provided a method for determining the classification of a characteristic of breast tissue comprising obtaining magnetic resonance spectra of a biopsy of breast tissue having unknown classification of a characteristic and comparing spectra with a classifier, said classifier having been obtained by:

(a) locating a plurality of discriminatory subregions in magnetic resonance spectra of biopsies of breast tissue having known classifiers of a characteristic;

5 (b) cross-validating the spectra by selecting a first portion of the spectra from each class of a characteristic, developing linear discriminant analysis classifiers from said first portion of spectra from each class and validating the remainder of the spectra from each class using the classifiers from the first portion of the spectra from each class, to obtain optimized linear discriminant analysis coefficients,

10 (c) repeating step (b) a plurality of times each time selecting as the first portion of the class a different portion of the spectra from each class to obtain a different set of optimized linear discriminant analysis coefficients for each of said plurality of times;

15 (d) obtaining an average of the linear discriminant analysis coefficients to obtain final classifier spectra indicating the classification of the characteristic based on the spectra; and

(e) wherein spectra from a biopsy of breast tissue of unknown classification of a characteristic may be compared to the final classifier spectra to determine the classification of the characteristic of the breast tissue.

20 **[0012]** According to a second aspect of the invention, there is provided an apparatus for determining the classification of a characteristic of breast tissue, comprising a spectrometer for obtaining magnetic resonance spectra of a biopsy of breast tissue having unknown classification of a characteristic, a classifier for statistically classifying the spectra by comparing the spectra with a reference classifications, said classifier being obtained by:

25 (a) a locator for locating a plurality of discriminatory subregions in magnetic resonance spectra of biopsies of breast tissue having known classifiers of a characteristic of breast tissue,

30 (b) a cross-validator for selecting a portion of the spectra from each class of a characteristic, developing linear discriminant analysis classifiers from said first portion of spectra, and validating the remainder of the spectra using the classifiers from the first portion of the spectra, to obtain optimized linear discriminant analysis coefficients, and developing and validating a plurality of times each time selecting a different portion of the spectra to obtain a different set of optimised linear discriminant analysis coefficients for each of said plurality of times, and

35 (c) an averager for obtaining an average of the linear discriminant analysis coefficients to obtain final classifier spectra indicating the classification of the characteristic based on the spectra, whereby spectra from a biopsy of breast tissue of unknown classification of a characteristic may be compared to the final classifier spectra to determine the classification of the characteristic of the breast tissue.

DESCRIPTION OF THE DRAWINGS

40 **[0013]**

Figure 1 shows malignant and benign spectra with relatively good SNR;
Figure 2 shows spectra with relatively poor SNR; and
Figure 3 shows a system for determining pathology, vascularization and nodal involvement according to the invention.

DETAILED DESCRIPTION OF THE INVENTION

METHODS

50 Preparation of patients:

55 **[0014]** Intra-operative FNAB were taken from 139 patients undergoing breast surgery for malignant and benign conditions (Table 1) by three surgeons in separate hospitals. In order to provide a sufficiently large data set for SCS an additional 27 patients joined the study (see Table 1). Impalpable breast lesions that had been localised by carbon track or hook wire were included except if the lesion was not palpable at excision or when the pathology specimen could have been compromised. All samples were taken during surgery under direct vision after the lesion had been identified and incised sufficiently widely to ensure that the FNAB and tissue specimens represented the same lesion and were thus comparable. The lesion was identified and incised *in-vivo* via the margin with the greatest apparent depth of normal

tissue between it and the lesion to ensure the pathologist could report upon the lesion according to a standard protocol. Malignant and suspicious lesions were orientated with sutures and radio opaque vascular clips (Ligaclips) for pathological and radiological orientation. The FNAB was collected by the surgeon using a 23-gauge needle on a 5ml syringe. The number of needle passes was recorded and the surgeon's evaluation of the quality of the aspirate was made. Before the needle was removed from the lesion, a tissue sample including the relevant part of the needle track was taken. The size of this tissue specimen was estimated and recorded by the surgeon.

[0015] Pre-operative clinical and investigative data included localised pain, nipple discharge or nipple crusting, details of previous mammography, and whether the lesion was detected through screening. The clinical, mammography, ultra sonographic, cytological, core biopsy and MRI details were recorded as malignant, suspicious, benign, impalpable, uncertain or not done.

[0016] The pathology specimen was sent on ice at the initial stages, but later in formalin, for standard histopathological reporting and hormone receptor analysis. The pathology report was issued in synoptic format (16).

[0017] Specific tumour-related clinical and sampling information was collected. These included a history of previous breast biopsies with dates, diagnoses, sizes and sites of these lesions along with the current lesion's duration, palpability, laterality, size and locality within the breast. The date of operation, the extent of breast surgery from open biopsy to total mastectomy, and axillary surgery from sampling to level 3 dissection was recorded.

Specimen preparation:

[0018] Following complete excision of the lesions the FNAB cytology and tissue specimens were placed in polypropylene vials containing 300ml phosphate-buffered saline (PBS) in D₂O. All specimens were immediately immersed in liquid nitrogen and stored at -70°C for up to 6 weeks until MRS analysis.

[0019] Prior to the proton MRS experiment, each FNAB specimen was thawed and transferred directly to a 5 mm MRS tube. The volume was adjusted to 300ml with PBS/D₂O where necessary. Proton MRS assessment of all specimens was performed without knowledge of the correlative histopathology, either from the synoptic pathology report or from sectioning of tissue used in MRS study.

[0020] The sample of tissue excised around the needle tract was similarly placed in polypropylene vials containing 300ml PBS/D₂O and immersed in liquid nitrogen as described above. This sample was later used for pathological correlation.

Data acquisition:

[0021] MRS experiments were carried out on a Bruker Avance 360 wide-bore spectrometer (operating at 8.5 Tesla) equipped with a standard 5 mm dedicated proton probehead. The sample was spun at 20 Hz and the temperature maintained at 37°C. The residual water signal was suppressed by selective gated irradiation. The chemical shifts of resonances were referenced to aqueous sodium 3-(trimethylsilyl)-propanesulphonate (TSPS) at 0.00 ppm. One-dimensional spectra were acquired over a spectral width of 3597 Hz (10.0 ppm) using a 90° pulse of 6.5 - 7 μs. 8192 data points. 256 accumulations and a relaxation delay of 2.00 seconds, resulting in a pulse repetition time of 3.14 seconds.

[0022] SNR was determined using the Bruker standard software (xwinmr). The noise region was defined between 8.5 to 9.5 ppm. The signal region was defined between 2.8 to 3.5 ppm.

Histopathology:

[0023] Diagnostic correlation was obtained by comparing spectral analysis with the hospital pathology report provided for each patient. Lymph node involvement and vascular invasion were determined from the reports only in cases where this information was complete. In the participating hospitals lymph nodes were embedded and serial sectioned in standard fashion. One 5μm section out of every 50 (i.e.. each 250μm) was stained and examined. All intervening sections were discarded.

[0024] In the initial phase of the study, cytological analysis of the aspirate after MRS analysis was attempted but cellular detail was compromised by autolytic changes and this approach was not pursued. In order to verify FNAB sampling accuracy, a separate histopathological assessment by a single pathologist (PR) was obtained from tissue removed from the aspiration site of the MRS sample. Tissue specimens were thawed, fixed in FAA (formalin/acetic acid/alcohol), paraffin-embedded, sectioned at 7 μm. stained with haematoxylin and eosin according to standard protocols and reviewed under the light microscope by the pathologist without access to the clinical or MRS data. Tissue preservation, abundance of epithelial cells relative to stroma, and presence of potentially confounding factors such as fat and inflammatory cells were reported in addition to the principal diagnosis.

Statistical Classification Strategy:

[0025] The general classification strategy has been developed and was designed specifically for MR and IR spectra of biofluids and biopsies. The strategy consists of three stages. First the MR magnitude spectra are preprocessed, (in order to eliminate redundant information and/or noise) by submitting them to a powerful genetic algorithm-based Optimal Region Selection (ORS_GA) (17), which finds a few (at most 5-10) maximally discriminatory subregions in the spectra. The spectral averages in these subregions are the ultimate features and used at the second stage. This stage uses the features found by ORS_GA to develop Linear Discriminant Analysis (LDA) classifiers that are made robust by IBD's bootstrap-based crossvalidation method (18). The crossvalidation approach proceeds by randomly selecting about half the spectra from each class and using these to train a classifier (usually LDA). The resulting classifier is then used to validate the remaining half. This process is repeated B times (with random replacement), and the optimized LDA coefficients are saved. The weighted average of these B sets of coefficients produces the final classifier. The ultimate classifier is the weighted output of the 500-1000 different bootstrap classifier coefficient sets and was designed to be used in a clinical setting as the single best classifier. The classifier consists of probabilities of class assignment for the individual spectra. For 2-class problems, class assignment is called *crisp* if the class probability is > 0.75%. For particularly difficult classification problems the third stage is activated. This aggregates the outputs (class probabilities) of several independent classifiers to form a Computerised Consensus Diagnosis (CCD) (13, 15). The consequence of CCD is that classification accuracy and reliability is generally better than the best of the individual classifiers.

[0026] Figure 3 shows a spectrometer 10, which may be a Bruker Avance 360 spectrometer operating at 8.5 Tesla. with equipped computer. The statistical classification strategy (SCS) computer 12 stores the SCS and other programs described herein. The clinical data base includes the information from the data acquisition and histopathology, used by the computer 12 to develop the classifier 16. The classifier 16 classifies the characteristics (e.g. pathology, vascularization and/or lymph node involvement) of the breast tissue under examination.

RESULTS

[0027] One hundred and sixty-six patients were involved in the study. A summary of the clinicopathological criteria is shown in Table 1.

Benign versus Malignant:

[0028] Proton MR spectra were recorded for each FNAB irrespective of the cellularity of the aspirate. However, those specimens with a SNR less than 10, which were shown to be inadequate for visual inspection (12) have been included in the SCS analysis without significantly compromising accuracy. Visual inspection of all spectra irrespective of signal to noise gave a sensitivity and specificity of 85.3% and 81.5% respectively (Table 2a), based on the creatine-to-choline ratio. When SCS-based classifiers were developed for all available spectra (Table 2b), 96% of the spectra were considered crisp and could be assigned unambiguously by the classifier as malignant or benign. Sensitivity and specificity were 93% and 92% respectively.

[0029] After removing the 31 spectra with the previously determined poor SNR (SNR < 10), a sensitivity and specificity of 98% and 94%, respectively, was achieved with crispness of 99% (Table 2c).

Prognostic factors:

[0030] With the addition of prognostic criteria to the database two further classifiers were created, namely, lymph node involvement and vascular invasion. A small number of known benign or pre-invasive cases were included in these subsets to assess the computer's ability to correctly define those cases in which no nodal involvement or vascular invasion was expected. These benign or pre-invasive cases were all correctly assigned by the computer into their respective uninvolved classes.

Lymph node Involvement:

[0031] There were 31 cases with nodal involvement and 30 without including 2 DCIS and 3 fibrocystic specimens. All spectra were included irrespective of SNR. Only those spectra for which complete pathology and clinical reports were available were included in this comparison (Table 1). The presence of lymph node metastases was predicted by SCS with a sensitivity of 96% and specificity of 94% (Table 3a).

Vascular Invasion:

[0032] SCS-based analysis of spectra was also carried out using vascular invasion as the criterion. There were 85 spectra for this analysis (Table 1). A sensitivity of 84% and specificity of 100% was achieved for the correct determination of vascular invasion, with an overall accuracy of 92% (Table 3b).

DISCUSSION

[0033] The introduction of preprocessing and SCS analysis of MR spectra has enhanced the ability to correlate spectroscopic changes with the pathology of human biopsies. It has also allowed specimens with sub-optimal cellularity to be analysed, and more importantly, provided a correlation with clinical criteria not apparent by visual inspection.

[0034] Visual inspection of spectra, like histopathology, is limited by the experience and skill of the reader for determining peak height ratios of metabolites (12). Visual inspection of spectra and the use of peak height ratio measurements of choline and creatine discriminated benign from malignant spectra with a higher degree of accuracy than standard triple assessment of breast lesions. However, to attain a high degree of accuracy, many spectra with poor SNR had to be discarded, reducing the effectiveness of the technique. Previous estimates of cellular material derived from FNAB, on which to perform MRS analysis reliably, have suggested that at least 10^6 cells are needed (6).

[0035] By using SCS-derived classifiers it was possible to distinguish malignant from benign pathologies with higher sensitivity 92% and specificity 96% for all FNAB spectra including those with low SNR (Table 2b) than by visual reading of these same spectra (Table 2a). That SCS-based analysis could more reliably classify a greater proportion of spectra than could be visually assessed is testament to the robustness and greater generality of the computer-based approach.

[0036] The SCS-based result is further improved by presenting to the computer spectral data with high SNR. The improvement in sensitivity and specificity gained for spectra with $SNR > 10$ (Table 2c) illustrates this point. Obtaining FNAB with adequate cell numbers can also enhance the results.

[0037] SCS permits classifiers to recognise patterns containing more complex information. The classifier has been validated to diagnose specimens with lymph node involvement and vascular invasion. The ability of the SCS-derived classifier to predict lymph node involvement with an accuracy of 95% and vascular invasion with an accuracy of 92% emphasises the wealth of chemical information that can be extracted, with the appropriate statistical approach, from an FNAB of a breast lesion (Table 3).

[0038] A major challenge in breast cancer is the need to identify and understand the factors that most influence the patient's prognosis and through timely and appropriate intervention influence this outcome. Adjuvant therapy can reduce the odds of death during the first ten years after diagnosis of breast cancer by about of 20-30% (19). The best prognostic indicator of survival in patients with early breast cancer has been shown to be axillary lymph node status (20-22).

[0039] Increasingly, sentinel lymph node biopsy is being investigated as a means to reduce the morbidity and cost of unnecessary axillary dissection in the two thirds of women with early invasive breast cancer who prove to be node-negative (23-25), while preserving the option of full axillary node clearance in those patients who are node-positive. MRS may possibly determine nodal involvement from the cellular material derived solely from the primary tumour, thus limiting the role of sentinel lymph node biopsy.

[0040] The results, that 52% of patients with lymph node involvement also had vascular invasion, is in agreement with Barth et al (26), who showed that peritumoural lympho-vascular invasion correlated with lymph node involvement (27) and was an independent predictor of disease free and overall survival (28-31).

[0041] A computer-based statistical classification strategy providing a robust means of analysing clinical data is becoming a reality. The power, speed and reproducibility of a computer-based diagnosis may lead to suitably programmed computers supplanting the human observer in the clinical laboratory. Patients increasingly expect certainty in diagnosis and optimum management.

[0042] Several important experimental factors should be noted. Presently, the MRS method according to the invention has thus far been demonstrated to work only on aspirated cells from the breast and not on core biopsies that contain a sufficiently high level of fat to mask diagnostic and prognostic information. The biopsy should be representative of the lesion and contain sufficient cellularity. Furthermore, sample handling is of paramount importance if the specimen is to be minimally degraded. Quality control in the spectrometer should be exercised with regard to pulse sequences, temperature, magnet stability, shimming and water suppression. The magnetic field at which the database reported herein was collected is 8.5 Tesla (360MHz for proton). Because spectral patterns are frequency dependent, a new classifier should be developed if one uses different magnetic field strengths.

[0043] The clinical and pathology databases used to train the classifier should be representative of the full range of pathologies or the complete demographics of the population, or else the classifier may be inadequately prepared for all the possibilities it might encounter in clinical practice. In developing a database for breast lesions, the training set should have adequate samples of all the commonly encountered breast pathologies and be updated upon detection of less common tumour types.

[0044] The invention is expected to provide a revolutionary impact on breast cancer management by the use of SCS computerised analysis of MR spectral features, by obtaining a much higher level of accuracy in diagnosis of the lesion and also an indication of its metastatic potential when compared to visual inspection of spectra. Most importantly, the invention facilitates identification of the stage of the disease from spectral information of FNAB collected only from the primary breast lesion.

[0045] The invention allows one to determine pathological diagnosis, the likelihood of axillary lymph nodal involvement and tumour vascularisation by SCS-based analysis of proton MR spectra of a FNAB taken from a primary breast lesion. The SCS-based method is more accurate and reliable than visual inspection for identifying complex spectral indicators of diagnosis and prognosis.

[0046] The ability of an SCS-based analysis of MRS data to provide prognostic information on lymph node involvement by sampling only the primary tumour may provide a paradigm shift in the management of breast cancer. The determination of vascular invasion from the same cellular material highlights the untapped potential of MRS to determine prognostic information.

[0047] Although one embodiment of the invention has been shown and described, numerous variations and modifications will readily occur to those skilled in the art. The invention is not limited to the preferred embodiment, and its scope is determined only by the appended claims.

Table 1 Summary of Clinico-pathological Data

	All patients (n=66)	Benign/Malignant (n=140)	Lymph Nodes (n=61)	Vascular Invasion (n=85)
Age Mean±SD (Range)	55.8±15.4 (20-101)	54.7±15 (20-90)	58.4±13.2 (29-85)	60.6±14.3 (29-101)
Pathology type				
Invasive Ductal	89	74	52	68
Invasive Lobular	8	8	3	5
Mixed Ductal/Lob.	1	1	1	
DCIS	10	1	2*	9*
Fibroadenoma	17	17		
Fibrocystic	22	22	3*	2*
Papilloma	3	2		
Radial Scar	2	2		
Gynaecomastia	1	1		
Misc. Benign	13	12		1
Total	166	140	61	85
*These preinvasive and benign lesions were included as known lymph node negative, vascular invasion negative cases to test the computer's ability to discern true negatives and positives. They were all correctly classified by the computer into their respective classes.				

Table 2

Malignant versus Benign

5

a. Visual Inspection: Malignant versus Benign

10

	Sensitivity	Specificity
For all Spectra		
Malignant (n=83)vs Benign (n=57)	85.3%	81.5%
Spectra SNR>10		
Malignant (n=60)vs Benign (n=49)	100%	87.3%

15

20

b. SCS: Malignant or Benign (All spectra): (M:83, B:57)

25

	B	M	Sensitivity	Specificity	PPV	%Crisp
B	51	4	92.7%	92.4%	92.4%	96.5%
M	6	73	92.4%	92.7%	92.7%	95.2%

30

Overall Accuracy: 92.6%

Overall % Crisp : 95.7% (134 of 140)

$\kappa = 0.922$

35

c. SCS: Malignant or Benign (SNR>10): (M:60,B:49)

40

	B	M	Sensitivity	Specificity	PPV	%Crisp
B	46	3	93.9%	98.3%	98.2%	100.0%
M	1	58	98.3%	93.9%	94.1%	98.3%

45

Overall Accuracy: 96.1%

Overall % crisp : 99.1% (108 of 109)

$\kappa = 0.922$

50

55

Table 3

SCS:-Prognostic Indicators

a. Lymph Node involvement: (P: (Present) 29, A: (Absent) 32)

	P	A	Sensitivity	Specificity	PPV	%Crisp
P	25	1	96.2%	93.8%	93.9%	89.7%
A	2	30	93.8%	96.2%	96.1%	100%

Overall Accuracy: 95.0%

Overall % crisp : 95.1% (58 of 61)

$\times = 0.899$

b. Vascular Invasion: (P: (Present) 33, A: (Absent) 52)

	P	A	Sensitivity	Specificity	PPV	%Crisp
P	26	5	83.9%	100.0%	100.0%	93.9%
A	0	49	100.0%	83.9%	86.1%	94.2%

Overall Accuracy: 91.9%

Overall % crisp : 94.1% (80 of 85)

$\times = 0.839$

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Claims

1. A method for determining the classification of a characteristic of breast tissue comprising:

obtaining magnetic resonance spectra of a biopsy of breast tissue having unknown classification of a characteristic and comparing the spectra with a classifier, said classifier having been obtained by

(a) locating a plurality of discriminatory subregions in magnetic resonance spectra of biopsies of breast tissue having known classifiers of a characteristic;

(b) cross-validating the spectra by selecting a first portion of the spectra from each class of a characteristic, developing linear discriminant analysis classifiers from said first portion of spectra from each class and validating the remainder of the spectra from each class using the classifiers from the first portion of the spectra from each class, to obtain optimized linear discriminant analysis coefficients, **characterised by**

(c) repeating step (b) a plurality of times each time selecting as the first portion of the class a different portion of the spectra from each class to obtain a different set of optimized linear discriminant analysis coefficients for each of said plurality of times;

(d) obtaining an average of the linear discriminant analysis coefficients to obtain final classifier spectra indicating the classification of the characteristic based on the spectra; and

(e) wherein spectra from a biopsy of breast tissue of unknown classification of a characteristic may be compared to the final classifier spectra to determine the classification of the characteristic of the breast tissue.

2. The method of claim 1 wherein the step of cross-validating the spectra comprises cross validating the spectra by randomly selecting about half of the spectra.

3. The method of any foregoing claim, wherein the step of repeating step (b) a plurality of times comprises repeating step (b) about 500-1000 times.

4. The method of any foregoing claim, further including the steps of obtaining a plurality of final classifier spectra independently, and aggregating the results of the independent classifiers to obtain a consensus diagnosis.

5. The method according to any foregoing claim, wherein the characteristic is pathology of the breast tissue and the classification indicates whether the pathology is malignant, benign or normal.

6. The method according to any of claims 1 to 4, wherein the characteristic is tumor vascularization and the classification indicates the extent of tumor vascularization.

7. The method according to any of claims 1 to 4, wherein the characteristic is tumor nodal involvement and the clas-

sification indicates the extent of tumor nodal involvement.

8. An apparatus for determining the classification of a characteristic of breast tissue, comprising: a spectrometer for obtaining magnetic resonance spectra of a biopsy of breast tissue having unknown classification of a characteristic; and a classifier for statistically classifying the spectra by comparing the spectra with a reference classifications, said classifier being obtained by

(a) a locator for locating a plurality of discriminatory subregions in magnetic resonance spectra of biopsies of breast tissue having known classifiers of a characteristic of breast tissue,

(b) a cross-validator for selecting a portion of the spectra from each class of a characteristic, developing linear discriminant analysis classifiers from said first portion of spectra, and validating the remainder of the spectra using the classifiers from the first portion of the spectra, to obtain optimized linear discriminant analysis coefficients, **characterized by** said cross-validator further being for selecting, developing and validating a plurality of times each time selecting a different portion of the spectra to obtain a different set of optimised linear discriminant analysis coefficients for each of said plurality of times, and

(c) an averager for obtaining an average of the linear discriminant analysis coefficients to obtain final classifier spectra indicating the classification of the characteristic based on the spectra, whereby spectra from a biopsy of breast tissue of unknown classification of a characteristic may be compared to the final classifier spectra to determine the classification of the characteristic of the breast tissue.

9. The apparatus of claim 8 wherein the cross-validator randomly selects about half of the spectra.

10. The apparatus of claim 8 or claim 9, wherein the cross-validator repeats step (b) about 500- 1000 times.

11. The apparatus of any of claims 8 to 10, wherein the characteristic is pathology of the breast tissue and the classification indicates whether the pathology is malignant, benign or normal.

12. The apparatus of any of claims 8 to 10, wherein the characteristic is tumor vascularization and the classification indicates the extent of tumor vascularization.

13. The apparatus of any of claims 8 to 10, wherein the characteristic is tumor nodal involvement and the classification indicates the extent of tumor nodal involvement,

Revendications

1. Procédé de détermination de la classification d'une caractéristique d'un tissu mammaire comprenant :

l'obtention d'un spectre de résonance magnétique d'une biopsie d'un tissu mammaire présentant une classification inconnue d'une caractéristique et la comparaison du spectre à un classificateur, ledit classificateur ayant été obtenu en

(a) localisant une pluralité de sous-*régions discriminatoires du spectre de résonance magnétique de biopsies de tissus mammaires ayant des classificateurs connus d'une caractéristique,

(b) validant de manière croisée le spectre en sélectionnant une première partie du spectre de chaque classe d'une caractéristique, en développant des classificateurs d'analyse discriminante linéaire à partir de ladite première partie de spectre de chaque classe et en validant le reste du spectre à partir de chaque classe en utilisant les classificateurs de la première partie du spectre de chaque classe, afin d'obtenir des coefficients d'analyse discriminante linéaire optimisés, **caractérisé par**

(c) la répétition de l'étape (b) une pluralité de fois en sélectionnant à chaque fois comme première partie de classe d'une partie différente du spectre de chaque classe pour obtenir un ensemble différent de coefficients d'analyse discriminante linéaire optimisés pour chacune de ladite pluralité de fois,

(d) l'obtention d'une moyenne des coefficients d'analyse discriminante linéaire afin d'obtenir un spectre de classificateur final indiquant la classification de la caractéristique sur la base du spectre, et

(e) où le spectre d'une biopsie d'un tissu mammaire présentant une classification inconnue d'une caractéristique peut être comparé au spectre de classificateur final afin de déterminer la classification de la caractéristique du tissu mammaire.

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2. Procédé selon la revendication 1, dans lequel l'étape consistant à valider de manière croisée le spectre comprend la validation croisée du spectre en sélectionnant de manière aléatoire environ la moitié du spectre.
- 5 3. Procédé selon l'une quelconque des revendications précédentes, dans lequel l'étape consistant à répéter l'étape (b) une pluralité de fois comprend la répétition de l'étape (b) d'environ 500 à 1 000 fois.
- 10 4. Procédé selon l'une quelconque des revendications précédentes, comprenant en outre les étapes consistant à obtenir une pluralité de spectres de classificateurs finaux indépendamment, et à rassembler les résultats des classificateurs indépendants pour obtenir un diagnostic consensuel.
- 15 5. Procédé selon l'une quelconque des revendications précédentes, dans lequel la caractéristique est une pathologie du tissu mammaire et la classification indique si la pathologie est maligne, bénigne ou normale.
- 20 6. Procédé selon l'une quelconque des revendications 1 à 4, dans lequel la caractéristique est la vascularisation d'une tumeur et la classification indique l'étendue de la vascularisation tumorale.
- 25 7. Procédé selon l'une quelconque des revendications 1 à 4, dans lequel la caractéristique est une atteinte ganglionnaire tumorale et la classification indique l'étendue de l'atteinte ganglionnaire tumorale.
- 30 8. Dispositif destiné à déterminer la classification d'une caractéristique de tissu mammaire comprenant : un spectromètre destiné à obtenir un spectre de résonance magnétique d'une biopsie d'un tissu mammaire présentant une classification inconnue d'une caractéristique, et un classificateur destiné à classifier statistiquement le spectre en comparant le spectre à des classifications de référence, ledit classificateur étant obtenu par
 - 35 (a) un localisateur destiné à localiser une pluralité de sous-régions discriminatoires dans un spectre de résonance magnétique de biopsies de tissus mammaires ayant des classificateurs connus d'une caractéristique de tissu mammaire,
 - 40 (b) un module de validation croisée destiné à sélectionner une partie du spectre de chaque classe d'une caractéristique, à développer des classificateurs d'analyse discriminante linéaire à partir de ladite première partie de spectre, et à valider le reste du spectre en utilisant les classificateurs de la première partie du spectre, pour obtenir des coefficients d'analyse discriminante linéaire optimisés, **caractérisé par le fait que** ledit module de validation croisée est en outre destiné à sélectionner, développer et valider une pluralité de fois chaque fois que l'on sélectionne une partie différente du spectre en vue d'obtenir un ensemble différent de coefficients d'analyse discriminante linéaire optimisés pour chaque fois de ladite pluralité de fois, et
 - 45 (c) un module de calcul de moyenne destiné à obtenir une moyenne des coefficients d'analyse discriminante linéaire afin d'obtenir un spectre de classificateur final indiquant la classification de la caractéristique sur la base du spectre, grâce à quoi le spectre provenant d'une biopsie d'un tissu mammaire présentant une classification inconnue d'une caractéristique peut être comparé au spectre de classificateur final pour déterminer la classification de la caractéristique du tissu mammaire.
- 50 9. Dispositif selon la revendication 8, dans lequel le module de validation croisée sélectionne de manière aléatoire environ la moitié du spectre.
- 55 10. Dispositif selon la revendication 8 ou la revendication 9, dans lequel le module de validation croisée répète l'étape (b) d'environ 500 à 1 000 fois.
11. Dispositif selon l'une quelconque des revendications 8 à 10, dans lequel la caractéristique est une pathologie du tissu mammaire et la classification indique si la pathologie est maligne, bénigne ou normale.
12. Dispositif selon l'une quelconque des revendications 8 à 10, dans lequel la caractéristique est la vascularisation d'une tumeur et la classification indique l'étendue de la vascularisation tumorale.
13. Dispositif selon l'une quelconque des revendications 8 à 10, dans lequel la caractéristique est une atteinte ganglionnaire tumorale et la classification indique l'étendue de l'atteinte ganglionnaire tumorale.

Patentansprüche

1. Verfahren zum Bestimmen der Klassifikation einer Eigenschaft von Brustgewebe, umfassend:

5 Erhalten von magnetischen Resonanzspektren einer Biopsie von Brustgewebe mit einer unbekanntem Klassifikation einer Eigenschaft und Vergleichen der Spektren mit einem Klassifizierer, wobei der Klassifizierer erhalten worden ist durch

10 (a) Lokalisieren einer Mehrzahl von diskriminierenden Unterregionen in magnetischen Resonanzspektren von Biopsien von Brustgewebe, das bekannte Klassifizierer einer Eigenschaft aufweist;

(b) Quervalidieren der Spektren durch Auswählen eines ersten Bereichs der Spektren aus jeder Klasse einer Eigenschaft, Entwickeln linearer Diskriminanten-Analyseklassifizierer aus dem ersten Bereich der Spektren aus jeder Klasse und Validieren des Rests der Spektren aus jeder Klasse unter Verwendung der Klassifizierer aus dem ersten Bereich der Spektren aus jeder Klasse, um optimierte lineare Diskriminanten-Analysekoeffizienten zu erhalten, **gekennzeichnet durch**

15 (c) Wiederholen von Schritt (b) mehrmals, wobei jedes Mal als der erste Bereich der Klasse ein anderer Bereich der Spektren aus jeder Klasse ausgewählt wird, um einen anderen Satz von optimierten linearen Diskriminanten-Analysekoeffizienten für jedes aus der Mehrzahl von Malen zu erhalten;

20 (d) Erhalten eines Durchschnitts der linearen Diskriminanten-Analysekoeffizienten, um endgültige Klassifizierer-Spektren zu erhalten, welche die Klassifikation der Eigenschaft basierend auf den Spektren anzeigen; und

(e) wobei Spektren von einer Biopsie von Brustgewebe unbekannter Klassifikation einer Eigenschaft mit den finalen Klassifizierer-Spektren verglichen werden können, um die Klassifikation der Eigenschaft des Brustgewebes zu bestimmen.

25 2. Verfahren nach Anspruch 1, wobei der Schritt des Quervalidierens der Spektren das Quervalidieren der Spektren durch zufälliges Auswählen von etwa der Hälfte der Spektren umfasst.

30 3. Verfahren nach einem der vorstehenden Ansprüche, wobei der Schritt des mehrfachen Wiederholens von Schritt (b) das 500-1000-malige Wiederholen des Schritts (b) umfasst.

35 4. Verfahren nach einem der vorstehenden Ansprüche, weiterhin umfassend die Schritte des unabhängigen Erhaltens einer Mehrzahl von finalen Klassifizierer-Spektren und des Aggregierens der Ergebnisse der unabhängigen Klassifizierer, um eine Konsens-Diagnose zu erhalten.

5. Verfahren nach einem der vorstehenden Ansprüche, wobei die Eigenschaft Pathologie des Brustgewebes ist und die Klassifikation anzeigt, ob die Pathologie bösartig, gutartig oder normal ist.

40 6. Verfahren nach einem der Ansprüche 1 bis 4, wobei die Eigenschaft Tumolvaskularisierung ist und die Klassifikation das Ausmaß der Tumolvaskularisierung anzeigt.

7. Verfahren nach einem der Ansprüche 1 bis 4, wobei die Eigenschaft Tumorknotenbeteiligung ist und die Klassifikation das Ausmaß der Tumorknotenbeteiligung anzeigt.

45 8. Vorrichtung zum Bestimmen der Klassifikation einer Eigenschaft von Brustgewebe, umfassend: ein Spektrometer zum Erhalten von magnetischen Resonanzspektren einer Biopsie von Brustgewebe mit einer unbekanntem Klassifikation einer Eigenschaft; und einen Klassifizierer zum statistischen Klassifizieren der Spektren durch Vergleichen der Spektren mit einer Referenz-Klassifikation, wobei der Klassifizierer erhalten wird durch

50 (a) einen Lokalisierer zum Lokalisieren einer Mehrzahl von diskriminierenden Unterregionen in magnetischen Resonanzspektren von Biopsien von Brustgewebe, das bekannte Klassifizierer einer Eigenschaft von Brustgewebe aufweist;

55 (b) einen Quervalidierer zum Auswählen eines Bereichs der Spektren aus jeder Klasse einer Eigenschaft, Entwickeln linearer Diskriminanten-Analyseklassifizierer aus dem ersten Bereich von Spektren und Validieren des Rests der Spektren aus jeder Klasse unter Verwendung der Klassifizierer aus dem ersten Bereich der Spektren, um optimierte lineare Diskriminanten-Analysekoeffizienten zu erhalten, **dadurch gekennzeichnet, dass** der Quervalidierer weiterhin zum mehrmaligen Auswählen, Entwickeln und Validieren dient, wobei jedes Mal ein anderer Bereich der Spektren ausgewählt wird, um einen anderen Satz von optimierten linearen Dis-

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5 kriminanten-Analysekoeffizienten für jedes aus der Mehrzahl von Malen zu erhalten; und
(c) einen Durchschnittsbilder zum Erhalten eines Durchschnitts der linearen Disknminanten-Analysekoeffizien-
ten, um endgültige Klassifizierer-Spektren zu erhalten, weiche die Klassifikation der Eigenschaft basierend auf
den Spektren anzeigen; wobei Spektren von einer Biopsie von Brustgewebe unbekannter Klassifikation einer
Eigenschaft mit den finalen Klassifizierer-Spektren verglichen werden können, um die Klassifikation der Eigen-
schaft des Brustgewebes zu bestimmen.

9. Vorrichtung nach Anspruch 8, wobei der Quervalidierer etwa die Hälfte der Spektren zufällig auswählt.

10 10. Vorrichtung nach Anspruch 8 oder 9, wobei der Quervalidierer Schritt (b) etwa 500 - 1000 mal wiederholt.

11. Vorrichtung nach einem der Ansprüche 8 bis 10, wobei die Eigenschaft Pathologie des Brustgewebes ist und die
Klassifikation anzeigt, ob die Pathologie bösartig, gutartig oder normal ist.

15 12. Vorrichtung nach einem der Ansprüche 8 bis 10, wobei die Eigenschaft Tumornaskularisierung ist und die Klassi-
fikation das Ausmaß der Tumolvaskularisierung anzeigt.

20 13. Vorrichtung nach einem der Ansprüche 8 bis 10, wobei die Eigenschaft Tumorknotenbeteiligung ist und die Klas-
sifikation das Ausmaß der Tumorknotenbeteiligung anzeigt.

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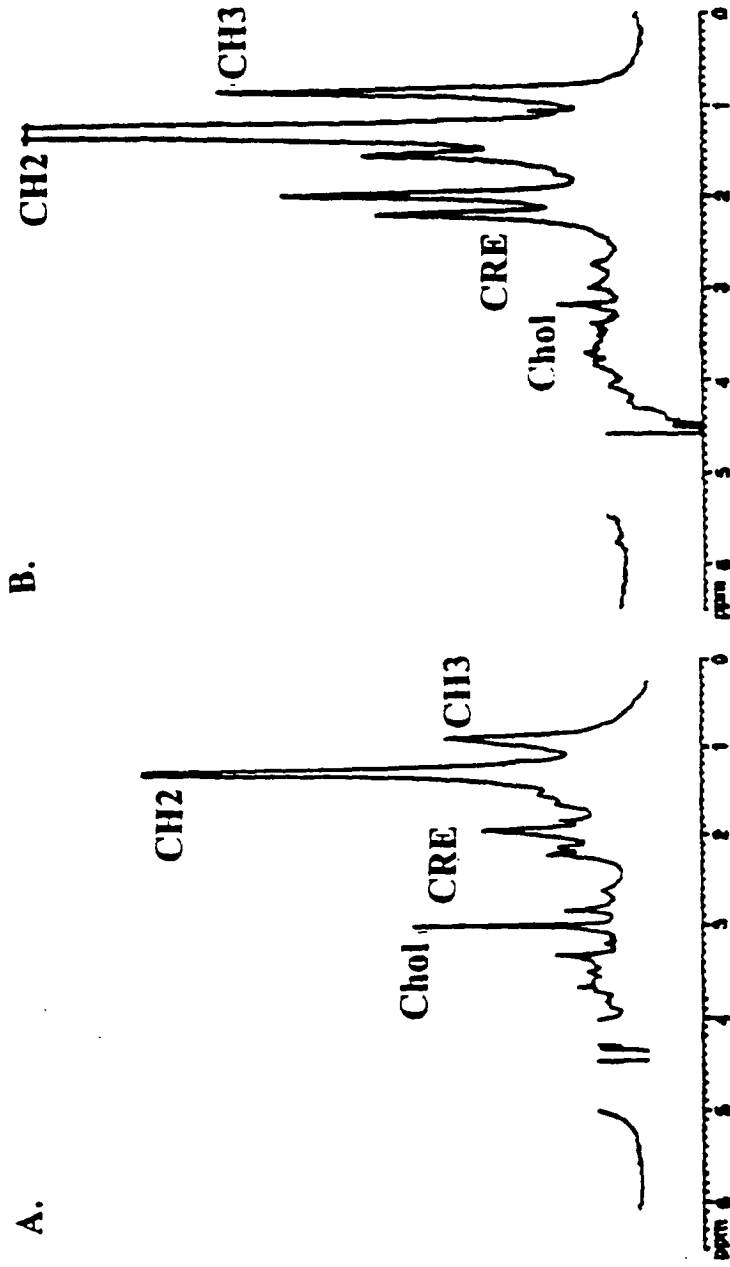
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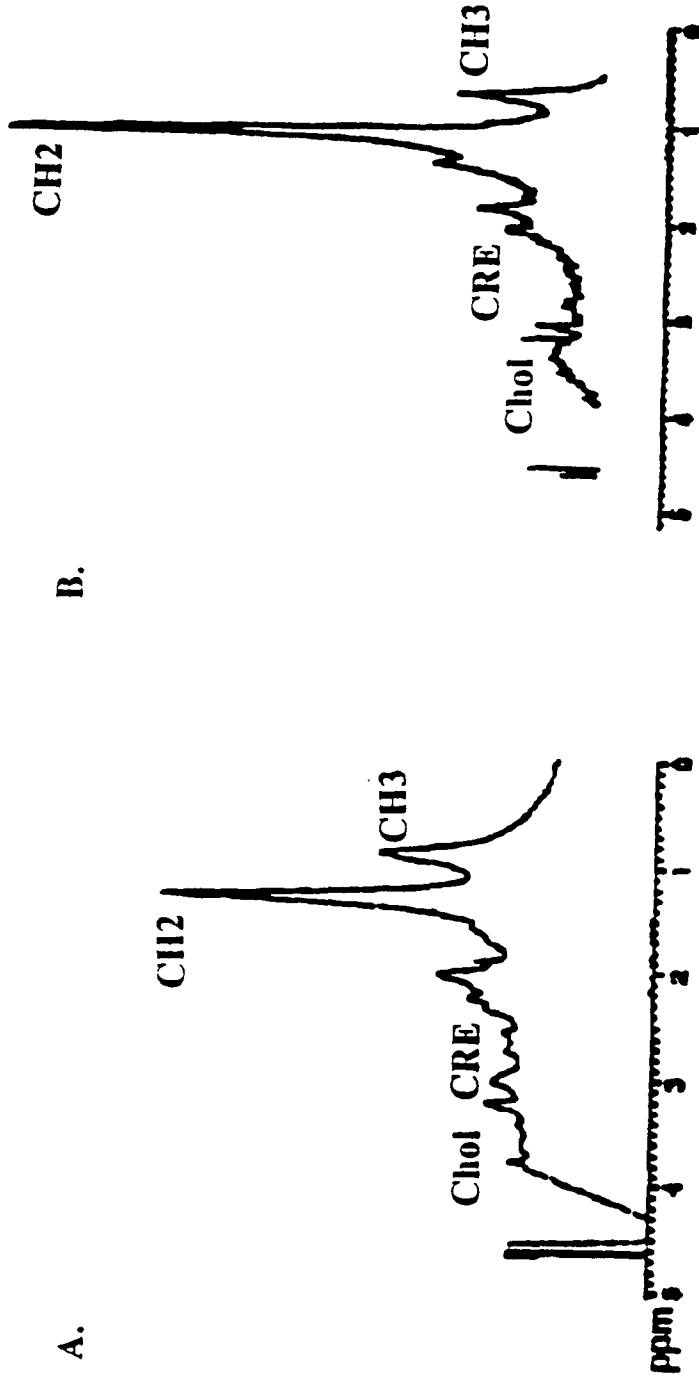
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**MR Spectra with SNR>10. (A) Malignant, (B) Benign
For acquisition parameters see Materials and Methods.
A line broadening of 3Hz was applied to both spectra.
The spectra were displayed in absolute intensity mode
(noiselevel similar in both spectra).**

Figure 1



MR Spectra with SNR<10. (A) Malignant, (B) Benign
For acquisition parameters see Materials and Methods.
A line broadening of 3Hz was applied to both spectra.
The spectra were displayed in absolute intensity mode
(noiselevel similar in both spectra).

Figure 2

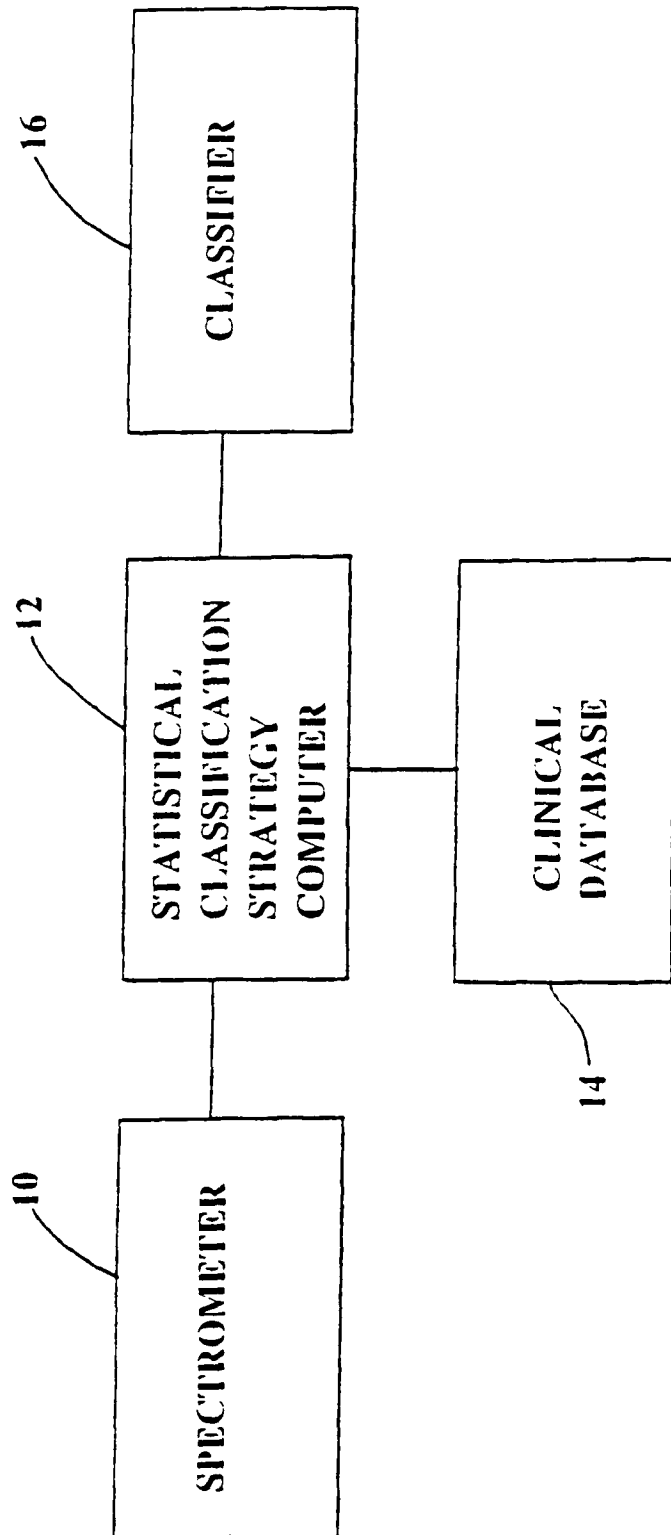


Figure 3

专利名称(译)	乳腺活检的磁共振波谱法确定病理学，血管化和淋巴结受累		
公开(公告)号	EP1223856B1	公开(公告)日	2006-02-08
申请号	EP2000971169	申请日	2000-10-18
[标]申请(专利权)人(译)	生物诊断技术 INST磁共振RES		
申请(专利权)人(译)	生物标志物研究所，国家研究委员会 学院磁共振研究		
当前申请(专利权)人(译)	加拿大国家研究委员会的 学院磁共振研究		
[标]发明人	MOUNTFORD CAROLYN RUSSELL PETER SMITH IAN C P SOMORJAI RAJMUND L		
发明人	MOUNTFORD, CAROLYN RUSSELL, PETER SMITH, IAN, C., P. SOMORJAI, RAJMUND, L.		
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摘要(译)

稳健的分类方法分析从乳腺肿瘤取出的细针抽吸物的磁共振波谱 (MRS) 数据 (光谱)。与组织病理学和临床标准相比较的结果数据提供了基于计算机化分类的诊断和预后，具有非常高的准确性和可靠性。在光谱和标准天气病理学发现之间进行的诊断相关性包含关于病理学 (恶性与良性)，原发性癌的血管侵入和切除的腋窝淋巴结的淋巴结受累的细节。分类策略包括三个阶段：MR幅度谱的预处理以识别最佳光谱区域，交叉验证的线性判别分析和通过计算机化共识诊断的分类聚合。恶性组织与良性病变不同，总体准确度为93%。从相同的光谱预测淋巴结受累的准确率为95%，肿瘤血管形成的总体准确度为92%。

Table 2
Malignant versus Benign

a. Visual Inspection: Malignant versus Benign

	Sensitivity	Specificity
For all Spectra		
Malignant (n=83)vs Benign (n=57)	85.3%	81.5%
Spectra SNR>10		
Malignant (n=60)vs Benign (n=49)	100%	87.3%

b. SCS: Malignant or Benign (All spectra): (M:83, B:57)

	B	M	Sensitivity	Specificity	PPV	%Crisp
B	51	4	92.7%	92.4%	92.4%	96.5%
M	6	73	92.4%	92.7%	92.7%	95.2%

Overall Accuracy: 92.6%
Overall % Crisp : 95.7% (134 of 140)
κ = 0.922

c. SCS: Malignant or Benign (SNR>10): (M:60, B:49)

	B	M	Sensitivity	Specificity	PPV	%Crisp
B	46	3	93.9%	98.3%	98.2%	100.0%
M	1	58	98.3%	93.9%	94.1%	98.3%

Overall Accuracy: 96.1%
Overall % crisp : 99.1% (108 of 109)
κ = 0.922