Review Articles

Endometrial cancer: asymptomatic endometrial findings. Characteristics of postmenopausal endometrial cancer

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Summary

Endometrial cancer affects patients at every age, however it occurs more frequently in menopause (> 50) and in postmenopause (> 70). The most frequent symptoms are bleeding and vaginal discharge. When hematometra or pyometra is present the patient may feel pain. In some cases endometrial adenocarcinoma is asymptomatic and the diagnosis is casually made during ultrasound examination or by histological examination of a uterus surgically removed for other indications. In these cases the most frequent findings are polyps and abnormally increased thickness of the endometrial mucosa. In postmenopause polyps and abnormal endometrial thickness are usually limited to a small area and surrounded by atrophic mucosa. Higher incidence rates of endometrial cancer were correlated with polyps and an increased number of serous type tumors were identified in the > 65-year age group. Endometrial carcinoma may be estrogen correlated or non-estrogen associated. Patients in postmenopause are often affected by non-estrogen correlated endometrial carcinoma. According to Kurman and other authors the first type of endometrial adenocarcinoma (estrogen correlated) is characterized by low-grade malignancy. On the contrary, non-estrogen correlated neoplasia is more aggressive. In our case series including 102 women aged > 70 years with endometrial carcinoma we found that survival was correlated with stage and grading - early stages were the most frequent and the grade increased with stage. In fact all the patients with relapses had grade 2 or 3 adenocarcinomas. Thirty-one patients > 70 years (30.69%) had a non-endometrioid type of cancer.

Key words: Endometrial cancer; Elderly patients; Asymptomatic findings.

Introduction

Endometrial cancer is the second most common gynecologic neoplasia after breast carcinoma. Nearly 170,000 new cases of endometrial carcinoma were estimated worldwide in 1997 [1] and the estimated annual incidence is 39,300 cases in the USA. Endometrial carcinoma mostly occurs in advanced age (postmenopausal), the mean age at diagnosis is 61 years, and only 5% of cases are below age 40 [2]. The etiology of endometrial cancer is not fully understood, but 10% of cases are hereditary. The risk of developing endometrial malignancy is ten times higher for women with autosomal dominantly inherited non-polyposis colorectal cancer (HNPCC) compared to the general population, a risk which appears directly related to age with endometrial carcinoma usually occurring 15 years earlier than typically found [3]. The risk factors for endometrial carcinoma are well known; they include obesity, type 2 diabetes mellitus and hypertension. Current estimations are that about 40% of endometrial cancers are related to excess body weight [4]. A plausible explanation that obesity is related to a high risk for endometrial cancer is found in the increased aromatization of androstendione to estrone in adipose tissue and also hyperadrenocorticism that with related hyperinsulinism. It is more common in obese individuals because estrogen metabolism is disturbed thus explaining the relationship between the higher frequency of endometrial cancer and diabetes mellitus. The major factors related to a high risk of endometrial neoplasia are prolonged or intensive exposure to estrogen, hyperestrogenism that may be caused by exogeneous (unopposed estrogen replacement therapy, tamoxifen) or endogeneous factors (early menarche, late menopause, nulliparity, polycystic ovarian syndrome, diabetes, hypertension and other estrogen producing tumors) [5-7]. Recently a case-control study identified antipsychotic drugs as a great risk factor for endometrial cancer producing metabolic side-effects that may influence endocrine background (obesity, insuline resistance, amenorrhea and hyperprolactinemia) [8]. Clinicopathological studies support a broad classification of endometrial carcinoma into two major types, designated as type I and type II, which correlate with their biological behavior [9]. Type 1 endometrial carcinoma is an estrogen-related endometrioid adenocarcinoma representing 60-80% of all cases. It tends to occur in nulliparous, obese, hypertensive and/or diabetic women, has a long history of being preceded by premalignant disease, is highly differentiated, low stage and low grade with positive estrogen and progesterone receptors, and has a favorable prognosis. Type 2 endometrial cancer is non estrogen-dependent, occurs in women who are not constitutionally predisposed, on a background of nonhyperplastic, often atrophic endometrium, and is represented by serous, clear cell histology with a short natural history, high grade, quick lymphatic spread and poor prognosis [10].

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Asymptomatic endometrial carcinoma

Screening for endometrial cancer

Most endometrial carcinoma are diagnosed at an early stage and have a good prognosis. The most common symptom is bleeding. Postmenopausal bleeding, even slight, is abnormal and deserves prompt investigation. To date there is no procedure that seems appropriate as a screening method for endometrial carcinoma; so far most epidemiological studies have failed to show significant effects of screening on mortality [11]. Gerber *et al.* in a retrospective analysis compared 190 postmenopausal women with bleeding with 123 women without symptoms but with a transvaginal ultrasound showing endometrial changes. They found that the asymptomatic women had no prognostic advantage over the symptomatic women if bleeding had occurred for less than eight weeks. They correlated the duration of postmenopausal bleeding with increased tumor stage and reduced overall survival [12]. The current guidelines of the American Cancer Society suggest informing patients of the risks and symptoms involved with endometrial cancer and firmly stress the importance of reporting unexpected spotting to their gynecologist. In some cases endometrial adenocarcinoma is asymptomatic and the diagnosis is casually made during ultrasound examination or by histological examination of a uterus surgically removed for other indications. In these cases the most frequent findings are polyps and abnormally increased thickness of the endometrial mucosa. According to Gerber *et al.* [12] transvaginal ultrasound used for measuring the endometrial rim in postmenopausal asymptomatic patients showed a very high negative predictive value (NPV) (99%) and high sensitivity (90%) but very low positive predictive value (PPV); as specificity is also low (48%) many of these women with > 5 mm endometrial mucosa need further investigations with a very low incidence of endometrial carcinoma detection [13]. In a study evaluating the results of outpatient hysteroscopy in menopausal women with atrophic endometrium at ultrasound (< 4 mm), 94% of the women were asymptomatic and of these, only 10% had endometrial pathology such as small polyps; only one case of endometrial carcinoma arising in a polyp was detected [14]. Hysteroscopy performed in asymptomatic women with > 4 mm endometrial rim at ultrasound may reveal a higher incidence of intracavitary benign focal lesions (up to 59%) while the incidence of carcinoma remains low [15]. These results point out that asymptomatic postmenopausal women do not usually need routine investigation as the probability of diagnosing endometrial cancer in these cases is very low. On the other hand, opportunistic findings of endometrial cancer arising on atrophic endometrium or on a polyp are rare but exist even when bleeding is lacking. Performing transvaginal ultrasound in asymptomatic postmenopausal women may make sense in order to rule out further surveillance for those patients with an increased thickness of the endometrial rim. In some cases Pap smears may lead to casual diagnoses of occult endometrial cancer. Detecting endometrial cells on a pap smear in asymptomatic postmenopausal women presents a 6% risk of having underlying endometrial carcinoma and about 13% will have endometrial hyperplasia [16]. Moreover, positive cervical cytology has been found to be correlated with nodal spread in 91% cases while the risk of lymph node spread in patients with normal cervical cytology was 2% [17]. The new Thin Prep cytology might have a role in the future in defining this important predictive association [18].

Polyps and endometrial cancer

Endometrial polyps are common findings in postmenopausal women and the prevalence rises with age [19]. The lower incidence of endometrial polyps in the younger age group may be related to a possible spontaneous regression mechanism due to physiologic cyclic endometrial transformation in fertile women. They are benign lesions characterized by irregular proliferative glands with a fibrotic stromal component containing thick-walled blood vessels. Hypertension associated with obesity and late menopause appear to be important factors for the development of polyps. Moreover, an association between endometrial polyps and tamoxifen use was found in 8% of cases of breast cancer patients [20].

Malignant transformation of endometrial polyps has been observed mainly in postmenopause [21]. A statistically significant age-dependent association with malignant involvement was pointed out in the age group > 65 years with 32% of polyps presenting malignant changes compared to only 2.5% in the age group > 35 [22]. More than half the patients with endometrial polyps in postmenopause are asymptomatic [20]. Endometrial polyps may range from atrophic to hyperplastic and carcinomatous. Some authors consider endometrial polyps as a marker of concurrent malignancy, with an incidence of twice the likelihood than in control uteri with endometrial carcinoma [23]. Therefore a possible association between endometrial polyps and malignancy in postmenopausal women has been suggested, even if there is no direct evidence for an increased propensity of polypoid endometrium to undergo malignant degeneration. Comparative analyses pointed out that endometrial hyperplasia was more frequent in endometrial specimens with polyps but the incidence of frank malignancy in polypoid and non-polypoid endometrium remained the same [24]. An interesting finding is that serous endometrial intraepithelial carcinoma, the early form of uterine serous papillary carcinoma, may sometimes be identified as very minute foci in endometrial polyps [25]. Serous endometrial tumors may present extrauterine involvement even in the absence of myometrial invasion. The same pattern of extrauterine invasion which by-passed myometrium involvement was seen by Silva *et al.* [26] in a study of endometrial polyps with serous carcinomatous degeneration. According to Hileeto *et al.* [22] the vast majority of endometrial carcinomas associated with endometrial polyps were endometrioid (87%) followed by serous type (9%), confirming the distribution of similar sub-

types of endometrial cancer in non-polypoid endometrium. Moreover, age distribution of histologic subtypes of endometrial carcinoma arising in polyps overlaps the general age distribution of endometrial cancer. All these findings suggest that cancer developed in endometrial polyps does non differ necessarily from cancer arising in adjacent non polypoid endometrium. Recent studies demonstrated that expression of estrogen and progesterone receptors in polyps is not significantly different versus normal endometrium, however growth of endometrial polyps does not entirely depend on estrogen receptors and stimulation: c-erbB2 overexpression in polyps with a subsequent higher proliferative rate may explain the presence of polyps associated with adjacent atrophic endometrium [27]. Overexpression of Bcl-2 proto-oncogene, which prolongs cell survival by inhibiting apoptosis, is found in hyperplastic polypoid endometrium, explaining the failure of polypoid tissue to normal cycling and shedding [28].

Tamoxifen and endometrial cancer

Tamoxifen, the most important anti-breast cancer drug, is a non steroidal derivate with clear antiestrogenic effects on the breast but with estrogenic activity on the female genital tract. Most common tamoxifen-induced uterine changes include endometrial thickening, endometrial polyps and increased risk of endometrial carcinoma [29, 30]. The annual incidence of endometrial cancer among women on tamoxifen is two per 1,000 and seems to be related to the cumulative dose [31]. Tamoxifen intake can lead to senile cystic atrophy of the endometrium with associated stromal hypertrophy, endometrial hyperplasia or polyps with increased endometrial thickness detected at ultrasound [32, 33], and high false-positive rates [34, 35]. There is an increased incidence of endometrial polyps during tamoxifen use and this might be explained by the stromal growth promoting effect of the drug (polyps have an important stromal-vascular component) and up to 3% of endometrial polyps in tamoxifen users may show malignant changes versus 0.5% among the general population [36]. A higher rate of mesenchymal tumors including malignant mixed mullerian tumors, stromal sarcomas, adenosarcomas and leiomyosarcomas have been recently described with tamoxifen use [37-40]. Bergman *et al.* [41] report worse prognoses for tamoxifen treated patients diagnosed with tumors in more advanced stages with more aggressive histological types and poorer survival. The discussion about the necessity of endometrial screening in these patients is still highly controversial, especially with regard to asymptomatic women. Many authors [42, 43] consider these patients a high-risk group and believe transvaginal ultrasound is an appropriate screening method but the cost/efficacy ratio of screening asymptomatic patients is not very favorable although a subgroup of women could benefit from it [44].

Postmenopausal endometrial carcinoma - case series

This is a two-decade retrospective analysis of our case series of postmenopausal endometrial carcinoma in women over 70 years. Between 1980 and 2000, 106 patients with endometrial carcinoma were registered at the Department of Gynecology and Obstetrics of Padua University; 103 out of 106 underwent surgery and three patients could not be surgically treated because of the advanced stage of the disease associated with severe clinical condition. The age distribution of endometrial carcinoma is shown in Figure 1. Most of the cases were concentrated between 70 and 80 years of age (83.49%).

Figure 2 describes stage distribution of endometrial tumors in this age group: 79 women (76.69%) were Stage I, nine Stage II (8.74%), eight Stage III (7.76%) and five Stage IV (4.85%). Two cases were diagnosed with endometrial intraepithelial neoplasia (EIN) according to the alternative classification scheme adopted by the World Health Organization. EIN is a precancerous process and encompasses approximately 80% of lesions that would otherwise be diagnosed as complex atypical endometrial hyperplasia; however, the terms are not synonymous. Cases of EIN come from all categories of endometrial hyperplasia, including both atypical and non-atypical, and simple and complex hyperplasias using new diagnostic criteria, which includes a lower percentage of stroma than glands in the diseased foci, as well as the more usual criteria of glandular complexity and nuclear pleomorphism [45]. The stage distribution in our case series overlaps with the literature [46, 47] demonstrating that even in the group of > 70-year-old women endometrial cancer is usually diagnosed in early stages. The risk factors for endometrial carcinoma in this age group were similar to the general population: 21.4% of the patients presented isolated hypertension while 15.5% cardiovascular

Figure 1. — Endometrial carcinoma - age > 70.

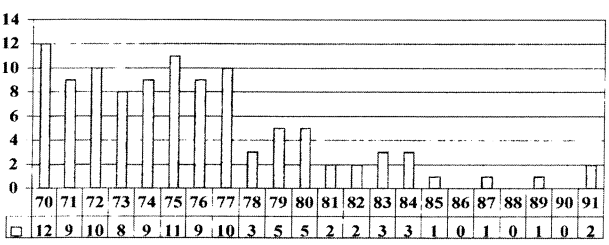


Figure 2. — Endometrial cancer > 70 yrs.

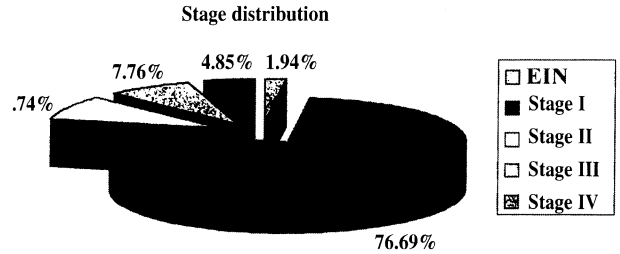
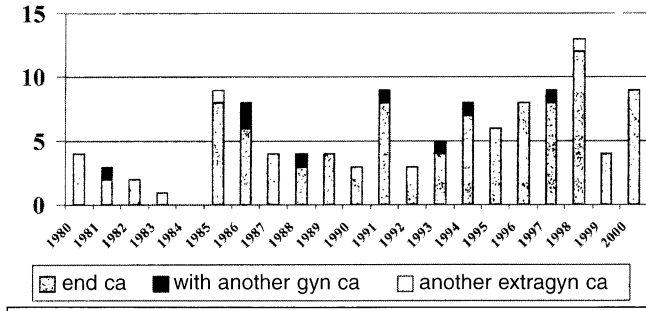


Figure 3. — Incidence of neoplasia associated with endometrial cancer



- 6 cases of associated breast cancer
- 2 cases of associated colon cancer
- 1 case of ovarian cancer
- 1 case of bladder cancer
- end ca = endametrial cancer; gyn ca = gynecologic cancer; extra gyn ca = extra gynecologic cancer.

Table 1. — Endometrial cancer > 70 yrs.

	HISTOLOGY ACCORDING TO STAGE							
Stage	No. of cases	Endometrioid carcinoma	Adeno squamous	Adeno acantoma	Serous papillary	Secretory mucinous	Clear cell	NE
I	79	51	8	4	7	3	1	5
II	9	3	3	–	1	–	–	2
III	8	5	1	–	1	–	–	1
IV	5	1	–	–	2	–	–	2
Total	101	60	12	4	11	3	1	10

- Three patients not surgically staged were excluded plus 2 with carcinoma in situ;
- NE: not evaluated.

Table 2. — Endometrial cancer > 70 yrs.

	GRADING ACCORDING TO STAGE				
Stage	No. of cases	G1	G2	G3	NE
I	79	36	25	9	9
II	9	1	3	3	2
III	8	0	3	2	3
IV	5	0	1	2	2
Total	101	37	32	16	16

- Three patients not surgically staged were excluded plus 2 with carcinoma in situ;
- NE: not evaluated.

Table 3. — Endometrial cancer > 70 yrs.

	THREE-YEAR SURVIVAL			
Stage	No. of cases	Patients evaluable for follow-up	Patients alive at 3 yrs	% alive at 3 yrs
I	79	60	43	71.60%
II	9	6	4	66.66%
III	8	8	3	37.50%
IV	5	5	0	0

Table 4. — Endometrial cancer > 70 yrs (6 patients).

	RELAPSES			
Patient age	Stage	Histotype	Grading	Site
70	IC	Endometrioid	G2	Vaginal cuff
75	IIIA	Serous papillary	G3	Vaginal cuff
77	IA	Clear cell	G3	Vaginal cuff
72	IA	Adenosquamous	G2	Abdominal wall
77	IC	Adenosquamous+ clear cell aspects	G2	Vaginal cuff
76	II	Endometrioid	G3	Vaginal cuff

pathology and 9.5% isolated diabetes. As shown in Figure 3, 11 out of 106 women with endometrial cancer had an associated malignancy: eight presented with a second gynecologic tumor (6 breast cancers, 1 ovarian endometrioid tumor and 1 cervical in situ carcinoma) and three with a second extragenital neoplasia (2 colon cancers and 1 bladder papillary malignant tumor). Five double neoplasias were synchronous.

Histology according to stage is described in Figure 4. First stage endometrial carcinomas occurred in 64.5% of endometrioid tumors while the incidence of more aggressive histological subtypes increased in higher stages: 44.4% in Stage II and 40% in Stage IV tumors.

With regard to grading, as shown in Figure 5, 45.55% of Stage I patients had a low-grade highly differentiated tumors while 11.3% had high-grade neoplasia. In advanced stages, a prevalence of high grades is reported: 33.3% of Stage II tumors were G2 and G3 and 40% of Stage IV tumors were G3. Considering the age of the patients (> 70) the median follow-up was 36 months (three years). Three-year survival was 71.6% for Stage I patients decreasing with stage: 66.6% for Stage II and only 37.5% for Stage III tumors. No Stage IV patient was alive after three years (Table 3).

Surgery was the treatment of choice also in the older age group, confirming that "surgery represents the backbone treatment" for endometrial cancer. In our case series, despite the older age and associated pathology 96% of patients underwent surgery. Only six relapses were registered after a period ranging from 18-60 months (Table 4). Relapses were related to cases with aggressive tumor subtypes and/or advanced stages.

Conclusion

Endometrial cancer is an increasing neoplasia in patients over 70 years, therefore all postmenopausal bleeding requires appropriate investigation in order to exclude malignancy. Routine screening for endometrial cancer is currently not justified as the detection of asymptomatic endometrial carcinoma is not related to a reduced mortality rate. A recent study by Jobo *et al.* [48] aimed to assess whether screening asymptomatic women is significant for early detection of endometrial malignancy. They pointed out a statistical difference in the histopathology and depth of myometrial invasion between the asymptomatic and symptomatic groups but no statistical differences were found in tumor grade, lymph node metastasis, cervical invasion, peritoneal cytology, surgical stage and patient age. The authors concluded that presence or absence of symptoms was not related to survival. Other authors [12] correlate the duration of symptoms (postmenopausal bleeding) with increased tumor stage and reduced overall survival.

Also in the group of > 70-year-old women Stage I tumors represented the majority of cases: 76.7% in our case series overlapping the general distribution trend

of endometrial carcinoma. A higher incidence (23.7%) of type 2 aggressive tumors was found in this age group. Associated pathology such as diabetes II, hypertension and cardiovascular disease was present in 25% of cases with endometrial cancer. Three-year survival for Stage I was 71.6% - 79% of these patients had G1 and G2 tumors. Radical surgery represented the first-line treatment even in elderly patients as 96% of all cases underwent surgery. The postoperatory course and quality of life of these patients were good after surgery. Only six relapses of the vaginal cuff were registered which were related to aggressive tumor subtypes and/or advanced stages. Adjuvant therapy must be personalized in high-stage tumors according to the general condition of this category of patients in order to obtain a good quality of life.

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