3-D fractal tumor growth of epithelial ovarian cancer

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Summary

Purpose: A fractal is a shape made of parts similar to the whole. Our objective was to determine whether surface growth patterns in malignant epithelial ovarian tumors are 3-D fractal, and if the mean fractal dimension differs according to histologic types.

Methods: After the images of photographs of 139 resected malignant epithelial ovarian tumors were digitized, the fractal dimensions of surface of solid portions were measured using 3-D fractal analysis software.

Results: The mean fractal dimensions of the surface of a solid area of tumor in serous, mucinous, endometrioid, and clear cell adenocarcinoma were 2.320, 2.224, 2.229, and 2.298, respectively. Those of serous and mucinous cystadenoma of low malignant potential (LMP) were 2.398 and 2.282, respectively. These values were significantly greater than the topological dimension of a surface (= 2).

The mean fractal dimensions of a solid area of tumor inside the cyst for serous, mucinous, endometrioid, and clear cell carcinoma were 2.347, 2.223, 2.228, and 2.310, respectively. The values for serous and mucinous cystadenoma of LMP were 2.398 and 2.282, respectively.

Conclusion: This study shows that the surface of a solid area of malignant epithelial ovarian tumors has a 3-D fractal structure, and the mean fractal dimension may differ according to histologic types.

Key words: Epithelial ovarian cancer; Fractals; Fractal analysis; Fractal dimension; Fractal geometry.

Introduction

Including ovarian cancer, various tumors show morphologically-complex growth patterns. Much medical investigation is concerned with the quantification of events. Although most of the existing methods of quantification rely on conventional Euclidean measurements, such as perimeter length and area, all attempts to describe such natural growth patterns by Euclidean geometry have failed. However, fractal geometry has emerged as a new tool for the characterization of irregularly shaped and complex figures, and may provide another way to fashion the answers.

The concept of fractal geometry was formulated by the mathematician Benoid Mandelbrot [1]. A fractal is a shape made of parts similar to the whole in some way [2]. This self-similarity occurs over an infinite range of scales in pure mathematical fractal structures such as a Koch curve (Figure 1), but over a finite range in many natural objects such as clouds, coastlines, snowflakes and cauliflowers. A cauliflower head contains branches or parts, which when removed and compared with the whole are very much the same, only smaller. The complexity of such natural forms cannot be described in terms of classical Euclidean geometry, largely because it is limited to considering structures in terms of their topological dimension (1 for a curve, 2 for a surface, and 3 for a solid), which is always an integer. Mandelbrot's solution to this was to plot the measured perimeter at different magnifications on a log-log graph, which gives a straight line, and to take the gradient of that line as the fractal dimension. He did this for the coastline of Britain and found that the fractal dimension was 1.25 [3]. The fractal dimension does not have to be an integer. Its value lies between the topological (Euclidean) dimension of the object and the object in which it is embedded. The fractal dimension is an index of the space-filling properties of an object so that the closer the dimension is to the topological dimension in which the object is embedded, the greater the space-filling properties. Fractals result from simple mathematical formulas that are iterated many times, and the results of each iteration are accumulated into a series of self-similar shapes.

Cancer is often characterized as having a chaotic, poorly regulated growth pattern. Autonomous and uncoordinated proliferation of epithelia leads to various well-known growth patterns. The irregularity of a tumor surface remains at a constant level over a wide range of magnifications like a cauliflower. Some studies applied fractal analysis focused on specific tumor shapes. Ovarian tumors have a wide variety of histologic types, each of which is different in biologic behavior. In our previous study, we reported that the surface of solid components in cystic epithelial ovarian cancers had a fractal structure, and that the mean fractal dimension might differ according to stages of the disease and histologic types [4]. In contrast to the previous work, where the 2-D fractal dimension of outlines of solid components in cystic epithelial ovarian cancers was determined using sonograms, in this article we examined the 3-D fractal dimension of the surface growth patterns of epithelial ovarian cancers.

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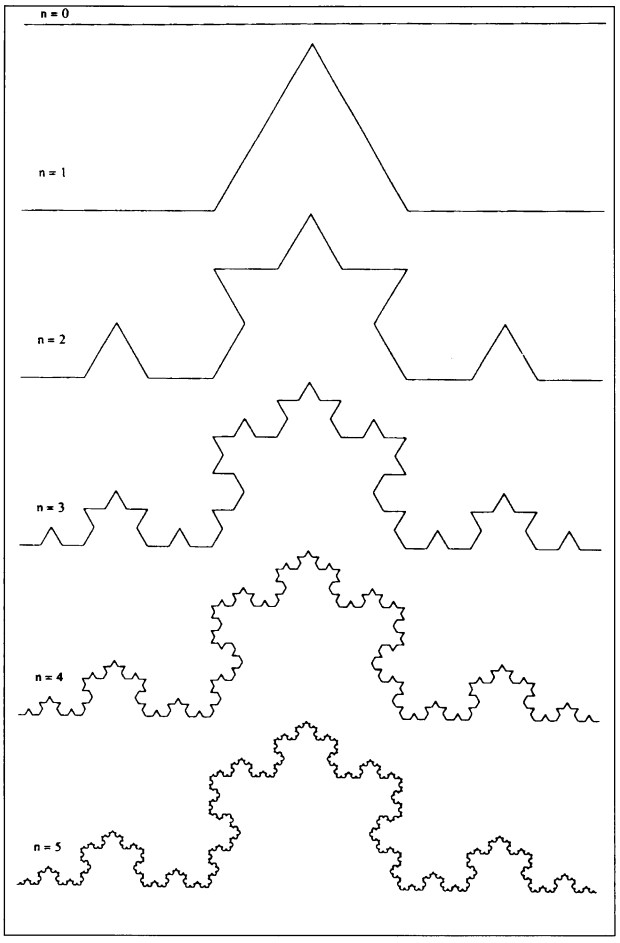


Figure 1. — Construction of the Koch curve.

Materials and Methods

Medical records from women operated on at Tokyo University Hospital due to malignant primary ovarian epithelial tumors were scrutinized for the period 1984-2001. Inclusion in the study was considered for patients who had undergone surgery for primary treatment and a histopathologic diagnosis of a surgical specimen had been made. At the time of surgery, gross visual examination and description of the resected ovarian tumor was done and a photograph was taken as part of the surgical pathology report before fixation. Any evidence of possible serosal involvement by tumor was examined macroscopically. When the tumor was cystic, the cyst wall was opened and a solid area of tumor in the cyst was fully examined. The following conditions stipulated exclusion from analysis: poor image quality of a photograph of the resected ovarian tumor, macroscopically unremarkable solid lesions, a small solid area of tumor less than 32 * 32 pixels in digitized images. An EPSON scanner GT-9700F connected to a personal computer (TOSHIBA DynaBook T4 495CME) was used to digitize all photographs in this study.

Fractal analysis was done using the fractal analysis software developed by Sasaki (http://cse.naro.affrc.go.jp/sasaki/index-e.html) [5]. After the color image was turned to gray scale, the surface of the solid area of the tumor was selected as the region of interest (ROI) for each photograph. When the solid tumors were found both inside the cyst wall and outside the serosa, the lesion inside the cyst wall was selected. According to the instructions by Sasaki, the image size of the ROI should be set as factorial of 2 (2, 4, 8, 16, 32, 64, 128, etc.), for example, 512 * 256 pixels, to calculate accurate fractal dimension when using this software. Thus paying special attention to this rule, as large an area within the tumor surface as possible was selected as the ROI for each case. If we regard the pixel intensity as the height above a plane, then the intensity surface of an image can be viewed as a rugged surface. Pentland shows that if a natural surface is fractal, then the image intensity surface is also fractal, and that the reverse is also true [6]. The fractal dimension of the ROI's was calculated by the box-counting method with this software. Box counting is one of the standard methods for estimating fractal dimension [7, 8]. The box counting estimator of fractal dimension is based on the fact that the number of cubes $N(L)$ having a side length of L needed to cover a fractal surface varies as L^D where D is the fractal dimension that is to be estimated [9]. Two dimensions correspond to the length and width of the image and the third dimension corresponds to the gray level. If $N(L)$ is computed for several values of L, then D can be estimated as the slope of a least squares linear fit of the data {log(L), -log(N(L))}. In each case, the relationship between the size of boxes and the count was displayed on log-log plots and the correlation coefficient was calculated to confirm whether the straight line could be fitted to the log-log plot. These procedures have been explained in detail elsewhere [10].

When we compute D on a gray level image, considered as a 3-D shape, we always find a number between 2 and 3. If we obtain $D = 2$, it means that the studied surface is not a fractal. The higher the dimension, the more the fractal surface "fills" the underlying space and the "rougher" the surface appears. A surface with a dimension closer to 3 is supposed to fill a three-dimensional cube, so the surface must be highly convoluted at all resolutions.

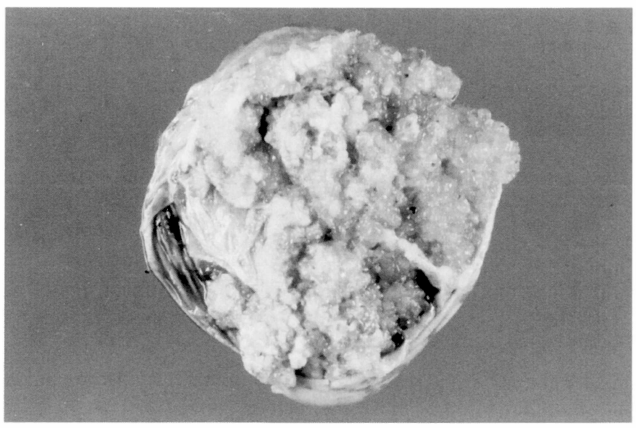
The values for the measurement of fractal dimension were tested for normal distribution by a correlation method. When they were found to follow a normal distribution, a single sample t-test was used to determine whether the mean fractal dimensions differed from the topological dimension (= 2), and two group continuous data were compared using the Student's t-test. A p value of less than .05 was considered to indicate a statistically significant difference.

Results

The study population included 139 patients. The mean patient age was 50.8 years ± 12.9 (standard deviation) (range, 15-92 years). The results of fractal analysis of malignant epithelial ovarian tumors are summarized in Table 1. Staging [11] in cases with different histologic types of adenocarcinoma is presented in Table 2. All of 19 cases with cystadenoma of low malignant potential (LMP) were Stage I.

In each case, the log-log plots for the box counting method lay along almost perfectly straight lines, and correlation coefficients were within 0.992-1.000. The mean fractal dimensions and 95% confidence intervals of the surface of a solid area of tumor in serous, mucinous, endometrioid, and clear cell adenocarcinoma were 2.320 (range 2.284-2.356), 2.224 (range 2.173-2.276), 2.229 (range 2.145-2.314), and 2.298 (range 2.243-2.353), respectively. Those of serous and mucinous cystadenoma of LMP were 2.398 (range 2.190-2.607) and 2.282 (range 2.156-2.408), respectively. Figure 2 shows a photograph of a resected ovarian tumor with serous adenocarcinoma. The fractal

g. 2



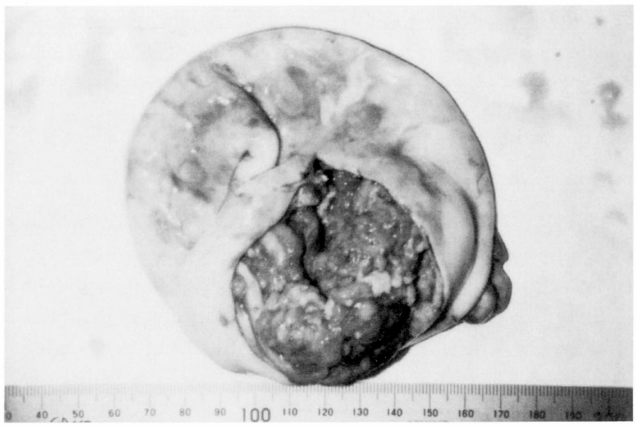


Fig. 3

Figure 2. — Photograph of a resected ovarian tumor with serous adenocarcinoma.
Figure 3. — Photograph of a resected ovarian tumor with endometrioid adenocarcinoma.

Table 1. – *Results of fractal analysis of malignant epithelial ovarian tumors.*

Histologic diagnosis	Solid area of tumor: No. (fractal dimension)	Solid area of tumor: Inside the cyst No. (fractal dimension)	Solid area of tumor: Outside the serosa No. (fractal dimension)
Adenocarcinoma			
Serous	64 (2.320 ± 0.143)*	32 (2.347 ± 0.145)*	32 (2.293 ± 0.138)*
Mucinous	19 (2.224 ± 0.107)*	18 (2.223 ± 0.110)*	1 (2.247)
Endometrioid	9 (2.229 ± 0.110)*	8 (2.228 ± 0.118)*	1 (2.241)
Clear cell	28 (2.298 ± 0.142)*	24 (2.310 ± 0.148)*	4 (2.243, 2.122-2.304)**
Cystadenoma of low malignant potential			
Serous	5 (2.398 ± 0.168)*	5 (2.398 ± 0.168)*	0
Mucinous	14 (2.282 ± 0.219)*	14 (2.282 ± 0.219)*	0

* Data of fractal dimension are expressed as mean ± standard deviation.
** Data of fractal dimension are expressed as median, range.

Table 2. — *Number of patients according to FIGO staging of ovarian adenocarcinoma.*

Histologic diagnosis	No.	FIGO stage I No.	II No.	III No.	IV No.
Serous	64	8	7	37	12
Mucinous	19	12	5	2	0
Endometrioid	9	2	4	2	1
Clear cell	28	6	7	15	0

dimension of the surface of the papillary projections into the cyst cavity in this case was 2.514. Figure 3 shows a photograph of an endometrioid adenocarcinoma and the value was 2.168. The surface of the papillary projections looks more complex in Figure 2 than in Figure 3, the fractal dimension being greater in the former. Since the mean fractal dimension of each of the six different histologic types was significantly greater than the topological dimension of 2, surface of solid tumor growth of malignant epithelial ovarian tumors was found to be fractal.

Among the six different histologic types, the mean fractal dimension of serous adenocarcinoma was significantly higher than that of mucinous adenocarcinoma ($p = 0.009$). And the value of serous cystadenoma of LMP was significantly higher than that of mucinous adenocarcinoma ($p = 0.009$) and that of endometrioid adenocarcinoma ($p = 0.04$).

Stages of the disease and fractal dimensions

Although not statistically significant, the mean fractal dimension of serous adenocarcinoma was higher in Stage I or II ($D = 2.371$) than Stage III or IV ($D = 2.304$) ($p = 0.11$). In clear cell adenocarcinoma, the value was 2.308 in Stage I or II and 2.289 in stage III ($p = 0.72$), so these values were not statistically different.

Location of a solid area of tumor and fractal dimensions in serous adenocarcinoma

Although not statistically significant, the mean fractal dimension of a solid area of tumor inside the cyst ($D = 2.347$) was higher than that outside the serosa ($D = 2.293$) ($p = 0.13$).

Fractal dimensions of a solid area of tumor inside the cyst among the six different histologic types

Considering the possible relations between location of a solid area of tumor and fractal dimensions, the mean fractal dimensions of lesions inside the cyst between different histologic types were compared. The values for serous, mucinous, endometrioid, and clear cell carcinoma were 2.347 ± 0.145, 2.223 ± 0.110, 2.228 ± 0.118, and 2.310 ± 0.148, respectively. The values for serous and mucinous cystadenoma of LMP were 2.398 ± 0.168 and 2.282 ± 0.219, respectively (Table 1). The mean fractal dimension of the surface of a solid component inside the cyst in mucinous adenocarcinoma was significantly lower than that of serous ($p = 0.003$), clear cell ($p = 0.04$) carcinoma, and serous cystadenoma of LMP ($p = 0.01$). And the value in serous carcinoma was significantly higher than that of endometrioid carcinoma ($p = 0.04$).

Serous cystadenoma of LMP vs serous adenocarcinoma

Although the mean fractal dimension of serous cystadenoma of LMP (= 2.398) was greater than that of serous adenocarcinoma (= 2.320), they were not significantly different.

Mucinous cystadenoma of LMP vs mucinous adenocarcinoma

Although the mean fractal dimension of mucinous cystadenoma of LMP (= 2.282) was greater than that of mucinous adenocarcinoma (= 2.224), they were not significantly different.

Discussion

The results show that for each of four histologic types of epithelial ovarian cancer and two histologic types of LMP tumors, the mean fractal dimension of the surface of a solid area of tumor exceeded the topological dimension (= 2). Thus empirically, over the range of scales examined, growth patterns of these neoplasms fulfill the mathematical definition of fractal structures [1], which accords with their subjectively self-similar morphology.

An accurate morphological description of complex biological structures using mathematical models is difficult. The fractal concept developed by Mandelbrot [1] provides an excellent explanation of the ruggedness of natural surfaces, and many other natural phenomena. Fractal geometry deals with the analysis of complex irregular shapes which cannot well be described by the classical Euclidean geometry. The main interest of fractal geometry is that it gives a way to quantify irregularity, and thus allows differentiation between two seemingly chaotic images. In contrast to our previous work [4], where the 2-D fractal dimension of outlines of solid components in cystic ovarian cancers was determined using sonograms, in this paper we examined the 3-D fractal dimension of the surface growth patterns of malignant epithelial ovarian tumors. Since the surface of tumor growth is a 3-D structure, its 3-D fractal dimension yields a more meaningful and holistic representation of its structure than the 2-D fractal dimension. The fractal dimension of a surface corresponds quite closely to our intuitive notion of roughness [6].

Cancer is a nonlinear dynamic system that is discontinuous in space and time, and advances through qualitatively different states. Complex and dynamic systems can be described mathematically by the chaos theory, which becomes visualized in fractal geometry [12]. The biochemical pathways leading to the heterogeneous moulding of epithelial ovarian neoplasias are unknown but probably related to multiple different and specific roles played by growth factors, growth factor receptors, angiogenic stimuli, and paracrine interactions between stromal and epithelial tumor cells. However, considering the tumor growth as complex systems as a whole, the surface morphology of the cancer is the end result of physical and biological processes that modify shape through local action. And such processes will, after innumerable repetitions, typically produce a fractal surface shape. Since in this sense it has been speculated that fractal structures do not evolve by chance but are a consequence of biologic and pathological mechanisms [13], fractal analysis may give a clue in predicting the behavior of malignant epithelial ovarian tumors.

Although not statistically significant, the mean fractal dimension of serous adenocarcinoma was higher in Stage I or II (D=2.371) than Stage III or IV (D=2.304) (p=0.11). It is said that poorly differentiated (high-grade) carcinomas are most common in the advanced stages while the vast majority of grade 1 carcinomas are of low stage [14]. The well-differentiated (low grade) carcinomas usually have broad and finely branched papillations. Overgrowth of epithelial cells results in anastomosing bridges of tumor cells that interconnect adjacent papillae. Stromal invasion is usually obvious but infiltrative growth into ovarian parenchyma may be minimal or difficult to identify. On the other hand, moderately and poorly differentiated carcinomas have more alveolar and medullary configurations, with solid sheets of cells surrounding irregular small spaces; cysts and papillae are less conspicuous. The least differentiated and most aggressive variants are predominantly solid adenocarcinomas. While we could not obtain the information on an exact grade of the tumor from pathological reports, these facts may explain why we observed higher mean fractal dimensions in early-stage patients with serous adenocarcinoma.

Although not statistically significant, the mean fractal dimensions of serous and mucinous cystadenoma of LMP were greater than those of serous and mucinous adenocarcinoma, respectively. It is reported that not infrequently, the differentiation between borderline tumors and frank malignancy must be made on the architectural basis of invasion (pushing borders versus destructive invasion, respectively) rather than on a cytological basis of the cells themselves [15]. An uncoordinated, marked overgrowth of atypical cells and destructive stromal invasion cause necrosis and hemorrhage in malignant ovarian tumors. In a cellular automata system simulating tumor growth, Smolle examined which factors were able to modulate fractal dimensionality of the resulting simulated tumor pattern [13]. In his model, destructive growth, which has often been considered a feature of malignancy, diminished and expansive growth increased fractal dimension. The observed higher mean fractal dimensions in our serous and mucinous LMP tumors than in serous and mucinous carcinomas, respectively, may be a reflection of differences in these biologic features.

Although not statistically significant, the mean fractal dimension of a solid area of tumor inside the cyst was higher than that outside the serosa in serous adenocarcinoma. Patterns of intracystic tumor growth must be different from those outside the serosa. Natural growth processes do not expand indefinitely, and their progress is influenced by their environment. The surrounding tissue as well as the desmoplastic reaction influences the expanding tumor in a kind of feedback mechanism in a mechanic and humoral way. Intracystic expansive-growing patterns presented a higher degree of dimension, which illustrates their relatively unimpaired growing advantage in the cystic cavity. On the other hand, a lower dimensions of solid cancers outside the serosa may illustrate the strength of capsular resistance by its consistency.

Although not statistically significant, the mean fractal dimension of serous adenocarcinoma was higher in Stage I or II (D = 2.371) than Stage III or IV (D = 2.304) (p =

0.11). In clear cell adenocarcinoma, the value was 2.308 in Stage I or II and 2.289 in Stage III ($p = 0.72$), so these values were not statistically different. It seems that local tumor growth patterns of primary sites in clear cell carcinoma may be in a relatively steady state regardless of stages.

The mean fractal dimension of serous adenocarcinoma was significantly higher than that of mucinous adenocarcinoma. In mucinous adenocarcinoma, papillations tend to be a little blunter and not so fine and delicate as those seen in serous tumors [16].

The mean fractal dimension of the surface of a solid component inside the cyst in serous adenocarcinoma was significantly higher than that of endometrioid carcinoma. Papillations are present in about one half of the cases with endometrioid carcinoma, but they are blunt, in contrast to the more finely branching papillae of serous carcinoma [16].

Some studies applied fractal analysis focused on specific tumor shapes. In a study by Landini and Rippin, the epithelial-connective tissue interface of the oral mucosa was examined, and the fractal dimension of carcinoma was 1.41 ± 0.08 [17]. Cross et al. measured the fractal dimensions of images from hematoxylin and eosin-stained sections of colorectal polyps (tubulovillous adenomas, tubular adenomas, villous adenomas, metaplastic polyps, and inflammatory polyps) and reported that the median values were 1.74, 1.70, 1.76, 1.61, and 1.49, respectively [18]. Velanovich performed mammographic examinations of benign and malignant breast lesions, and found that the mean composite fractal dimension (= addition of the craniocaudal and mediolateral views) for invasive cancer was 2.636 ± 0.039, which was higher than that for benign lesions [19]. We believe that these newer fractal models and ours give insights into tumor morphology and provide useful tools for diagnostic and prognostic purposes.

This study is limited because it was retrospective and the sample size was small. Further studies with a larger number of patients are needed. However, this report proposes a new way of looking at well known phenomena in ovarian tumor pathology. We believe that our newer fractal methods give insights into tumor morphology and will become useful tools for analyzing complex and irregular tumor growth patterns mathematically.

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References

[1] Mandelbrot B.B.: "The fractal geometry of nature". New York, Freeman, 1982.
[2] Feder J.: "Fractals". New York, Plenum, 1988, 11.
[3] Mandelbrot B.B.: "How long is the coast of Britain? Statistical self-similarity and fractional dimension". *Science,* 1967, *156,* 636.
[4] Kikuchi A., Kozuma S., Sakamaki K., Saito M., Marumo G., Yasugi T., Taketani Y.: "Fractal tumor growth of ovarian cancer: Sonographic evaluation". *Gynecol. Oncol.*, 2002, *87,* 295.
[5] Sasaki H., Shibata S., Hatanaka T.: "An evaluation method of Japanese lawn grass (Zoysia japonica STEUD.) for three different ecological functions (in Japanese with English summary)". *Bull. Natl. Grassl. Res. Inst.,* 1994, *49,* 17.
[6] Pentland A.P.: "Fractal-based description of natural scenes". IEEE Trans. Pattern Anal Machine Intell., 1984, PAMI-6, 661.
[7] Keller J.M., Chen S., Crownover R.M.: "Texture description and segmentation through fractal geometry". Computer Vision, Graphics, and Image Processing, 1989, 45, 150.
[8] Theiler J.: "Estimating fractal dimension". *J. Opt. Soc. Amer. A.*, 1990, *7,* 1055.
[9] Huang Q., Lorch J.R., Dubes R.C.: "Can the fractal dimension of images measured?". *Pattern Recognition*, 1994, *27,* 339.
[10] Kikuchi A., Kozuma S., Yasugi T., Taketani Y.: "Fractal analysis of surface growth patterns in endometrioid endometrial adenocarcinoma". *Gynecol. Obstet. Invest.*, 2004, *58,* 61.
[11] FIGO Cancer Committee: "Staging announcement". *Gynecol. Oncol.*, 1986, *25,* 383.
[12] Sedivy R., Mader R.M.: "Fractals, chaos, and cancer: Do they coincide?". *Cancer Invest.,* 1997, *15,* 601.
[13] Smolle J.: "Fractal tumor stromal border in a nonequilibrium growth model". *Analyt. Quant. Cytol. Histol.*, 1998, *20,* 7.
[14] Hart W.R.: "Pathology of malignant and borderline epithelial tumors of ovary". In: Coppleson M. (ed.). Gynecologic Oncology, 2nd edition, Edinburgh, Churchill Livingstone, 1992, 863.
[15] Ozols R.F., Rubin S.C., Thomas G.M., Robboy S.J.: "Epithelial ovarian cancer". In: Hoskins W.J., Perez C.A., Young R.C. (eds.): Principles and Practice of Gynecologic Oncology, 3rd edition, Philadelphia, Lippincott Williams & Wilkins, 2000, 981.
[16] Wheeler J.E.: "Pathology of malignant ovarian epithelial tumors and miscellaneous and rare ovarian and paraovarian neoplasms". In: Rubin S.C., Sutton G.P. (eds.): Ovarian Cancer (2rd edition), Philadelphia, Lippincott Williams & Wilkins, 2001, 99.
[17] Landini G., Rippin J.W.: "Fractal dimensions of the epithelial-connective tissue interfaces in premalignant and malignant epithelial lesions of the floor of the mouth". *Anal. Quant. Cytol. Histol.,* 1993, *15*, 144.
[18] Cross S.S., Bury J.P., Silcocks P.B., Stephenson T.J., Cotton D.W.K.: "Fractal geometric analysis of colorectal polyps". *J. Pathol.,* 1994, *172,* 317.
[19] Velanovich V.: "Fractal analysis of mammographic lesions: A prospective blinded trial". *Breast. Cancer Res. Treat.,* 1998, *49,* 245.

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