Actual trends in screening, diagnosis and prognosis of endometrial cancer

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Summary

Endometrial cancer is today the first ranking malignancy of the female genital tract in civilized countries. We stress the importance of screening and an early accurate diagnosis with personalized therapy.

Personalized therapy is particularly important considering that there are two main forms of these neoplasms: the endometrioid form, hormonodependent and with a good prognosis, and a serous autonomous form, which has a poor evolution.

Studying the cases in the I[st] Clinic of Gynecology, Timişoara, we analyzed the incidence of these forms, their particularities and diagnostic possibilities.

Key words: Endometrial cancer; Diagnosis; Prognosis.

Introduction

Endometrial cancer is today considered the most frequent pelvic malignancy of women in civilized countries. This depends not only on the diminishing incidence of cervical cancers due to prophylactic screening and treatment of precancerous pathology, but also on the conditions of modern life with predisposing factors like longevity, obesity, diabetes mellitus, hypertension and estrogen therapy.

Fortunately, most endometrial cancers are determined in initial stages due to uterine bleeding which alarms patients and brings them to the physician, thus making an early diagnosis and a high percentage of recovery and survival possible.

These factors justify all efforts for an efficient screening and an accurate early diagnosis, on which the therapeutic strategy and prognosis depend.

The epidemiology of endometrial cancer shows that the risk of disease in symptomatic patients (with postmenopausal uterine bleeding) is 3.2-9.5%, while asymptomatic women have such a risk only in 0.13-0.69% [1, 2].

This suggests the importance of screening both symptomatic patients and those considered to have specific risk factors by global screening of genital and breast cancer as proposed by Onnis [13].

Among the methods recommended for the screening of endometrial cancer the following should be considered:

1. Cervico-vaginal cytology that has a viability of 60-80% [3].
2. Cytology of endouterine material obtained by aspiration, curettage or uterine washings, rather difficult to perform, offers no better results [4].
3. The progesterone test (Erny) which induces uterine bleeding more than two years after menopause, is considered to imply a risk for endometrial cancer.
4. Abdominal, and particularly vaginal sonography, measuring of the endometrial thickness is a non-invasive procedure and well accepted by patients [4].

A study carried out in our clinic on 86 menopausal women (with at least 2 years of amenorrhea), among them 41 without and 45 with uterine bleeding, were examined sonographically to measure the endometrial thickness.

All cases with an endometrial thickness of more than 4 mm, like those presenting with bleeding, had a D&C and histopathologic exam of the endometrium.

None of the patients with an endometrial thickness of less than 4 mm had endometrial cancer. There were two endometrial cancers found in those presenting with uterine bleeding and an endometrial thickness of more than 4 mm [5] (Table 1).

Patients considered on the basis of screening to be at risk or suspect for endometrial cancer should be further explored by:

a) Ultrasonic or radiological hysterography,

b) Hysteroscopy and targeted biopsy,

c) D&C for histopathologic examination of the endometrium (mandatory for symptomatic bleeding patients).

Table 1. — *Sonography of endometrial thickness after menopause and endometrial cancer.*

		Total 86	No bleeding 41	Bleeding 45
Endometrial thickness < 4 mm	Total	43	23	20
	Cancer	0	0	0
Endometrial thickness > 4 mm	Total	43	18	25
	Cancer	6	2	4

For a complete diagnosis and individualized therapy the following are useful:

1. Surgical staging (proposed by A. Onnis and now generally agreed upon) based on hysterometry, existence and deepness of myometrial invasion, high or low topography of the lesion, presence of malignant cells in the peritoneal washing, presence and location of lymph-node metastases (lombo-aortic for highly situated endometrial cancers, iliac for the juxta-cervical ones).

2. Histopathological type, nuclear grading, the pattern of the non-malignant endometrium outside the lesion, presence and quantity of cell receptors for estrogen and progesterone in the tumor, nuclear ploidy of the cancer cells and S phase determined by flux cytometry, and particular tumoral markers, offer the possibility of the most accurate diagnosis and prognosis in view of a personalized therapeutic strategy.

Most authors now accept a dualistic model of endometrial carcinogenesis, based on two different pathways, with particular epidemiologic risk factors, histopathologic pattern and molecular aspects [6].

The classic model presumes that endometrial cancer develops on the basis of an endometrial hyperplasia in a hyperestrogenic environment. This cancer is often associated with obesity, hyperlipidemia, hyperglicemia, arterial hypertension, infertility, late menopause, hyperplasia of the endometrium and ovarian stroma.

The histopathologic pattern of these cancers includes the endometrioid varieties [7].

It is important to mention that a papillar pattern of endometrial carcinoma, classically considered of great malignant aggressivity, includes two forms: simple papillary adenocarcinoma related to the endometrioid form and serous papillary adenocarcinoma [8].

Endometrioid endometrial cancers and the related varieties have a common precursor – atypical endometrial hyperplasia (Figures 1, 2).

They affect rather young women (perimenopausal), have a high topographic situation, delayed invasion and metastases, present cell receptors for steroid hormones, and generally have a good post-therapeutic prognosis (in young women even fertility is preserved after only progestin treatment [9].

The second variety of endometrial cancer affects older women, has no relation with hyperestrogenia and shows a definitely more aggressive character.

Histopathologically it develops on a rather atrophic endometrium that presents typical aspects of endometrial intraepithelial carcinoma (EIC) [10].

EIC replaces the superficial layers of this atrophic endometrium by cells with anaplastic nuclei suggesting a serous carcinoma.

This type of endometrial cancer includes serous carcinomas and related forms (with clear cells, non differentiated, mixed), shows a high nuclear gradient and lack of sex steroid cell receptors (Figures 3, 4, 5, 6).

Nuclear ploidy and S phase, determined by flux cytometry, are considered important indices of malignancy and prognosis.

In 1969 Katayama [11] characterized the endometrial cell ploidy as follows:

1. normal endometrium - diploidy;
2. hyperplastic endometrium - endoreduplication;
3. initial endometrial carcinoma - tetraploidy;
4. advanced endometrial carcinoma - pluritriploidy.

Wilson [12] considers nuclear ploidy as the most accurate prognostic index.

A diploidy of the tumoral cells would assure a survival rate of 88% independent of the stage and grading, while an aneuploidy under the same conditions offers a survival rate at five years of only 57%.

Likewise, a high percentage of S phase tumoral cells is considered an index of unfavorable prognosis.

Molecular biology also differs for these two main forms of endometrial cancer [6].

1. Mutations in the suppressor gene p53 and accumulations of p53 protein are present in 90% of serous carcinomas and EIC, but rarely in endometrioid cancers.

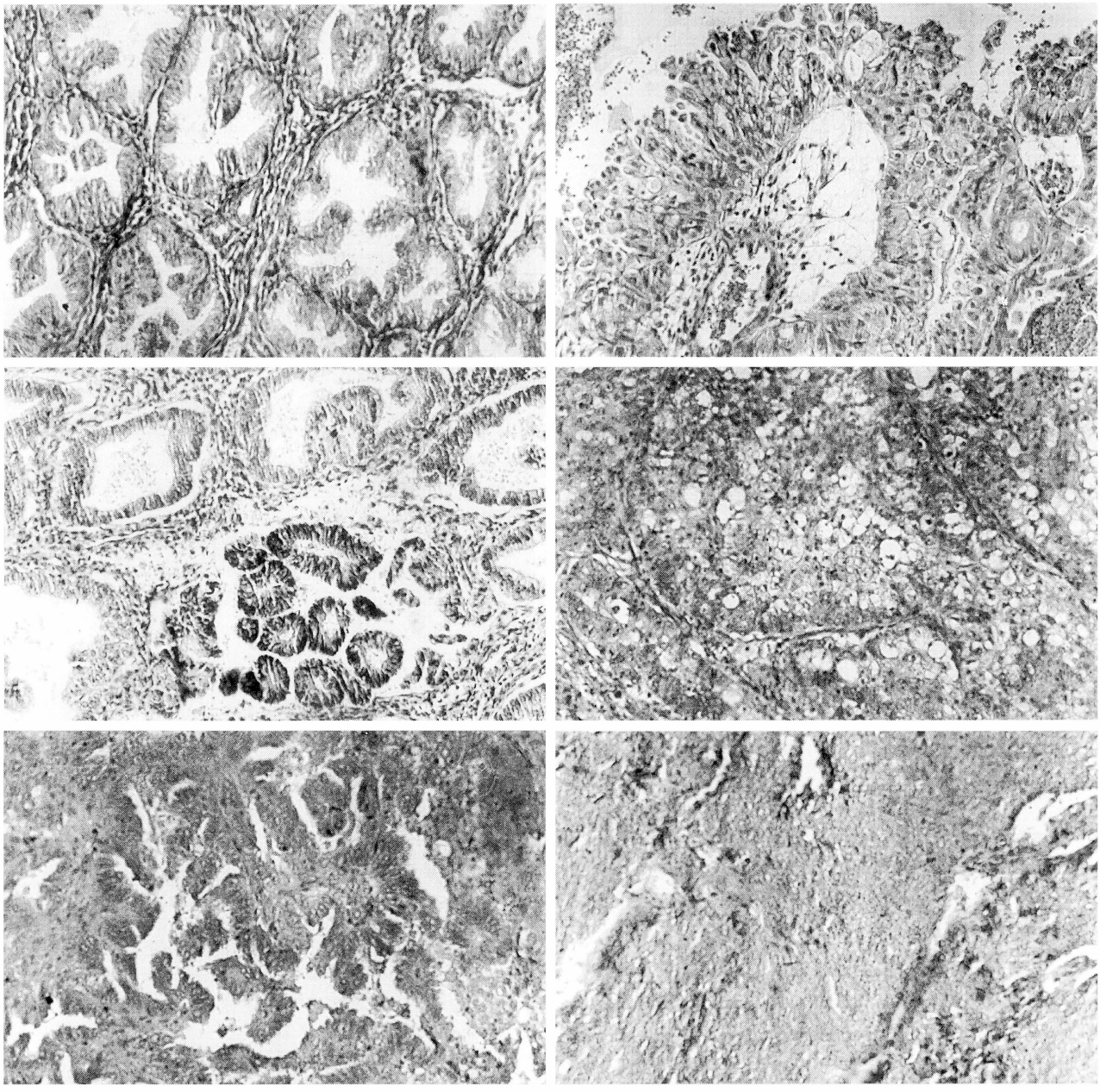

Figure 1. — Endometrioid adenocarcinoma G1, based on atypical complex endometrial hyperplasia
Figure 2. — Papillary adenocarcinoma G1 with limited myometrial invasion.
Figure 3. — Serous papillary carcinoma G2.
Figure 4. — Clear cell carcinoma.
Figure 5. — Papillary adenocarcinoma with large zones of solid anaplastic carcinoma.
Figure 6. — Solid anaplastic carcinoma G3 with tumoral necrotis

2. Mutations in PTEN (tumor suppressor gene) were identified in up to 86% of endometrioid cancers, particularly in grade 1 with a good prognosis.

3. Mutations in the ras oncogene were present in about 20% of endometrioid carcinomas, but were not found in serous tumors.

4. BCL2, the protein that inhibits cell apoptosis, if absent in the tumor cells seems correlated to tumor recurrence and a low survival rate.

5. Likewise, the expression of glutation -S- transpherase and C + jun, are correlated with a poor prognosis.

Table 2. — *Histopathologic pattern and grading of endometrial cancers (87 cases).*

Histopathologic type	Total	G1	G2	G3
1. Pure endometrioid adenocarcinoma	9 (10.34%)	8	1	–
2. Papillary adenocarcinoma	5 (5.74%)	–	5	–
3. Adenosquamous carcinoma	13 (14.94%)	3	9	1
4. Mixed endometrioid and papillary adenocarcinoma	32 (36.78%)	–	32	–
Total type I	*59 (67.81%)*	*11 (18.64%)*	*47 (79.66%)*	*1 (1.69%)*
5. Serous papillary adenocarcinoma	3 (3.44%)	–	3	–
6. Clear cell adenocarcinoma	3 (3.44%)	–	2	1
7. Anaplastic non differentiated carcinoma	3 (3.44%)	–	–	3
8. Mesonephroid adenocarcinoma	1 (1.14%)	–	1	–
9. Papillary and non-differentiated adenocarcinoma	13 (14.99%)	–	–	13
10. Mixed papillary and serous papillary adenocarcinoma	5 (5.74%)	–	5	–
Total type II	*28 (32.18%)*	–	*11 (39.28%)*	*17 (60.71%)*

Table 3. — *Endometrial pattern outside of the cancerous endometrium. Histopathologic features (87 cases).*

Histopathologic types	Hyperplastic endometrium			Atrophic endometrium	No malignant endometrium found
	Glandulocystic hyperplasia	Complex hyperplasia hyperplasia	Atypical adenomatous		
1. Pure endometrioid adenocarcinoma	1	4	3		1
2. Papillary adenocarcinoma	1	1		1	3
3. Adenosquamous carcinoma	1	4	1		7
4. Mixed endometrioid and papillary adenocarcinoma	3	5	1		21
Total type I 58	*6*	*14*	*5*	*1 (55.17%)*	*32*
5. Serous papillary adenocarcinoma					3
6. Clear cell adenocarcinoma					3
7. Anaplastic non differentiated carcinoma					3
8. Mesonephroid adenocarcinoma					1
9. Papillary and non differentiated adenocarcinoma	1		1		11
10. Mixed papillary and serous papillar adenocarcinoma	2				4
Total type II 29	*3*	*0*	*1*	*0 (86.20%)*	*25*
Total	**9 (10.34%)**	**14 (16.09%)**	**6 (6.89%)**	**1 (1.14%)**	**57 (65.51%)**

Material and Methods

Clinical, histopathologic, genetic and molecular characteristics of the endometrial cancer varieties – many of these specifically grouped – were studied at the I[st] Clinic of Gynecology, Timişoara, in the 3-year period from 1999-2001.

Among 87 cases of endometrial cancer we found 67.81% type 1 tumors (endometrioid and related) and 32.19% serous tumors (Table 2).

The histopatologic pattern, anatomic situation, myometrial and cervical invasion, and nuclear grading were correlated as previously discussed (Tables 3, 4 and 5).

These factors permit conclusions concerning the diag-nosis, prognosis and therapeutic strategy even in the absence of more sophisticated investigations of genetic factors, hormonal cell receptors and markers of tumoral biology.

Conclusions

1. The best method of screening for endometrial cancer – non-invasive and well accepted by the patients – is sonographic measurement of the endometrial thickness in women after two years of menopause, in particular the at-risk group, even if asymptomatic.

2. Patients with an endometrial thickness of more than 4 mm should be further explored by cytology, hysterograpy or rather by hysteroscopy and targeted biopsy.

3. Symptomatic cases (bleeding after menopause) like those suspected of endometrial cancer after previous investigations, need a D&C for a careful histopathologic investigation.

4. A histopathologic diagnosis of endometrial cancer has to specify the type and risk factors of the tumors.

5. Surgical staging is mandatory for the therapeutic strategy and can be aided by an immediate histopathologic exam on frozen tissue or by imprinting of the tumor.

Table 4. — *Topographic status of malignancy (surgical staging - 49 cases).*

Histopathologic type		Topographic situation	
		Low	High
1. Pure endometrioid adenocarcinoma		1	7
2. Papillary adenocarcinoma			3
3. Adenosquamous carcinoma		3	2
4. Mixed endometrioid and papillary adenocarcinoma		5	8
Total type I:	*29*	*9 (31.03%)*	*20 (68.96%)*
5. Serous papillary adenocarcinoma		1	
6. Clear cell adenocarcinoma			1
7. Anaplastic non-differentiated carcinoma		2	
8. Mesonephroid adenocarcinoma			1
9. Papillary and non-differentiated adenocarcinoma		4	5
10. Mixed papillary and serous papillary adenocarcinoma		2	4
Total type II:	*20*	*9 (45%)*	*11 (55%)*
Total:	**49**	**18 (36.73%)**	**31 (63.26%)**

Table 5. — *Myometrial and cervical invasion (surgical staging - 49 cases).*

Histopathologic types		No invasion	Myometrial invasion			Cervical invasion
			1/3	2/3	Total	
1. Pure endometrioid adenocarcinoma		5	2			1
2. Papillary adenocarcinoma			3			
3. Adenosquamous carcinoma				4	1	2
4. Mixed endometrioid and papillary adenocarcinoma			4	7	3	3
Total type I:	*29*	*5*	*9*	*11*	*4*	6
5. Serous papillary adenocarcinoma				1		
6. Clear cell adenocarcinoma					1	
7. Anaplastic non-differentiated carcinoma			1	1		
8. Mesonephroid adenocarcinoma				1		
9. Papillary and non-differentiated adenocarcinoma			1	5	3	3
10. Mixed papillary and serous papillar adenocarcinoma			1	5		2
Total type II:	*25*	–	*3*	*13*	*4*	*5*
Total:	**49**	**5 (10.2%)**	**12 (24.48%)**	**24 (48.97%)**	**8 (16.32%)**	**11 (24.44%)**

6. The necessity of adjuvant therapy (radio, chemo or hormonal) should be determined considering detailed post-surgical histopathologic findings, if possible supported by investigations of some prognostic factors like grading, steroid cell receptors, ploidy and molecular markers.

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