Fractal Analysis in Cancer Diagnosis

Detecting Patterns within Patterns

A method of cancer diagnosis for the assessment of the level of malignancy of a tumor utilizes the relationship between its structural complexity with the aggressivity of the tumor. We use a marker-free, cost-effective interference contrast microscopy method, with which adhesion topologies and contours of tumor cells can be imaged and use fractal analyses to classify the cells and derive possible statements about their potential for metastasis.

Tumor Diagnosis
The correct recognition of tumor cells and their categorization in a "grading system" is an important aspect of tumor diagnosis, in order to specify a treatment which promises success. The usual standard methods for estimating the malignancy of a tumor are immuno-histochemical staining of biopsy samples and determination of the lymph nodes which have been permeated. These methods are not only very time-consuming and expensive; they are often not definitive, are not standardized so that the potential for metastasis and the quality of the prognosis can only be determined indirectly. A small, dense tumor which is highly aggressive can be incorrectly categorized as having a low malignancy and the patients are not optimally treated. The objective is to develop new methods which enable standardized and forecast values for a tumor on the basis of automated image detection, with a direct statement with regard to the potential for metastasis, without the use of additional expensive reagents.

What Are Fractals?
The method shown here is based on the fractal analysis of the adhesion patterns of cancer cells. Fractals are patterns which repeat themselves at various size levels. This is known as self-similarity and independence of scale. The closer the pattern is zoomed in, the more details can be recognized. The term „fractal" was coined by Benoit Mandelbrot in the 1960’s and expresses the fact that these objects have complex geometrical forms and cannot be described by integer dimensions. The best known example of a fractal comes from the publication „How long is the coast
of Great Britain?[1]. The length of the coastline becomes longer as it is measured in greater detail.

The Fractal Dimension (FD) describes the degree of ruggedness of the coast, or in general how quickly structural details increase as the pattern is zoomed in.

The relationship between fractal and geometrical dimensions can be illustrated with the example of a line, a square and a cube. If the linear dimension of the objects are reduced by the scaling factor $1/r$, the dimensions of length, area and volume change by $N=r^D$ times the original size. If this equation is solved for $D$, a generalized form of the dimension is obtained according to Hausdorff, for which non-integer values are also possible. The same rule is also used for fractal geometries, e.g. the Koch curve. If the fractal line is measured with a tape measure with a particular length and then measured again with a tape measure with a reduction factor of $1/3$, the curve is however not $3x$ as long as previously, but rather $4x$, i.e. $N=4$ and $r=3$. The FD of the Koch curve is therefore $D=\log(4)/\log(3)=1.26$ and possesses area-occupying character. For natural fractals, the FD must be determined empirically from the slope of the regression lines from a log-log plot of the number of tape measures required against the size of the tape measure. Examples of natural fractals are chains of mountains, snowflakes, romanesco broccoli, or the neuron networks, capillary systems and the structure of the lungs and blood vessels of living creatures. Dynamic processes such as the rhythm of heartbeats or blood pressure may also have fractal structures.

**Cancer and Fractality**

The occurrence of cancer can be considered as a deviation from equilibrium structures, causing chaos and therefore a higher degree of complexity. This applies on the level of tumor morphology down to intracellular compartments such as the cell nucleus and correlates with the aggressivity of the tumor [2]. Many cellular processes are linked to cell adhesion, therefore the observation of the precise
adhesion pattern enables quantification of even minimal changes due to dysregulation. Tumor progression is often accompanied by reduced expression of cell adhesion proteins in favor of migration-promoting proteins e.g. in the case of an epithelial mesenchymal transition.

**Cell Adhesion Topologies with RCIM**

Reflection interference contrast microscopy (RICM) offers a unique method for imaging cell adhesion topographies without previous marking, with an axial resolution limit of approx. 1 nm. Furthermore, it enables the imaging of very fine cell contours. The contrast of the image results from the interference of polarized light, which is reflected at the boundary surfaces of the glass-buffer and buffer-cell membrane. Both this roughness of the cell as well as the contour are a part of the characteristic fingerprint of the cell and have fractal geometries. We first examined the FD of tumor cell lines by means of RICM images and were able to identify tumor cell lines with variously pronounced aggressivity, but originating from the same tissue, by means of the features of cell topology and cell contour. The more aggressive form always had a higher FD. As an illustration of the precision of the method, two pancreas sister cell lines PaTuS (benign) and PaTuT (malignant) are cited, for which the probability of failure to recognize the malignant form is only 3% and therefore significantly better than the current standard methods [3].

To make the identification of the cells and the derived prognosis more precise, further static and dynamic adhesion-associated classification parameters from the RICM images were used. As the next step, the authors would like to work with primary cells from biopsy samples and compare the tumor grading data with the results from a pathology laboratory, and if possible to correlate this with the course of the patients’ health. In the long term they would like to establish a computer-assisted diagnostic system, in which the fractal analysis of RICM images functions as the primary identification method for tumor cells and additionally as a new forecasting biomarker for the potential for metastasis.

**Literature**


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