

Multicontrast MRI-based radiomics for the prediction of pathological complete response to neoadjuvant chemotherapy in patients with early triple negative breast cancer

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2 *<u>Title page</u>*

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5 cancer

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- 27

28	Abstract

29 Introduction:

To assess pre-therapeutic MRI-based radiomic analysis to predict the pathological complete response
 to neoadjuvant chemotherapy (NAC) in women with early triple negative breast cancer (TN).

32 Materials and methods:

33 This monocentric retrospective study included 75 TN female patients with MRI (T1-weighted, T2-34 weighted, diffusion-weighted and dynamic contrast enhancement images) performed before NAC. For 35 each patient, the tumor(s) and the parenchyma were independently segmented and analyzed with 36 radiomic analysis to extract shape, size, and texture features. Several sets of features were realized 37 based on the 4 different sequence images. Performances of 4 classifiers (random forest, multilayer 38 perceptron, support vector machine (SVM) with linear or quadratic kernel) were compared based on 39 pathological complete response (defined on the excised tissues), on 100 draws with 75% as training set 40 and 25% as test.

41 Results:

The combination of features extracted from different MR images improved the classifier performance (more precisely, the features from T1W, T2W and DWI). The SVM with quadratic kernel showed the best performance with a mean AUC of 0.83, a sensitivity of 0.85 and a specificity of 0.75 in the test set.

46 Conclusion:

47 MRI-based radiomics may be relevant to predict NAC response in TN cancer. Our results promote the
48 use of multi-contrast MRI sources for radiomics, providing enrich source of information to enhance
49 model generalization.

50

51 Keywords

52 Breast Cancer; Radiomics; Multi-contrast MRI; Triple Negative Breast Cancer.

53

54 Abbreviations

- <u>AUC:</u> Area Under the Curve ROC
- 56 <u>DCE:</u> dynamic contrast enhancement

57	•	HER: Human Epidermal Growth Factor
58	•	<u>VOI:</u> volume of interest
59	•	MLP: multilayer perceptron
60	•	MRI: magnetic resonance imaging
61	•	NAC: neo-adjuvant chemotherapy
62	•	pCR: pathological complete response
63	•	ROC: receiver operating characteristic
64	•	SVM: support vector machine
65	•	TN: triple negative
66	•	TNM: tumor, node, metastases
67	•	T1W: T1-weighted imaging
68	•	T2W: T2-weighted imaging
69	•	DWI: diffusion weighted imaging
70	•	GLCM: Gray-level co-occurrence matrix
71	•	GLSZM: Gray-level size zone matrix
72	•	<u>NGTDM</u> : Neighborhood gray tone difference matrix
73	•	SURF: Speed-Up Robust Features

• <u>SUB3</u>: subtraction between the image 3 min post-injection and the image pre-injection

75 <u>TEXT</u>

76 **INTRODUCTION**

77 Breast cancer is the most frequently diagnosed cancer in women with 2,090,000 new cases and 78 627,000 deaths worldwide in 2018 [1]. Among the different types of breast cancer, triple negative 79 (TN) cancer is characterized by estrogen and progesterone receptor level lower than 10%, and an 80 absence of over-expression of HER-2 (Human Epidermal Growth Factor Receptor-2). TN cancers 81 account for 10 to 24% of all breast cancers, and 57 to 88% of cancers with BRCA1 mutation in women 82 [2]. TN tumors are generally larger, diagnosed at the highest grade, and associated with worse 83 prognosis [3]. At early stage, patients with TN cancer receive systemic treatments generally limited to 84 cytotoxic chemotherapy, no targeted therapies are currently proposed. Neoadjuvant chemotherapy 85 (NAC) treatment are used: i) to reduce the initial tumor volume in order to allow a conservative 86 surgical treatment; ii) to better eradicate the micrometastatic disease; iii) to assess tumor chemo-87 sensibility to determine the most appropriate adjuvant treatments [4]. The pathological complete 88 response (pCR) to NAC is an important prognostic factor for the disease-free survival and overall 89 survival in breast cancer [5, 6]. The efficacy of NAC varies according to the tumor's genetic profile 90 and pCR levels from 10 to 50% [7]. Therefore, there is a clinical need to identify patients who will not 91 respond to NAC to eventually direct them to alternative therapeutic strategies.

92 According to the latest EUSOBI recommendations [8], pre- and post-chemotherapy MRI examination 93 should be performed in women with early breast cancer receiving NAC. Since 2012 [9], a new 94 discipline called "radiomics" has drawn increasing attention in cancer research in disease detection, 95 diagnosis, and prediction of treatment response, and several studies investigated prediction of pCR to 96 breast cancer chemotherapy [10-14]. Radiomics is based on the hypothesis that genetics, molecular, 97 cellular and tissular modifications can be observed on images [15,16]. Technically, radiomics consist 98 in extracting a high number of quantitative parameters from radiologic images in order to determine 99 their relationships with the underlying pathophysiology [17,18]. Moreover, through functional and 100 anatomical information that MRI provided with on whole tissues, MRI-based radiomics allows to 101 access to quantitative information refining the entire tumor and its micro-environment, and to probe 102 tumor heterogeneity [19]. Some radiomic studies focused not only on the tumor, but also on the 103 surrounding mammary parenchyma. The tumor microenvironment is known to partly contribute to the 104 progression of breast cancer [20]. The radiomic analysis of the pre-tumoral environment was shown to

105 be as important as the tumor analysis itself [14].

106 In this study, we explored the performance of radiomics in tumor and ipsilateral parenchymal 107 mammary MRI to predict the pCR to NAC in TN breast cancer female patients.

108

109 **METHOD**

110 Study design

111 Patients enrolled in this retrospective study underwent a pre-therapeutic MRI protocol between 112 January 2008 and Jun 2017 in the French comprehensive cancer center "Centre Léon Bérard". All 113 patients had an early triple negative breast cancer (i.e. without metastasis) and were treated with 114 neoadjuvant chemotherapy (NAC) before a surgical treatment. All women received a sequential NAC 115 therapy based on anthracyclines-cyclophosphamide, then taxanes. Data were excluded for: i) poor 116 quality of MRI imaging (moving artifacts, missing of some images); ii) NAC treatment initiated prior 117 to MRI. This retrospective study was approved by our institutional review board and the requirement 118 to obtained informed consent was waived.

119

120 Pre-therapeutic MRI protocol

121 All breast MRI examinations were performed at Leon Berard center with patient in prone position 122 using a 1.5T Achieva system (Philips Healthcare, Best, Netherlands) and with the use of a dedicated 123 seven-channel or sixteen-channel breast surface coil (SENSE-Breast-7 or SENSE-Breast16M). The 124 pre-therapeutic MRI protocol was sequentially composed of a T1-weighted imaging, a T2-weighted 125 imaging, a diffusion weighted imaging and a dynamic contrast enhanced imaging (Figure 1). MRI 126 protocol parameters are summarized in Table 1. Dynamic contrast enhancement (DCE) MR imaging 127 was acquired after intravenous injection of 0.1 mmol/kg gadolinium-based contrast agent. Images 128 noted "SUB3" were obtained subtracting images acquired 3 min after the injection and those acquired 129 before injection using DCE-MRI.

130

131 Segmentation of volume of interest

132 The 3D volume of interest (VOI) was delineated manually using itk-SNAP software

133 (www.itksnap.org) on few slices of SUB3 images; the inter-slice interpolation option was used to 134 complete the mask between slices to have a 3D volume. More precisely, for each patient, tumor and 135 parenchyma were initially segmented by a radiologist intern PC, after correcting by a senior 136 radiologist (more than 10 years of experience in breast imaging AC). In the case of multiple lesions, 137 each of them was considered independently with separate 3D binary mask. The delineation of the 138 parenchyma included the fibroglandular tissue and the adipose tissue and excluded the skin and the 139 tumor. The segmentations of tumor and parenchyma resulting from the consensus of the two 140 radiologists PC and AC were then used for the extraction of size, shape, intensity distribution, and 141 other texture features. Areas impacted by the presence of a clip were excluded from the VOI for the 142 computation of intensity distribution and texture features (but not for shape and size features). An 143 affine transformation was used to reposition VOIs segmented on SUB3 images on the other images 144 (T1W, T2W and DWI) using matrix dimension and patient position information. A third expert FB 145 was asked to delineate a subset of twenty-four tumors in order to analyze the variability of 146 segmentations with the difficulty to have any access to the assessment of the other two radiologists 147 and without access to the patient file.

148

149 **Features extraction**

150 We tested multiple configurations. We first use only SUB3 images with features extracted from lesion 151 and parenchyma, and progressively include features from T1-weitghted images, T2-weitghted images, 152 and DW images in the feature set. Extraction of feature set was performed with MATLAB 2019a (The 153 Mathworks, Natick, MA, USA) using an in-house software. 3D-image intensities were filtered using 154 Collewet method [21]. The initial feature set of a ROI was composed of 342 features: 96 shape and size characteristics, 14 intensity distribution characteristics, and 232 textural characteristics. As shown 155 156 in the Figure 2, size and shape features were directly extracted from the binary masks and were based 157 on morphological skeletonization and distance transforms, affine moment invariants [22], Hu moment 158 [23], Zernike moment [24, 25], and conventional metrics. Intensity distribution features were extracted 159 from masked MR images from the histogram built with 256 bins (14 features: average, standard 160 deviation, full width at half maximum, variance, minimum, maximum, range, interquartile range, 161 kurtosis, skewness, entropy energy, root mean square, mean deviation, median deviation). Before the

162 extraction of texture features, voxels were isotropically resampled using an affine transformation and a 163 nearest-neighbor interpolation and then discretized in a smaller number of gray levels. This operation 164 was done using an equal probability algorithm to define decision thresholds in the volume such as the number of voxels for a given reconstructed level is the same in the quantized volume for all gray 165 166 levels. Images were discretized in 8, 16, 24, 32, 48 and 64 grey levels and for each level four matrix 167 were built: GLCM (Gray-level co-occurrence matrix) (n=21), GLRLM (Gray-level run length matrix) 168 (n=13), GLSZM (Gray-level size zone matrix) (n=13) and NGTDM (Neighborhood gray tone 169 difference matrix) (n=5) from which characteristics were extracted. Frequency domain-based texture 170 features were extracted from the Gabor filters responses and from features extracted from image 171 spectrum after 2D discrete Fourier transform. GLCM and GLRLM will be computed for 4 directions 172 (0°, 45°, 90° and 135°) with an offset of 1 pixel. For GLSZM and NGTDM, a 26-pixel connectivity 173 will be used. For Gabor filtering, 5 scales, 6 orientations, and a minimal wavelength of 3 were used. 174 Other texture feature based on images primitive were also extracted using different detectors and 175 descriptors (such as Speed-Up Robust Features (SURF) detector, Local Oriented Statistics Information 176 Booster (LOSIB) descriptor, Harris detector); lacunarity computation or quad tree decomposition.

177 These features were already described in previous studies [10,11,26]. For multiparametric case, only 178 textural and intensity features (set of 492 features) were computed on the other imaging (T1W, T2W 179 and DWI) and added to the initial feature set as illustrated in Figure 2.

180

181 Data mining

182 The test set included 25% of the total number of tumors, randomly selected from the whole data set, 183 with a balance between pCR and non-pCR. One hundred different configurations of the training and 184 test sets were used. Z-score normalization was applied on each features of the feature set. Then, a 185 dimension reduction was applied using ReliefF method [27] to select the twenty most relevant features 186 on the whole data set. From the reduced feature set, supervised machine learning was used to build the 187 prediction model. Four classifiers were evaluated: a multilayer perceptron (MLP) trained with a 188 stochastic gradient algorithm using an adaptive learning rate and a regularization of the synaptic 189 weights ($\Box = 0.1, 5$ mini-batches, 30 hidden nodes, and 60 epochs); a support vector machine (SVM) 190 with a linear kernel; a SVM with a quadratic kernel (trained with box-constraint c = 1) and a random 191 forest (3 splits and 50 learning cycles). The difference between the AUC for the training set and for 192 the test set was used to evaluate the overfitting of the classification method. We evaluated the 193 performance of the classification models thanks to the area under the curve (AUC) of the receiver 194 operating characteristic (ROC). The difference in AUC between the training and the testing sets was 195 used as an indicator for the predictive model to generalize the estimation.

196

197 Statistical Analysis

A Sørensen–Dice index was computed to compared the delineation given by various radiologists. An intraclass correlation coefficient (ICC) for each radiomic features was computed using package psych in R software. As we compared the radiomic features from three segmentations (initial P.C, corrected by A.C. and independent F.B.), we used the "ICC2" definition (this measure is one of absolute agreement in the ratings and could be generalize to other observers).

A linear mixed regression model with random intercept was used to evaluate the effect of the multicontrast feature sets, the effect of the choice of classifier, and the effect of additive information from the parenchyma in the feature set on the AUC values (details in supplementary information). T-test was performed for specific pairwise comparison. Analyses were made using R software, v. 3.6.1 (Vienna, Austria).

208

209 Pathological examination and response to treatment

210 The breast cancer was diagnosed on biopsy. All anatomopathological diagnostics were realized by 211 expert pathologists specialized in breast cancer from our institution. The expression of estrogen 212 receptor, progesterone receptors, and HER-2 status was determined on histopathological pre-213 therapeutic biopsy samples. Hormone receptor negative status was defined if less than 10% of cells 214 revealed staining for estrogen and progesterone receptors. The expression of HER-2 was considered 215 negative if lower than 1+ in immunohistochemistry. Tumors with a score at 2+ required additional in 216 situ hybridization to determine the amplification or non-amplification of HER-2. After a 6-month 217 NAC treatment, all patients underwent breast surgical intervention (lumpectomy or mastectomy). The 218 complete pathological response was defined by the absence of invasive residual tumor in the resected 219 tissues (carcinoma in situ could be found) and the absence of axillary nodal metastasis. The TNM stage was ypT0 ypNO or ypTis ypNO, according to 2012 seventh editions of the AJCC CancerStaging Manual 2012[28].

222

223 **RESULTS**

224 Clinical characteristics

Among 79 patients eligible for study enrolment, four patients were excluded: one for MRI-protocol performed one week after the treatment initiation, and three because the SUB3 images were missing or not complete after the data transfer from the archive server. Among the 75 patients enrolled, 11 patients presented two lesions, and 3 patients presented three lesions. Two patients presented bilateral tumors. Lesions were analyzed independently. 14 out of these 92 tumors had a clip. Three lesions were excluded for inadequate size to perform radiomic processing. Tumor characteristics are summarized in Table 2.

8 out of the 75 patients underwent MRI protocol using the SENSE-Breast-7 coil, and the remaining patients the SENSE-Breast16M. No significant difference in signal-to-noise ratio was observed between images acquisitions with the SENSE-Breast-7 and the SENSE-Breast16M coils (t-test, pvalue = 0.33). For some patient, images from the pre-therapeutic MRI images were missing; details are summarized in Table 3 and reported the proportion of pCR and non-pCR.

237

238 Comparison of multi-contrast imaging features

Out of the 89 tumors analyzed, 70 used the whole MRI protocol (T1W, T2W, DWI, and DCE).
Multiple combinations of feature set were tested to evaluate the necessity of multiple contrasts
imaging (Figure 3). Moreover, different classifiers were used and their performances were compared.

Based on the AUC in the training set, the SVM with a quadratic kernel showed the best results (mean AUC of 0.99, Figure 3J). Random Forest and Multilayer perceptron also provided very good results with a mean AUC of 0.93 and 0.90, respectively, for the training set. The "SVM order 1" classifier showed the smallest difference in AUC between the training and test sets reflecting the smallest overfitting (Figure 3 C, F, I, L), or largest bias.

247 The random forest, "SVM order 2", and the MLP classifiers suggest advantages in adding information

248 from different images issued from different MRI sequences. The most interesting configuration of

feature set appeared to be the combination of DWI, T1W, and T2W features: firstly, the AUC in the validation set was larger than in other configurations even considering the configuration with only T1W features (+ 0.034, p <0.001, linear mixed model with Dunnett post-hoc test, details in supplementary information); secondly, the overfitting expressed by the difference in AUCs was in the same range than that of the "SVM order 1" (+0.008, p =0.564, t-test).

The same parameters were used without any characteristics of parenchyma while keeping selected the 20 most relevant parameters. A significant decreased in AUC for the test set was observed for "SVM order 2" (- 0.047, p <0.001, linear mixed model with Dunnett post-hoc test, details in supplementary information). These results showed that the characteristics of both parenchyma and tumors seemed to allow a better prediction of pCR. Unfortunately, the AUC results depended on the repartition of the data in the training set and in test set, and the ranges of AUCs in the test set were large.

To go further, it would be interesting to accurately identify the non-pCR patients to avoid exposure to ineffective systemic treatment. In that case, the specificity of the predictive model was the most important. We observed that sensitivity was higher than specificity in our series (Figure 4).

263

264 Effect of features selected

The "SVM order 2" combined with DWI, T1, and T2 features seemed to better predict pCR. 265 266 Therefore, we analyzed the effect of the number of features selected before applying classification. 267 The ReliefF method allowed to promptly classify the most independent features (Table 4). The 268 textural features appear more relevant than shape and 1er order textural features (26 textural features 269 against 4 shape feature). The Figure 5 shows: i) an increase in AUC, specificity and sensitivity values 270 from 1 to 9 parameters; ii) a plateau from 9 to 24 parameters; iii) a slight decrease after 24 parameters. 271 The nine most relevant features appeared as sufficient. In relevant shape feature, the one from 272 parenchyma was very interesting because it reflects the proportion of the sane parenchyma against the 273 tumor (the tumor area was removed from the parenchyma delineation in the binary mask). For the 274 T1W without fat suppression, lobules, ducts and bloods vessels appear in lower values than fatty 275 tissue. The features Short-Run Low Gray-level is the distribution of the short homogeneous runs with 276 low grey-levels and appeared to be a relevant textural feature from parenchyma on T1W imaging.

279

Variability of intra-observer delineation and radiomic feature implications

280 The variability analyses were done on a subset of 24 lesions. The segmentation approved by the 281 radiologist AC was considered the reference. A mean DICE coefficient of 0.95 ± 0.07 (range of 0.74 -282 1.00) reflecting the concordance between the two radiologists (PC and AC). The mean DICE 283 coefficient was 0.84 ± 0.10 (range of 0.56 - 0.99) comparing the delineation approved by AC and FB. 284 The worst result (DICE = 0.56) came from a stack of images where the contrast enhancement was very 285 low and therefore difficult to segment without information on the pathology. The majority of DICE 286 coefficient was over 0.80. To measure the impact of delineation variation on radiomic features, an ICC 287 was computed for each feature. On the most relevant features highlighted by the ReliefF method in our 288 study, we observed that textural features have a good ICC (mean 0.88 range 0.65-0.98) but the shape 289 features have a worst ICC2 (mean 0.44 range 0.31-0.56). The textural features represented 75% of the 290 nine most relevant features.

291

292 **DISCUSSION**

This study shows that multi-contrast MRI-based radiomics allows to predict the neo-adjuvant chemotherapy response in patients with early triple negative breast cancer with good performances.

295 This study also showed that the choice of classifier strongly influences model performances. While 296 SVM with a linear kernel generalized well, probably due to lower variance and higher bias 297 (highlighted by lower AUC in the training set), other non-linear classifiers such as neural network, 298 quadratic-kernel SVM, and Random Forest, increase performances by reducing bias effect (high 299 performances in the training set), and increase variance and therefore overfitting, as indicated by 300 increased AUC differences between dataset. However, the increase in variety of processable data 301 combining different sources of radiomics (multi-contrast MRI) reduced variance effect as evidenced 302 by reduced AUC differences between dataset when radiomics aggregated from different contrasts. Our 303 results showed that the best model (AUROC at 0.83) was obtained with SVM with a quadratic kernel 304 trained from aggregated radiomics extracted from T1, T2, and diffusion weighted images.

305 From a clinical point of view, radiomic signature could help to better predict pathological complete

306 response, and enhanced stratification of patients with an excellent prognosis, and patients at high risk 307 of chemoresistance. In the latter population, systemic treatment combined to the standard NAC 308 (anthracycline/taxane) may be added, such as platinum-based NAC [29], a PARP inhibitor [30], or 309 even an immune-checkpoint-inhibitor. Indeed, the KEYNOTE-522 trial [31] investigating the addition 310 of prembrolizumab to neo-adjuvant standard chemotherapy showed an increase of 64.8% of 311 pathological complete response, compared with 51.2% in the placebo control group. Therefore, it 312 seems important to appropriately select patients who may benefit the most from appropriate systemic 313 treatment, highlighting the medical need for these non-invasive stratification methods.

314 The most informative sequences identified were the association of T1/T2 morphological sequences 315 and diffusion sequence. However, these results also depend on the DCE-MRI sequence used for the 316 segmentation of the lesion. Indeed, we observed some pixels in the fat surrounding the tumors in the 317 mask registered on T1W images; which would not have been integrated if the segmentation had been 318 directly performed on T1W images. The parenchyma features appeared to be relevant in this study. 319 The shape feature computed on the parenchyma binary mask (the difference between the parenchyma 320 and the tumor delineation) appeared to be more relevant than the shape feature computed on tumor 321 binary mask. More generally, the most relevant features were high order of textural features. These 322 textural features would reflect the textural complexity from a macroscopic point of view but the tumor 323 heterogeneity in a microscopy point view. Moreover, the textural features appeared to be more robust 324 to inter-observer variability (different delineation) with high intraclass correlation coefficient.

Our results are consistent with previous studies showing that AUC ranged from 0.67 to 0.87 [10– 12,14], allow to predict the response to breast cancer chemotherapy. Among these studies, Braman and collaborators showed that the triple negative subgroups had the best results with a 0.93 AUC, and Liu and colleagues reported AUC at 0.86 with fewer TN patients. Our series showed that 64% of the patients achieved a pathological complete response; this rate is higher than that reported in previous studies with 31% of patients complete pathological responses in [32].

331

332 Our study has some limitations. First, the size of our population was limited to 75 patients and the 333 multiparametric radiomic analyses were only achieved in 70 lesions. However, to the best of our 334 knowledge, this TN cohort was the largest cohort dedicated to radiomic studies. The lesion 335 segmentation was done manually, which may introduce a degree of subjectivity. In addition, this study 336 was performed in a single institution study; and extrapolating results to population of another center is 337 limited. Lastly, MRI protocols are not standardized between centers in the field of breast cancer 338 analyses inducing variability in the radiomic feature sets. Several studies have shown the sensitivity of 339 radiomic parameters to machine's change or reconstruction parameters [33–35].

340 Those results have to be confirmed in an external validation cohort with multicentric and prospective341 data, and more patients.

342

To conclude, our results confirm that MRI-based radiomics may be relevant to predict neoadjuvant chemotherapy response in early triple negative breast cancer. In addition, our results highlight the interest of using multi-contrast MRI as sources of radiomics to improve model generalization thanks to increased information variety.

347

348 Authors' Contribution

349 Nemeth: Study conception and design, Analysis and interpretation of data, Drafting of350 manuscript, Critical revision

- 351 Chaudet: Study conception and design, Acquisition of data, Analysis and interpretation of
- 352 data, Drafting of manuscript
- 353 Leporq: Study conception and design, Analysis and interpretation of data, Critical revision
- 354 Heudel: Study conception and design, Acquisition of data
- 355 Barabas: Acquisition of data, Analysis and interpretation of data
- 356 Tredan: Study conception and design
- 357 Treilleux: Study conception and design
- 358 Coulon: Study conception and design, Acquisition of data, Analysis and interpretation of data,
- 359 Drafting of manuscript
- 360 Pilleul: Analysis and interpretation of data, Critical revision
- 361 Beuf: Analysis and interpretation of data, Critical revision
- 362 **Declarations**

363 *Ethics approval*

Ethical approval was waived by the local Ethics Committee of our institution in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

367

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480 Figure 1. Two triple-negative breast cancers imaged with pre-therapeutic MRI protocol. First

- 481 line: a mass tumor is shown; second line: a non-mass tumor is illustrated. Segmentation of tumor (in
- 482 yellow) and segmentation of parenchyma (in green excluding tumor area) were made on derived DCE-
- 483 MRI. For non-mass tumor, the option "snake" of ITK-SNAP was used to perform the segmentation.



487 Figure 2. Pipeline of radiomic feature extraction and combination of feature sets.









495 Figure 4: ROC curves for the SVM classifier with quadratic kernel. The most interesting

496 configuration of feature set appeared to be the combination of DWI, T1W and T2W features with

497 AUC =0.83, sensitivity =0.85 and specificity =0.75.



501 Figure 5: Variation of model performances in training and test sets according to the number of

502 feature selected with the ReliefF method.

5	0	5
\mathcal{I}	v.)

imaging), DWI (diffusion weighted imaging) and DCE (dynamic contrast enhancement).

	T1W	T2W	DWI	DCE
Pulse-sequence	TSE	SPAIR (TSE)	SE	TRIVE (TFE)
Flip angle	90°	90°	90°	12°
TE	7 ms	70 ms	75 ms	2.73 ms
TR	600 ms	2.8 s	3.5 s	5.5 ms
Slice thickness	3 or 3.5 mm	3 or 3.5 mm	2 mm	2 mm
Pixel resolution	$0.45 \times 0.45 \text{ mm}^2$	$0.55 \times 0.55 \text{ mm}^2$	$1.17 \times 1.17 \text{ mm}^2$	$0.75\times0.75~\text{mm}^2$
Fat suppression	no	yes	yes	yes
b (s/mm ²)	/	/	700	/
Contrast agent	no	no	no	yes

Patients	75
Characteristics	(n=89)
BRCA1 Mutation	11
Mean age in years (range)	48 (26 – 75)
Tumor size in mm (range)	38 (20 - 92)
- T1 (< 2cm)	3
- T2 (2-5cm)	55
- T3 (> 5cm and < 5cm)	9
- T4 (Any size tumor with direct extension to chest wall or skin)	22
Masses	83
- Shape:	
o Oval	4
• Round	6
• Irregular	73
- Margin:	
• Circumscribed	7
• Not circumscribed irregular	58
• Not circumscribed spiculated	18
Internal enhancement characteristics:	
• Homogeneous	3
• Heterogeneous	53
• Rim enhancement	27
- Kinetic curve assessment:	
• Persistent : type 1	1
• Plateau : type 2	33
• Washout : type 3	39
• Not reported	16
- T2 signal intensity:	
• Hypointense/isointense	25
• Hyperintense	64
Non Mass enhancement	6
- Distribution:	
• Focal	0
o Linear	0
• Segmental	2
• Regional	2
• Multiple regions	0
• Diffuse	2
- Internal enhancement patterns :	
• Homogeneous	1
• Heterogeneous	3
• Clumped	2
 Clustered ring 	0
Adenopathy	
- Axillary	53
- Internal mammary	20
Pathologic complete response	
- Yes	57
- No	32
Histologic types	
- Infiltrating ductal carcinoma	78
- Infiltrating ductal carcinoma + ductal carcinoma in situ	6
Others (metaplastic carcinoma, myoepithelial carcinoma	•
medullary carcinoma)	´5
· · ·	

Table 2. Patient information and tumor characteristics

Type of surgery	
- Lumpectomy	33%
- Mastectomy	67%

512 Table 3. Number of lesions imaged with DCE-MRI, T1W, T2W, and DWI sequences.

	SUB3 (N=89)	T1W (N=86)	T2W (N=76)	DWI (N=72)
pCR	57	56	47	45
non-pCR	32	30	29	27

Order	Type of	Type of	Type of	Function	Parameter names	
(ReliefF)	tissue	imaging	features			
1	Tumor	T2W	Textural	SURF	std_blobs_strength	
2	Parenchyma	Binary	Shape	Affine	Affine_moment_invariant_6	
		mask		moment		
3	Tumor	T2W	Textural	Quadtree	sum_blocks	
4	Parenchyma	T1W	Textural	GLRLM	Short_Run_Low_Gray_Level_Emphasis	
5	Tumor	T2W	Textural	Quadtree	mean_c	
6	Tumor	T1W	Textural	SURF	std_blobs_strength	
7	Tumor	Binary	Shape	Zernike	Zernike_moment_Phi8	
		mask		moment		
8	Tumor	Binary	Shape	Hu	Hu_moment_1	
	_	mask		moment		
9	Tumor	T1W	Textural	Gabor	Gabor_square_energy_s1	
10	Tumor	T2W	Textural	Quadtree	mean_r	
11	Tumor	T1W	Textural	Grad	G2_y_sum	
12	Tumor	DWI	Textural	SURF	mean_blobs_strength	
13	Tumor	T1W	Textural	Gabor	Gabor_square_energy_s2	
14	Tumor	T1W	Textural	Grad	G1_y_sum	
15	Tumor	T1W	Textural	Grad	L4_sum	
16	Tumor	T1W	Textural	Grad	L2_sum	
17	Tumor	T1W	Textural	Grad	L1_y_sum	
18	Tumor	T1W	Textural	Grad	G1_x_sum	
19	Tumor	T1W	Textural	Grad	G2_x_sum	
20	Tumor	T1W	Textural	Grad	L3_sum	
21	Parenchyma	T1W	Textural	GLCM	Information_measure_of_correlation_2	
22	Tumor	T1W	Textural	Grad	L1_x_sum	
23	Tumor	T1W	Textural	Gabor	Gabor_square_energy_s5	
24	Tumor	Binary	Shape	Skelet	std_2	
		mask		features		
25	Parenchyma	DIFF	Textural	GLCM	Correlation	
26	Tumor	DIFF	Textural	FFT	rank_F_orient1	
27	T	DIFF	T . 11	reatures		
27	Tumor	DIFF	Textural	++1	rank_F_orient2	
20	Tumor		Toytural		rank E priont?	
28	rumor	DIFF	rextural	footures	Talik_F_OHERIUS	
20	Tumor	T1\A/	Toytural	Cabor	Cabor square operation	
29	Tumor		Toxtural	Quadtrac	longth quadtroo	
	Turnor		TEXCUIDI	Quautree	iengui_quautiee	

519 Supplementary information

520 Statistical analyses

- 521 The aim of this supplementary information is to provide complete statistical analyses about
- 522 the impact of different configuration of feature set on classifier performance. Indeed, in the
- 523 paper, only the most relevant results were illustrated.
- 524 <u>Multiple effects were analyzed:</u>
- 525 1. Multiple configurations of feature sets from multi-contrast imaging (ex: combining
 526 features from the DWI and T1W).
- 527 528

2. Effect of adding information from parenchyma (combining features from the parenchyma and from the tumor).

- 529 3. Effect of the classifier chose.
- 530

531 For each of the 100 random draws of training/validation set (performing with "cvpartition" 532 Matlab function), fifteen configurations of feature set were tested. For each feature set, 4 533 classifiers were applied to provide a predictive model and the AUC was used to evaluate the 534 performance of each classifier. To compare the fifteen configurations of feature, a linear mixed-effect model (LMM) was performed on AUC of validation set (or AUC of training set) 535 for each classifier using "lmer" R function. For the design of the LMM, we considered 536 537 repeated measurements on training/test set (100 different cases) with three fixed factors: 538 Configurations (15 possibilities), Type of initial features set (tumor only or tumor + 539 parenchyma) and Classifier (4 possibilities: SVM order 1, Random Forest, Multilayer 540 perceptron and SVM order 2); and a random effect. The normality of each distribution was 541 validated by a quantile-quantile plot. Figures S1, S2, S3 and S4 shows boxplot of the fifteen possible configurations with data "tumor only" for A,B and C graphs and with data "tumor + 542 543 parenchyma" for D, E and F. The fixed-effect results of LMM were summarized in table S5. 544 The LMM demonstrated a significant effect of adding information from the parenchyma with 545 greater values of AUC_training and AUC_validation (mean difference of respectively 0.020 and 0.047 after the correction of "configurations" effect and "classifier" effect). Most of 546 547 configurations using multi-contrast imaging have higher AUC values than using only one contrast; expect for the configuration "DWI + T2W". The classifier with the highest AUC 548 549 values in both training and validation sets was the SVM with quadratic kernel.



Figure S1 (Support vector machine with linear kernel): Boxplot of AUC distribution in the training/validation set and the difference of the AUC of the two sets. Feature set used for the classification was designed as follow: "1" designs T1-weighted imaging, "2" for T2-weighted imaging, "D" for diffusion weighted imaging and "S" for the subtraction of DCE-MRI. The initial feature set was composed of tumor features for A, B, C. The initial feature set was composed of tumor and parenchyma features for D, E, and F.



Figure S2 (Multilayer perceptron classifier): Boxplot of AUC distribution in the training/validation set and the difference of the AUC of the two sets. Feature set used for the classification was designed as follow: "1" designs T1-weighted imaging, "2" for T2weighted imaging, "D" for diffusion weighted imaging and "S" for the subtraction of DCE-MRI. The initial feature set was composed of tumor features for A, B, C. The initial feature set was composed of tumor and parenchyma features for D, E, and F.



Figure S3 (Random Forest classifier): Boxplot of AUC distribution in the training/validation set and the difference of the AUC of the two sets. Feature set used for the classification was designed as follow: "1" designs T1-weighted imaging, "2" for T2weighted imaging, "D" for diffusion weighted imaging and "S" for the subtraction of DCE-MRI. The initial feature set was composed of tumor features for A, B, C. The initial feature set was composed of tumor and parenchyma features for D, E, and F.



Figure S4 (Support vector machine with quadratic kernel): Boxplot of AUC distribution in the training/validation set and the difference of the AUC of the two sets. Feature set used for the classification was designed as follow: "1" designs T1-weighted imaging, "2" for T2-weighted imaging, "D" for diffusion weighted imaging and "S" for the subtraction of DCE-MRI. The initial feature set was composed of tumor features for A, B, C. The initial feature set was composed of tumor and parenchyma features for D, E, and F.

Table S5: Mean difference from reference of fixed effect of linear mixed model with

586 random intercept applied on AUC_training results and AUC_validation results. Dunnett

post-hoc analyses were made to evaluate the significance of difference. *** p<0.001

	Mean difference from reference		
	AUC Training	AUC Validation	
Initial feature set			
Tumor only (reference)			
Tumor + parenchyma	0.020 ***	0.047 ***	
Configurations			
Sub3 (reference)			
T1W	0.008 ***	0.049 ***	
T1W + T2W	0.016 ***	0.073 ***	
T2W	0.030 ***	0.011 (p = 0.502)	
DWI	0.016 ***	-0.013 (p = 0.252)	
DWI + T1W	0.028 ***	0.075 ***	
DWI + T1W + T2W	0.024 ***	0.083 ***	
DWI + T2W	-0.006 (p = 0.088)	-0.021 (p = 0.005)	
Sub3 +T1W	0.018 ***	0.060 ***	
Sub3 + T1W + T2W	0.001 (p = 1.000)	0.072 ***	
Sub3 + T1W + T2W + DWI	0.010 ***	0.077 ***	
Sub3 + T1W + DWI	-0.001 (p = 1.000)	0.036 ***	
Sub3 +T2W	0.010 ***	0.003 (p = 1.000)	
Sub3 +T2W + DWI	0.028 ***	0.040 ***	
Sub3 + DWI	0.026 ***	0.022 (p = 0.002)	
Classifier		_	
SVM order 1 (reference)			
MLP	0.075 ***	-0.019 ***	
Random Forest	0.143 ***	0.031 ***	
SVM order 2	0.186 ***	0.073 ***	