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FROM THE DEPARTMENTS OF OBSTETRICS AND GYNECOLOGY, TUMOR PATHOLOGY, AND GYNECOLOGICAL ONCOLOGY, RADIUMHEMMET, KAROLINSKA INSTITUTE AND HOSPITAL, STOCKHOLM, SWEDEN.

THE PROGNOSTIC SIGNIFICANCE OF GROWTH PATTERN AND ITS RELATION TO TUMOR CELL NUCLEAR DNA CONTENT IN ENDOMETRIAL CARCINOMA

B. MOBERGER, G. AUER, N. EINHORN and G. MOBERGER

Abstract

Hysterectomy specimens from 21 endometrial carcinoma patients, who died from their disease, and 23 patients selected at random from 307 survivors, were analysed for tumor growth pattern and tumor cell nuclear DNA content. The results indicate that tumor growth pattern, reflected by the mode of infiltration, is significantly correlated to the clinical course of the disease. Patients with carcinomas exhibiting contiguous growth pattern had a better outcome than patients with discontiguously growing carcinomas. It was also found that tumor growth pattern correlated well with tumor nuclear DNA content. It is suggested that the pattern of infiltration of the tumors is a sensitive predictor of prognosis and that this prognostic information, which only can be obtained postoperatively, to a large extent is reflected by tumor cell nuclear DNA content in curetted diagnostic material, obtained prior to treatment.

Key words: Endometrial carcinoma, growth pattern, DNA measurements, prognosis.

The overall cure rate of endometrial carcinoma is known to be high. A 5-year survival rate of 67% was reported during the years 1973–1975 from 11500 cases in 86 clinics (1). Numerous factors are known to influence the outcome of the disease, such as the patient's age, the extent of cancer spread (clinical stage), the degree of differentiation (histologic grade) and the mode of treatment (surgery, irradiation). Lack of precise objective criteria to distinguish adenomatous hyperplasia from highly differentiated adenocarcinoma may lead to an unknown number of cases of non-malignant lesions being included in the reported series of treated cancer patients and hence explain some of the discrepancies in cure rates which are reported from different departments. Also uncertainties regarding the cause of death in fatal cases from departments with a low autopsy rate may create errors in death rates attributed to the cancer. It is, however, a widely accepted concept that the clinical stage of the disease and the degree of differentiation of the tumors are the two main parameters correlated to the survival rates.

It has been known for a long time that the growth pattern in endometrial carcinoma, as reflected by depth of tumor infiltration, has prognostic impact. Thus, patients exhibiting tumors deeply invading the myometrium have been reported to have an unfavorable prognosis compared to that of patients with superficially growing tumors (2–5).

In recent years, a number of studies have documented a close correlation between the degree of aneuploidy of human malignant tumors, as revealed by nuclear DNA measurements, and the prognosis of the disease (6–11). The prognostic significance of DNA levels of endometrial carcinomas has previously been reported by Atkin (12), Moberger et al. (13), Iversen & Laerum (14), Oud et al. (15, 16) and by Lindahl et al. (17, 18).

The aims of this study were 1) to investigate whether histopathologic tumor growth characteristics, other than depth of infiltration, can be used as prognostic markers in endometrial carcinomas, and 2) to evaluate whether there is a relationship between growth pattern and tumor nuclear DNA content.

Material and Methods

It has previously been demonstrated that reliable analyses of nuclear DNA can be performed on thin sections

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from archival paraffin blocks of tumor material (19). This makes it possible to correlate nuclear DNA levels with other parameters influencing the survival rates. The patient material at the Department of Gynecological Oncology at Radiumhemmet, Karolinska Hospital, Stockholm, facilitates such studies due to a uniform clinical stage classification, standardized and uniform therapy, and a well-organized, complete follow-up system, including a high rate of autopsies. The tumor material is available in the form of slides and paraffin blocks in the archives of the Department of Tumor Pathology and other departments of pathology in the Stockholm area.

Patient material. During the years 1973–1975, 445 patients with a diagnosis of endometrial carcinoma were registered at Radiumhemmet. The patients were classified prior to treatment as being in stage I to IV according to the International Federation of Obstetrics and Gynecology (FIGO) 1961. Totally 307 patients were alive after 5 years whereas 63 patients died from their cancer and 66 from intercurrent diseases. Nine patients had other concomitant malignant tumors, such as primary ovarian or breast carcinoma. No patient was lost during follow-up. All cancer deaths were either verified by autopsy or had histologic/cytologic evidence of distant spread.

Histopathologic material. Histologic specimens of the initial curettings prior to treatment were reexamined and the tumors were graded according to the World Health Organization (WHO) criteria (20) into three grades: 1) well, 2) moderately, and 3) poorly differentiated carcinomas. Of the specimens from the 63 non-survivors 10 cases were excluded since histologic material was either not available or too sparse to perform DNA analysis. Seven patients in stage IV were excluded as there were no comparable survivors in this stage. Of the remaining 46 cases suitable for DNA studies only 21 had undergone hysterectomy and thus could be used for investigation of growth pattern.

To gather a comparable number of survivors, 51 patients were selected at random by chosing every sixth patient consecutively from the total of 307 endometrial carcinoma patients, who survived more than 5 years. Out of these 51 cases, 31 had undergone hysterectomy, and 23 such patients furnished material suitable for analysis of both DNA and growth pattern. In 4 cases the paraffin blocks from the primary curettage could not be traced and in another 4 cases the original slides and the paraffin blocks from the hysterectomy specimens were missing.

The slides were reviewed and the histologic grade of the tumors as well as the growth patterns in the hysterectomy specimens were studied.

DNA measurements. DNA measurements were performed on material from 44 patients including both survivors and non-survivors. Two consecutive 4 μm thick sections were made from paraffin blocks of the curetted material obtained prior to treatment. After removal of the paraffin, one section was stained with haematoxylin and eosin (H & E), while the other was refixed in buffered neutral 10% formalin. Staining was performed using Feulgen's technique (acid hydrolysis with 5-n HCl at 22°C for 60 min). Representative fields of view of the Feulgen-stained preparations were selected for photomicrography based on corresponding H & E stained sections. A Leitz photomicroscope was used with a 40×/1.0 oil objective (refractory index 1.518) in monochromatic light, wavelength 546 nm. The sensitivity of the film (Kodak Technical Pan 2415) was 29 DIN (64 ASA) and the developing time was 4 min at 22°C (Kodak D19). The exposure time was selected to give a density of the nuclear images falling within the straight portion of the density curve of the film emulsion. Cytophotometric measurements of the photomicrographs were performed with a photometric instrument which is a modification of that described by Adams (21). The light transmitted through the images of the nuclei was registered by a simple custom-computer service combined with a plotter, which printed histograms of 100 measured tumor cells from each tumor. Fifty internal control cells (stromal or endothelial) were measured to define the normal diploid DNA value. The DNA content was expressed in c-units, 2c being defined as the median value (P50) of the control cells. To distinguish diploid from non-diploid tumor populations, the normal control cell P90 value was used as the upper limit of the normal diploid region. In earlier work (13), tumors in which ≤60% of the cells having a DNA value above the normal P90 value were judged to be predominantly diploid tumors, and those in which >60% of the cells exceeded the P90 value were judged to be aneuploid. Since the fraction of cells exceeding the normal diploid region might include euploid S- and G_2 cells we have also calculated the percentage of tumor cells with DNA values above the normal tetraploid region (DNA values >2×P90) as a measure of aneuploidy. Based on earlier work (13) tumors with 4% or more of the measured population above this level were considered as predominantly aneuploid.

Results

DNA distribution. The results of the DNA measurements of the tumors from the 44 patients selected for this investigation are presented in Table 1 (23 survivors) and Table 2 (21 non-survivors). In the group of survivors, 17 of the 23 patients (74%) showed DNA levels below the 60% P90 level herein referred to as corresponding to diploid tumor cell populations. Out of the 21 non-survivors, 5 (24%) had tumors of the diploid type. Using the 2×P90 value of DNA as the basis for estimating aneuploidy and regarding tumors in which a minimum of 4% of the cells exceeded this value as predominantly aneuploid, the difference between survivors and non-survivors was increased. Of the 23 patients alive after 5 years, only three (13%) were found to have tumors above this level, all of which were of histologic grade 3. The corresponding fig-

Table 1

Survivors (>5 years) with endometrial carcinoma (23 patients)

No.	Age	Clinical stage	Histologic grade	Therapy[1]	Growth[2] pattern	% cells[3] >P90	% cells[3] >2×P90
1	62	I	1	S	C	23	0
2	35	I	2	R+S	O	34	2
3	55	I	2	R+S	O	38	0
4	70	I	2	R+S	O	39	3
5	54	I	1	S	C	39	1
6	65	II	2	R+S	O	41	0
7	51	III	1	S+E	C	42	2
8	54	I	2	R+S	O	44	0
9	47	I	3	R+S	C	44	0
10	60	II	2	R+S+E	O	46	0
11	52	I	2	R+S	O	48	0
12	52	I	3	R+S	O	52	2
13	49	II	3	R+S+H	O	52	0
14	75	I	2	R+S	C	55	0
15	74	I	3	R+S+E+H	D	56	0
16	53	II	3	R+S	O	58	1
17	50	III	2	R+S+E+H	D	60	2
18	48	III	1	R+S+E	O	61	3
19	65	I	1	S	C	62	0
20	74	I	2	R+S	O	65	0
21	39	I	3	R+S	O	67	6
22	67	I	3	R+S	C	77	12
23	72	I	3	R+S	O	93	10

[1] (R) Intracavitary irradiation, (S) Surgery, (E) External irradiation, (H) Hormonal treatment. [2] (O) No residual carcinoma in op. specimen, (C) Residual carcinoma with contiguous growth, (D) Residual carcinoma with discontiguous growth (see text). [3] See Material and Methods (DNA measurements).

ure in the non-surviving group was 14 out of 21 (67%). Thus, there is a higher representation of aneuploid tumors in the group of patients who died from their disease even when patients with tumors of clinical stage IV and patients who have not undergone surgery were excluded from the investigation.

Type of tumors. Forty of the 44 endometrial carcinomas studied were of the most common NSF (no specific features)-type. Four tumors were denoted as papillary carcinomas, all of which belonged to the non-surviving group of patients (cases No. 8, 9, 11 and 18 in Table 2). The overall number of cases examined is, however, too small to permit correlation studies between subtypes and clinical course as performed by Hendrickson et al. (22) and Christopherson et al. (23).

Growth pattern. Since the aim of the investigation was to study the growth pattern of the tumors in relation to the DNA distribution, only patients who had undergone hysterectomy were included in the material (23 survivors and 21 non-survivors). The therapy instituted in the individual cases is presented in Tables 1 and 2, which show that the primary treatment in 37 of the 44 patients was intracavitary irradiation by the 'Stockholm' packing method evolved by Heyman et al. (24). Seven patients, 4 survivors and 3 non-survivors, had primary surgery before admittance to Radiumhemmet. Among non-survivors in stage I only 3 had received postoperative external irradiation and among the survivors only one because of myometrial infiltration more than half the uterine wall. As a consequence of the intrauterine irradiation prior to the hysterectomies in the 37 patients, the histopathologic survey of the operation specimens revealed complete necrosis of the superficial portion of the carcinomas in 15 of the 20 surviving patients and in 10 of the 18 non-survivors. Thus, no major difference was found regarding the local necrotizing effect of the irradiation between survivors and non-survivors. All 7 patients who received primary surgery had residual cancer in their uteri. In the uteri of the 4 surviving patients, however, the carcinomas were limited to the mucosal layer, presenting either a sharp borderline towards the myometrium (Fig. 1) or, in one case, an extension into the myometrium in continuity with the superficial portion (Fig. 2). These two principal types of growth patterns have in the present investigation been denoted *contiguous growth pattern* (C in Tables 1 and 2). In contrast, the tumors of the 3 primarily hysterectomized patients in the non-surviving group exhibited infiltration of the myometrium in the form of isolated islands or

Table 2

Non-Survivors (>5 years) with endometrial carcinoma (21 patients)

No.	Age	Clinical stage	Histologic grade	Therapy[1]	Growth[2] pattern	% cells[3] >P90	% cells[3] >2×P90
1	70	II	2	R+S+E+H	D	42	1
2	66	I	2	S+E	D	47	0
3	56	II	2	E+R+S	D	47	0
4	74	I	2	R+S	D	53	1
5	58	II	3	R+S+E+H	D	56	2
6	65	I	2	R+S+H+C	O	64	0
7	55	III	3	R+S+E+H	D	69	4
8	56	III	2	R+S	D	70	3
9	63	I	2	R+S	C	73	5
10	73	I	3	S+E	D	74	4
11	62	I	2	R+S	C	76	10
12	70	I	2	R+S	D	78	21
13	67	II	3	R+S	O	79	10
14	58	I	3	R+S	D	80	9
15	64	I	2	R+S	O	81	13
16	67	I	2	R+S	D	81	5
17	61	I	2	R+S	D	85	10
18	66	II	2	R+S+E+H	D	86	8
19	63	I	3	R+S	D	89	19
20	68	I	3	R+S	C	95	21
21	58	I	1	S+E	D	100	44

[1] (R) Intracavitary irradiation, (S) Surgery, (E) External irradiation, (H) Hormonal treatment, (C) Chemotherapy. [2] (O) No residual carcinoma in op. specimen, (C) Residual carcinoma with contiguous growth, (D) Residual carcinoma with discontiguous growth (see text). [3] See Material and Methods (DNA measurements).

strands of cancer, most frequently in lymphatic vessels (Fig. 3). This type of growth was denoted *discontiguous growth pattern* (D in Tables 1 and 2). Metastases in the ovaries were occasionally found in the specimens from survivors (2 cases) and non-survivors (5 cases). Independent of whether cancer was present in the uterus of these patients such metastatic growth was also registered as a discontiguous pattern. The histologic survey of all operative specimens from the 44 patients included in the study revealed a marked difference in the growth pattern of the carcinomas between survivors and non-survivors, presented in Table 3. Among the 23 survivors the histologic findings at hysterectomy revealed no cancer in 14 cases, superficial, mucosal and/or contiguous residual growth in 7 and discontiguous growth in only 2 patients. One of these had no cancer in the uterus but had an ovarian metastasis and the other had a deep infiltration of the myometrium out to the serosa. Among the 21 non-survivors, discontiguous spread of cancer was found in 15 cases, either located outside the zone of necrosis or in the deeper portions of the myometrium (10 cases) or only in the ovaries (2 cases) and in primarily operated patients (3 cases). Three patients had superficial residual cancer in the uterus but no signs of deeper infiltration and another 3 patients had no residual cancer. All non-surviving patients developed distant metastases during the postoperative follow-up or revealed at autopsy.

Table 3

Growth pattern of endometrial carcinoma in hysterectomized patients (survivors >5 years and non-survivors <5 years)

	O	C	D	Total
Survivors	14 (61%)	7 (30%)	2 (9%)	23
Non-survivors	3 (14%)	3 (14%)	15 (72%)	21
Total	17 (39%)	10 (22%)	17 (39%)	44

(O) No residual carcinoma in op. specimen, (C) Residual carcinoma with contiguous growth, (D) Residual carcinoma with discontiguous growth (see text).

Table 4

Comparison between survivors and non-survivors (bivariate analysis)

	Survivors >5 years (n=23)	Non-survivors <5 years (n=21)	OR	p-value
Percentage with discontiguous growth	9% 2/23	72% 15/21	26.3	<0.001
DNA*	x̄=57.1 SD=18.3	x̄=69.0 SD=17.0	2.23*	<0.001

* = 10 units increase in DNA.

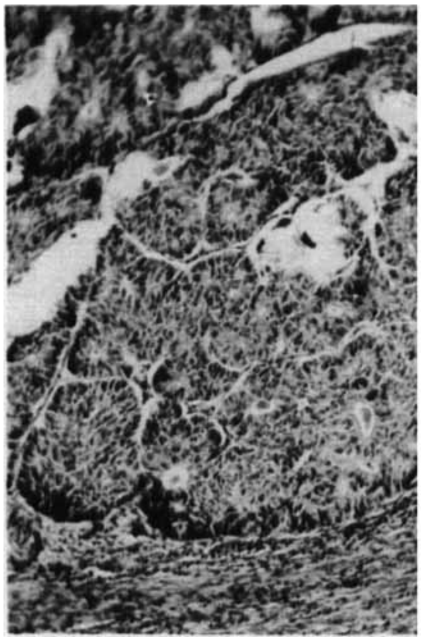

Fig. 1

Fig. 2

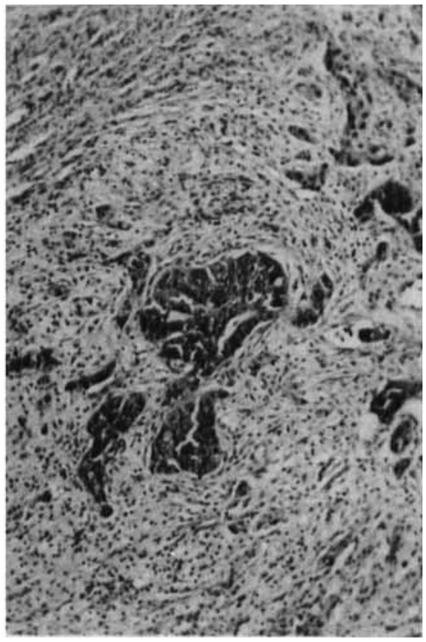

Fig. 3

Fig. 1. Endometrial adenocarcinoma of no specific feature (NSF) type. Contiguous growth on a broad front towards the myometrium. Photomicrograph ×350.

Fig. 2. Endometrial adenocarcinoma of no specific feature. (NFS) type. Contiguous superficial invasion of the myometrium. Photomicrograph ×350.

Fig. 3. Endometrial adenocarcinoma, grade 3. Discontiguous invasion of deep portion of the myometrium. Photomicrograph ×350.

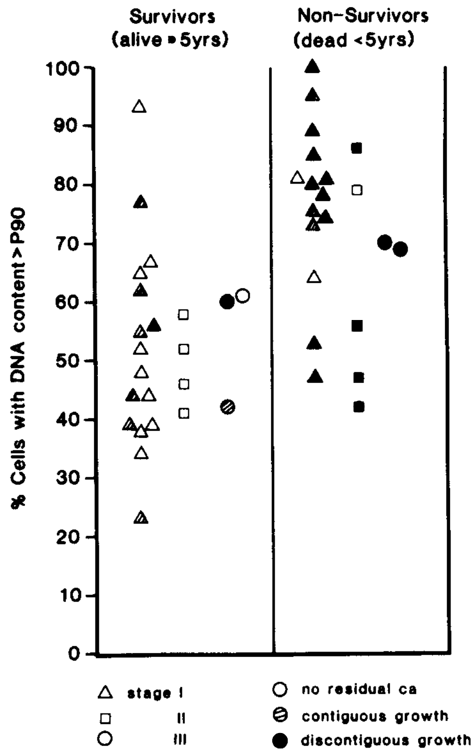

Fig. 4. Growth pattern of endometrial carcinomas in 44 hysterectomized patients, clinical stages I–III in relation to nuclear DNA values and 5 years survival ($p<0.05$).

DNA measurements in relation to growth pattern. The relation between the results of the DNA measurements, clinical stage and growth pattern is presented in Fig. 4. Although the number of patients in clinical stage I is almost equal among survivors and non-survivors (16/23 and 14/21 respectively), the number of aneuploid tumors with discontiguous growth is by far greater among non-survivors (7/12) since no such tumor was found in the group of surviving patients. Two non-survivors in stage I had diploid tumors, both of which, however, showed a discontiguous growth pattern. On the other hand, none of the 5 surviving patients in stage I with aneuploid DNA levels, showed discontiguous growth. The 4 stage II tumors among the survivors were diploid and had no residual cancer in their uteri whereas in the non-surviving group 4 out of the 5 stage II patients had tumors showing discontiguous growth. One of the patients with no residual cancer had a highly aneuploid tumor. The 3 surviving patients with stage III tumors were either diploid or exhibited DNA values close to the upper diploid value and only one had discontiguous residual cancer in the uterus. The 2 stage III tumors in the non-surviving group were both aneuploid and showed deep, discontiguous infiltration of the cancer in the uterine wall.

Statistical evaluation. The results in Table 4 give evidence that the factors growth pattern and DNA content both show significant correlation to survival. Using Student's t-test it is clear that the prognostic information reflected by growth pattern is significantly correlated ($r=0.32$; $p<0.05$) to that obtained by tumor nuclear DNA analysis (Fig. 4). In Table 5 a multivariate analysis (25) was performed which shows that the factors also had an 'independent' correlation to survival. Both factors hence contribute to explain the variation in survival but the most important factor which influenced survival was growth pattern.

Discussion

Endometrial carcinoma represents a type of cancer the incidence of which is rising in many countries. Numerous clinical factors are known to influence the prognosis of this disease, e.g. the patient's age, obesity, endocrine disorders, and, in particular, the extent of tumor growth (clinical stage) at the time of diagnosis. The aim of the investigation was to elucidate further prognostic factors which can be obtained from histologic and cytochemical examination of the tumor tissue itself.

Histologic grading is the most commonly practiced morphologic characterization of endometrial carcinomas. Poorly differentiated, grade 3 carcinomas have in general a worse prognosis than well differentiated carcinomas (26). Variations of differentiation within different parts of the same tumor may, however, occasionally be encountered. Another obstacle to an adequate estimation of the degree of differentiation is the lack of objective, well defined criteria to distinguish between grade 1 and grade 2 carcinomas. Whereas many pathologists only regard the type of tumor also denoted 'adenoma malignum' as a truly highly differentiated carcinoma, grade 1, others include in grade 1 tumors those with irregularly crowded, well formed glandular structures. Similar difficulties are encountered for an accurate distinction between grade 2 and grade 3 carcinomas. The occurrence of solid proliferations of the carcinomatous cells, independent of the cellular structures, is an unreliable measure of the degree of differentiation. Errors of these kinds may explain some of the discrepancies between histologic grades and survival rates in endometrial carcinomas. Additional parameters for a more objective pretherapeutic estimation of the biological malignancy of the tumors are therefore badly needed.

DNA measurements. Since Caspersson opened the door to the wide field of quantitative cytochemistry more than 50 years ago (27), increasing attention has been focused on the clinical significance of nuclear DNA content. It reflects the total quantity of genetic material of the cell and correlates with the number of chromosomes. Experimental and human malignant tumors have long been known to be distinguished by a great variation in the DNA content of individual cells (28–31). In the last decade, the prognostic significance of DNA measurements of human malignancies has been established for a number of tumors (6–11). A correlation between the levels of nuclear DNA content and the prognosis of endometrial carcinomas has also been demonstrated (12–18, 32). Well and moderately differentiated endometrial carcinomas have in general a diploid DNA pattern whereas poorly differentiated tumors are mostly aneuploid (12–14).

Table 5

Multivariate logistic regression analysis with 5 year survival as dependent variable. Odds ratios (OR) and their 95% confidence intervals (CI) are also shown

Predictor	Beta coefficient $\hat{\beta}$	p-value	OR (multiple)	95% CI
Intercept	−7.386			
Growth pattern	3.611	0.001	37.00	(4.02–340)
DNA*	0.96	0.007	2.61	(1.29–5.30)

* = 10 units increase in DNA, range 23–100.
$\hat{\beta}$ = estimated log (e) relative risk.
Coding: Growth pattern: 0 = no residual carcinoma + contiguous growth, 1 = discontiguous growth.

In the present investigation 29 of 44 patients had well or moderately differentiated carcinomas. Out of these, however, no less than 13 tumors presented with an aneuploid DNA distribution and 10 of these patients died from their disease within 5 years. A well or moderately differentiated tumor may thus exhibit a high degree of biological malignancy, reflected in an aneuploid tumor cell population. On the other hand, out of 15 patients with poorly differentiated carcinomas, 6 were diploid and as many as 5 of these patients were survivors. The investigation has thus given further support to the previously reported (12, 13) importance of nuclear DNA measurements as an additional method for obtaining preoperative information regarding the biological malignancy and, consequently, the prognosis of endometrial carcinomas.

Growth pattern. The results from the investigation indicate that the mode of infiltration of the endometrial carcinomas is related to the outcome of the disease. A majority of well or moderately differentiated carcinomas extend towards the myometrium on a broad front (contiguous growth) whereas poorly differentiated tumors more frequently infiltrate in the form of isolated cords and strands in the uterine wall (discontiguous growth). These different types of growth pattern are considered to reflect the degree of biological malignancy of the tumors. A discontiguous growth pattern parallels a high frequency of metastases and a high death rate. A contiguous growth pattern, on the other hand, seems to be a sign of a low grade malignant tumor with delayed spread and fewer metastases before therapy can be instituted. The potential usefulness of the growth pattern for decisions regarding postoperative treatment of the patient stresses the importance of careful examination of operation specimens after hysterectomy.

As illustrated in Fig. 4 there is a significant correlation between the mode of infiltration and tumor nuclear DNA content. Tumors with a discontiguous growth pattern showed predominantly aneuploid profiles whereas tumors exhibiting a contiguous growth pattern were mainly diploid. It thus occurs that tumor malignancy potential as indicated by growth pattern is to a great extent reflected by tumor nuclear DNA content and that aggressive growth patterns of the tumors followed by a high death rate can be predicted by cytochemical investigations of curetted material.

In conclusion, the data presented in this work, indicate that both tumor growth pattern and tumor DNA content can be used as valuable predictors of tumor aggressiveness in patients suffering from endometrial carcinoma. Since growth pattern analysis can be performed only postoperatively, DNA analysis of diagnostic endometrial curettings occurs to be of major importance as a guide to therapeutic alternatives.

Request for reprints: Dr Birgitta Moberger, Dept. of Gynecology, Karolinska Hospital, S-10401 Stockholm, Sweden.

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