Pathological findings in early-stage endometrial cancer

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Summary

Objective. The aim of this study was to assess the pathological characteristics of early-stage endometrial cancer, with regard to endometrioid versus serous papillary adenocarcinoma.

Methods. Sixty-six cases of early-stage endometrial carcinoma were classified into two groups: group I – 36 cases of endometrioid endometrial cancer, staged IA-IB and graded G_1 - G_2; group II – 30 cases of Stage I serous papillary endometrial cancer. The pathological characteristics compared between the two groups included features such as tumor location in the uterine cavity, tumor focality, lymphovascular invasion, as well as the status of the uninvolved endometrium, adjacent to the tumor. Patient clinical characteristics were obtained from the medical records.

Results. Significantly more patients with endometrioid endometrial cancer were premenopausal ($p < 0.0001$), obese ($p < 0.02$), had hypertension ($p < 0.00001$) and familial cancer ($p < 0.0001$). On the other hand, significantly more patients with serous papillary cancer had another primary malignancy ($p < 0.001$). Considering the pathological characteristics, 75% of endometrioid as compared with 6.7% of serous papillary cancer cases were found in the upper uterine segment only ($p < 0.0001$). Multifocality was observed in 16.7% of endometrioid as compared with 100% of serous papillary cancer cases ($p < 0.0001$). Lymphovascular space invasion was absent in all cases of endometrioid cancer, while present in 90% of serous papillary cancer cases ($p < 0.0001$). Seventy-five percent of endometrioid and 100% of serous papillary cancer cases were associated with an atrophic endometrium.

Conclusion. The clinical and pathological features of early-stage endometrial cancer differ according to the histological type of the cancer. The majority of endometrioid cancers are probably associated with an atrophic or normally cycling endometrium, and not with endometrial hyperplasia.

Key words: Early-stage endometrial cancer; Endometrioid endometrial cancer; Serous papillary endometrial cancer; Clinicopathological findings; Endometrial hyperplasia; Atrophic endometrium.

Introduction

Endometrial carcinoma is the most common gynaecological malignancy in many parts of the world, including North America and Northern Europe [1, 2]. The pathogenesis of endometrial cancer has been previously discussed [3, 4]. The division of endometrial cancer into two types: the type associated with endometrial hyperplasia and the type associated with atrophic endometrium, has been well established [5, 6]. Adenocarcinomas arising from hyperplasias are invariably of the endometrioid cell type, whereas those developing from an atrophic or a rather weakly proliferating endometrium are of the non-endometrioid cell type [7, 8].

Yet, there is probably another type of endometrial cancer of the endometrioid cell type which is associated with an atrophic endometrium [2, 9-11]. The fact that we have been observing quite a great majority of endometrioid adenocarcinomas developing from an atrophic endometrium prompted us to evaluate the pathologic characteristics of early-stage endometrial carcinoma with special reference to the two main histologic types: endometrioid versus serous papillary endometrial cancer.

In the current study we examined the precise location of the early-stage tumor, the focality, as well as the association with atrophic versus hyperplastic endometrium. Clinical characteristics are also presented.

Material and Methods

All cases of endometrial cancer, diagnosed between January 1996 and January 2002 were reviewed by a single pathologist (S.Z). The cases were staged using the criteria of the International Federation of Gynecology Oncology (FIGO) [13]. The histologic type of the tumor specimens was assessed according to the guidelines of the 1994 WHO Classification of Tumors of the Femal Genital Tract [13], and the nuclear grade was classified according to Kurman *et al.* [14]. Sixty-six cases were assigned to two groups: group I – 36 cases of endometrioid carcinoma, staged IA-IB and graded G_1 – G_2, group II – 30 cases of Stage I serous papillary endometrial cancer.

In all studied cases, uterine specimens were sectioned into 12 sections, encompassing the corpus (10 sections) and the cervix (2 sections). Uterine corpi were divided into an upper segment (containing fundus and both cornua) and a lower segment (containing right, left, anterior and posterior wall, and anterior and posterior isthmus). The status of the uninvolved endometrium adjacent to the tumor was examined and divided into an atrophic, weakly proliferating or normally cycling endometrium, and to a hyperplastic endometrium. Features such as multifocality and lymphovascular invasion were assessed.

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The patients' records were reviewed. Clinical characteristics, such as patient age, weight, parity, as well as the percentage of women with hypertension, diabetes mellitus, second primary malignancy and familial cancer were compared between the two study groups.

All patients in this study underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy and pelvic and paraaortic lymph node sampling. The group of patients with serous papillary carcinoma underwent also infracolic omentectomy.

The significance of differences between the two groups was assessed using the chi-square test and the two-tailed Student's t test; $p < 0.05$ was considered statistically significant.

Results

Clinical characteristics of patients from both study groups are presented in Table 1. There was no significant difference in mean patient age nor in parity. Conversely, there was a significant difference in patient weight ($p < 0.02$), being significantly higher in the endometrioid cancer group. Moreover, there were no premenopausal patients in the group with serous papillary cancer, as opposed to 38.9% of premenopausal patients in the endometrioid cancer group ($p < 0.0001$). Significantly more patients with endometrioid cancer had hypertension ($p < 0.00001$), as well as familial cancer ($p < 0.0001$). On the other hand, significantly more patients with serous papillary cancer had another primary malignancy ($p < 0.001$). There was no difference between the two groups considering the percentage of patients with diabetes mellitus (Table 1).

Table 1. — *Clinical characteristics.*

	Endometrioid n = 36	Serous papillary n = 30	Significance p
Mean age	56.9	66.3	NS[a]
Mean weight	81.9	67.5	0.02
Parity	3.1	2.0	NS
Premenopausal (%)	(14/36) 38.9	0	0.0001
Hypertension (%)	(22/36) 61.1	0	0.00001
Diabetes mellitus (%)	(11/36) 30.6	(8/30) 26.7	NS
Second primary malignancy (%)	0	(7/30) 23.3	0.001
Familial cancer (%)	(14/36) 38.9	0	0.0001

[a]NS – not significant

The difference between the two groups regarding the pathological characteristics was even more remarkable (Table 2). Twenty-seven of the 36 endometrioid cancer cases (75%) as compared with two of the 30 serous papillary cancer cases (6.7%) were found in the upper uterine segment only ($p < 0.0001$). Conversely, only 25% of endometrioid as compared with 93.3% of serous papillary cancer cases were found in both uterine segments: the upper and the lower one ($p < 0.00001$). No case of endometrioid nor serous papillary cancer was limited to the lower uterine segment only. Multifocality was observed in only 16.7% of endometrioid cancer cases, while it was common among all cases (100%) of serous papillary cancer ($p < 0.00001$). The same significant difference ($p < 0.0001$) was found regarding lymphovascular space invasion, being absent in all cases of endometrioid cancer and present in 90% of cases of serous papillary cancer. The issue of adjacent benign endometrium was also evaluated. Twenty-seven of the 36 patients (75%) with endometrioid cancer had an associated atrophic endometrium, and only 25% of patients presented hyperplasia-associated cancer. On the other hand, all cases of serous papillary cancer were associated with an atrophic endometrium (Table 2).

Table 2. — *Pathological characteristics.*

	Endometrioid n = 36	Serous papillary n = 30	Significance p
Upper segment only (%)	(27/36) 75	(2/30) 6.7	0.0001
Lower segment only (%)	0	0	NS[a]
Both segments (%)	(9/36) 25	(28/30) 93.3	0.00001
Multifocal (%)	(6/36) 16.7	(30/30) 100	0.00001
Atrophic endometrium (%)	(27/36) 75	(30/30) 100	0.003
Hyperplasia (%)	(9/36) 25	0	0.003
Lymphovascular invasion (%)	0	(27/30) 90	0.00001

[a]NS – not significant

Discussion

In the current study we examined the pathologic characteristics of early-stage endometrial carcinoma. We assessed the status of the adjacent non-neoplastic endometrium, the location of the endometrial cancer in the uterine cavity, the focality as well as the lymphovascular invasion. We compared the two quite separate forms of endometrial carcinoma: one being of the endometrioid cell type while the other being of the non-endometrioid cell type. The distinction between these two groups in terms of the clinical and endocrine profile appears to be quite established [4-6, 15, 16]. The difference between these two groups regarding patient clinical characteristics was also demonstrated in the current study.

A more interesting aspect of this study was the pathological examination of the removed uteri. Seventy-five percent of the endometrioid compared with only 6.7% of the serous papillary endometrial cancer cases ($p < 0.0001$) were located in the upper uterine segment (fundus and/or cornua only). The importance of this data might be related to the ability to attain a precise preoperative diagnosis, assessed by endometrial biopsy. If a pipelle or novak is not introduced deep enough into the uterine cavity the endometrial biopsy might not be performed from the fundus or cornua, thus missing the right diagnosis. From the pathological point of view, the sequential involvement of the lower uterine segment, as well as further invasion of the myometrium by the endometrioid endometrial cancer probably follows the appearance of the tumor in the fundus and/or cornua, although according to Phelan *et al.*, the extension of tumor to the lower uterine segment is not correlated with a worse outcome [17].

Furthermore, most of the endometrioid cancer cases were unifocal (83.3%) as opposed to the serous papillary cases which were 100% multifocal ($p < 0.00001$). The finding of multifocality in serous papillary, and not in endometrioid endometrial cancers, has been previously reported [18].

The examination of adjacent, non-malignant endometrium revealed that 75% of the endometrioid cancer cases were associated with atrophic endometrium, similarly to cases of serous papillary carcinoma, always developing in atrophic endometrium ($p < 0.003$). Endometrial hyperplasia related to endometrioid carcinoma was found only in 25% of endometrioid carcinoma cases. This issue is worth discussing. While it has been quite acceptable that endometrioid cell type endometrial cancer is associated with hyperplastic endometrium (simple, complex, atypical) [4, 5, 16, 19], we, like Sivridis *et al.* [9, 10], observed that the great majority of endometrioid endometrial cancers are unrelated to endometrial hyperplasia and develop from an atrophic or a normally cycling endometrium. This is quite a new concept, distinguishing between the two types of endometrioid endometrial cancer [2, 8, 11]. According to Sivridis *et al.* [9, 10], endometrioid adenocarcinomas, arising from a non-hyperplastic endometrium, tend to be of higher grade and stage, more deeply invasive of the myometrium and more commonly invasive of lymphatic spaces than the endometrioid carcinomas arising from a hyperplastic background. The 10-year survival rate for women with endometrioid carcinoma associated with hyperplastic endometrium was reported to be 92%, while that for patients with endometrioid adenocarcinomas, arising from an atrophic or normally cycling endometrium, was reported to be 76% [10]. None of the cases of endometrioid cancer, as opposed to 90% of Stage I serous papillary cases, demonstrated lymphovascular invasion, thus emphasizing the different pathogenetic pathway of these diseases.

In conclusion, the current study presents the pathological features of early- stage endometrial cancer, differentiating between the endometrioid and the serous papillary histologic types. An interesting finding concerning endometrioid cancer was its association with an adjacent non-malignant endometrium, being atrophic or normal in the majority of cases (as is characteristic of serous papillary cancer), in addition to its unifocality and fundal location. This is opposite to serous papillary cancer which is multifocal and usually found in the upper and lower part of the uterine cavity. The therapeutic implications of these pathological findings have yet to be studied.

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