MEDICAL IMAGING MUTIFRACTAL ANALYSIS IN PREDICTION OF EFFICIENCY OF CANCER THERAPY

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ABSTRACT

Based on pressing need for predictive performance improvement, we explored the value of pre-therapy tumour histology image analysis to predict chemotherapy response. It was shown that multifractal analysis of breast tumour tissue prior to chemotherapy indeed has the capacity to distinguish between histological images of the different chemotherapy responder groups with accuracies of 91.4% for pPR, 82.9% for pCR and 82.1% for PD/SD.

KEYWORDS

breast cancer; prediction; histology; chemotherapy, fractal; multifractal; drug response

1. INTRODUCTION

An ideal predictive marker should reliably predict chemotherapy responses in breast cancer and thus determine the right treatment for each individual patient. Consequently, an effort to improve the accuracy of predictive markers is expected to provide a reduction of relapse rates and prolonged survival.

In parallel to standard molecular approaches, digital pathology emerged as a structure analysis tool to aid in detection, diagnosis(Cross 1997; Vasiljevic, Reljin et al. 2012), risk assessment (Vasilescu, Giza et al. 2012), chemotherapy efficacy assessment (Li, Hu et al. 2014) and therapy prediction for cancer (Laurinavicius, Plancoulaine et al. 2014). It is based on computational analysis of medical images by use of texture or fractal algorithms. Studies indicate an association between multifractal parameters of breast tumour histology and pathologic tumour grade (Braverman and Tambasco 2013), fractal dimension of breast malignant epithelium and survival

Natarajan Meghanathan et al. (Eds) : ACSIT, SIPM, CMIT, CoNeCo - 2016
pp. 61–67, 2016. © CS & IT-CSCP 2016 DOI : 10.5121/csit.2016.60806

(Tambasco, Eliasziw et al. 2010) and breast tumour MRI fractal geometry and response to neoadjuvant chemotherapy (Di Giovanni, Ahearn et al. 2012).

Surprisingly, although fractal analysis is known as powerful morphometry tool for quantitative assessment of complex pathological structures (Huang and Lee 2009), its usefulness in breast cancer therapy prediction has not been investigated. Therefore, in this study we exploit the multifractals to discriminate between breast tumours with different sensitivity to chemotherapy. This task was approached by a neoadjuvant therapy model which has been accepted as an ideal in vivo assessment of therapy response, with a consequent wide use for evaluation of predictive markers (Kanjer, Tatic et al. 2013). The specific objective of this study was to identify the fractal parameter which provides the most accurate prediction of the chemotherapy response.

2. MATERIALS AND METHODS

Patients

Patients received neoadjuvant, anthracycline-based chemotherapy at our institution between 1999 and 2003. Criteria for the selection of patients were as follows: 1) an incisional biopsy of the primary breast cancer confirming invasive carcinoma before commencing the treatment and 2) primary locally advanced breast cancer that was strictly not operable. Patients with bilateral or metastatic disease were not included in the analysis.

Patient treatment and assessment of the response to therapy

Prior to surgery, all patients were treated with standard anthracycline-based chemotherapy (5-fluorouracil 500 mg/m2, doxorubicin 50 mg/m2 and cyclophosphamide 500 mg/m2 intravenously). Breast tumour response was evaluated after chemotherapy completion by pathohistological examination of the resected surgical material including measurement of the residual tumor size, optical microscopy and immunohistohemical analysis according to recommendations of International Expert Panel (Kaufmann, Hortobagyi et al. 2006), as previously described in detail (Kanjer, Tatic et al. 2013).

Multifractal analysis

Sections were cut at 5-μm thickness from the paraffin blocks and stained with haematoxylin / eosin stain as previously described (Kanjer, Tatic et al. 2013). Representative tissue sections were selected for each patient by a pathologist and digital microscopic images acquired at x400 magnification using Olympus BX-51 light microscope and a mounted Olympus digital camera. For each of the three groups, 350 images were again selected by a pathologist (1050 in total). Multifractal analysis of digital medical images was performed by use of free FracLac software and the stratification accuracy of each parameter was subsequently calculated by use of the classification type Single Tree (MATLAB 2010 and DTREG predictive modeling software version 10.3.0). Accuracy refers to the proportion of true results. Other calculated parameters included precision or positive predictive value as the proportion of patients with the disease who are correctly predicted to have the disease. F-Measure is the harmonic mean of precision and recall to give an overall measure of the prediction quality. Recall or negative predictive value is the proportion of patients who do not have the disease who are correctly predicted as not having the disease.

The main multifractal parameter is the Hölder's exponent which depends on local regularity of the observed structure (Evertsz, Mandelbrot et al. 1992).

$$\alpha = \frac{\log \mu \text{ (box)}}{\log \varepsilon}$$

where μ (box) represents the signal measurement within the box and ε is the box size. The distribution of α is known as the multifractal spectrum, f (α), describing the global regularity of observed structure. Multifractal analysis permits the description of structure features from both local and global points of view. For instance, high values of Hölder exponent α denote high local changes, while high multifractal spectrum f (α) values denote frequent events – isolated parts in the whole structure having particular value of α (Reljin, Paskas et al. 2011).

3. RESULTS AND DISCUSSION

3.1 Analysis of microscopic images

The primary tumour of patients with early breast cancer is the main source of information for assessment of the disease recurrence risk and the choice of the most appropriate systemic treatment. Assessment of the predictive potential of multifractal analysis was performed on the patient group which was preoperatively treated with anthracycline-based chemotherapy. Such neoadjuvant model is particularly suitable for characterization of chemotherapy predictors as it allows for exact evaluation of the chemotherapy response with the tumour remaining *in situ* throughout treatment. Multifractal analysis was performed on digital images of tumour tissue sections obtained prior to therapy application. As the study was retrospective, the patient stratification into three response categories was done according to their actual response to therapy: partial pathological response (pPR), pathological complete response (pCR) and progressive/stable disease (PD/SD). Representative images for each of these categories are shown respectively on Figs. 1a, c, e. For multifractal analysis these images were transformed from colour to binary as depicted in Figs. 1b, d, f. At this x400 magnification, the histology of sensitive and resistant tumours was visually similar (Figs. 1a, c, e). Such histological similarity also remained at higher and lower magnifications (not shown).

3.2 Prediction of response to chemotherapy by multifractal analysis

Table 1 indicates that fractal dimension predicts response to chemotherapy with high accuracy. pCR and PD/SD are the extreme groups and thus most important as they give clear guidance regarding the therapy sensitivity or resistance (Cortazar, Zhang et al. 2014), while the clinical use of stratification into partial response pPR group is more limited. Importantly, the prediction accuracies of over 82% achieved for pCR and PD/SD groups are in line with those previously obtained by the standard prediction marker Ki67 and the advanced PET/CT system which even had an advantage of predicting on the basis of the actual response to the first chemotherapy cycle (Sheri and Dowsett 2012; Lee, Bae et al. 2014; Sueta, Yamamoto et al. 2014). Taken together, our results indicate a potentially superior predictive performance of fractal analysis in comparison to existing prediction approaches, with an added advantage of cost effectiveness.

3.3 Importance of multifractal parameters in prediction of chemotherapy response

Multifractal analysis delivers a number of parameters which necessitated a need for evaluation of their relative predictive power. The ranking was based on the information about the role of variables as primary splitters and surrogate splitters. A variable is thus more important if it was selected as a primary splitter early in the Single Tree model.

4. CONCLUSIONS AND FUTURE WORK

Histological examination is mostly used for diagnosis, whereas immunohistochemical and genetic tests are utilized for treatment decisions. We hypothesized that breast tumour histological examination by fractal analysis may be of use for prediction of chemotherapy response, based on its known morphometric discriminating capacity when dealing with irregular tumour tissue structures. Improvements in chemotherapy response prediction are of high clinical relevance due to the major impact of chemotherapy on quality of life and survival. Multifractal analysis of breast tumour tissue prior to chemotherapy was here shown for the first time to differentiate between tissues based on their actual chemotherapy sensitivity. Usefulness of this methodology relies on its high accuracy and also cost-effectiveness deriving from rapid analysis of standard clinical material. Exploration of the predictive usability among obtained multifractal parameters indicated the critical importance of the $f(\alpha)_{max}$, the maximum of multifractal spectrum. It can be speculated that the observed predictive power of the multifractal analysis is based on the detection of unknown structural clues which indicate the response to chemotherapy. Additional investigation is necessary to characterize the value of $f(\alpha)_{max}$ for the prediction of drug resistance.

ACKNOWLEDGEMENTS

This work was supported by the Ministry of Education and Science, Republic of Serbia, Science and Technological Development grants ON175068, III 45005 and TR32037.

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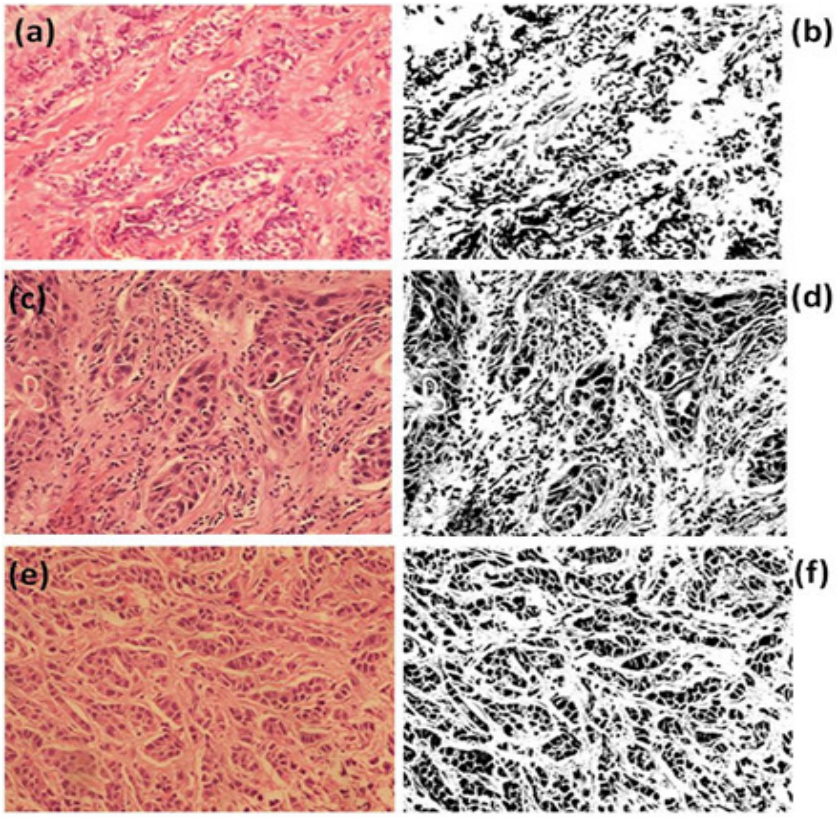

Fig. 1. Primary breast tumour tissue sections before therapy. (a) Partial pathological response in colour and (b) as binary image. (c) Pathological complete response in colour and (d) as binary image. (e) Progressive/stable disease in colour and (f) as binary image. Sections were stained with hematoxylin and eosin, magnification x400.

Table 1 Comparison of groups with different response to chemotherapy by multifractal analysis

	Partial pathological response	Pathological complete response	Progressive/stable disease
Accuracy	91.4 %	82.9 %	82.1 %
Sensitivity	85.1 %	80.3 %	69.1 %
Specificity	94.6 %	84.1 %	88.6 %
Geometric mean*	89.7 %	82.2 %	78.3 %
Precision	88.7 %	71.7 %	75.1 %
F-Measure	0.87	0.76	0.72

*Geometric mean of sensitivity and specificity

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