Can routine gynecologic examination contribute to the diagnosis of cervical involvement by primary endometrial cancer?

G. Pristauz, *M.D.*; **R. Winter,** *M.D.*; **E. Fischerauer,** *M.D.*; **J. Haas,** *Ph.D.*; **V. Bjelic-Radisic,** *M.D.*; **A.A. Bader,** *M.D.*; **E. Petru,** *M.D.*

Department of Obstetrics and Gynecology, Medical University of Graz (Austria)

Summary

Objective: There are few data in the literature as to whether findings at routine preoperative gynecologic examination of patients with primary endometrial cancer including cervical cytology, colposcopy and rectovaginal bimanual pelvic exam could predict cervical extension of the disease. *Methods and Materials:* The present retrospective study was undertaken to preoperatively identify potential clinical parameters associated with the histological diagnosis of cervical involvement by primary endometrial cancer in the hysterectomy specimen. We reviewed the records of 104 patients with Stage II endometrial cancer treated at our institution between 1985 and 2005 by simple or radical abdominal hysterectomy with special emphasis on cervical Pap smear, colposcopy, cervical palpation as well as rectal parametrial assessment. Patients with Stage I disease operated on before and after each study patient were selected as controls (n = 208). Patients with more advanced disease were excluded. *Results:* Overall, 312 records of patients with primary endometrial cancer were reviewed. Patients with Stage II disease had a significantly lower prevalence ($p < 0.0001$) of endometrioid carcinomas and a significantly higher ($p < 0.01$) prevalence of G3 tumors compared to the control patients. Pap smears and colposcopic findings were abnormal in 39% of patients with Stage II and in 9% and 10% of patients with Stage I disease ($p < 0.0001$). Of patients with Stage II disease, 42% had a suspicious cervical palpation compared to only 4% of patients with Stage I disease ($p < 0.0005$). Parametrial assessment was suspicious in 16% of patients with Stage II disease and in no patient with Stage I disease ($p < 0.001$). *Conclusion:* The four routine clinical parameters Pap smear, colposcopy, cervical palpation and rectal parametrial examination are significantly more often pathologic in patients with Stage II than in Stage I disease. The majority of patients with Stage II disease had at least one of these tests positive. Thus they may be useful to preoperatively detect cervical involvement by primary endometrial cancer.

Key words: Endometrial; Cancer, cervical involvement; Routine gynecological examination.

Introduction

Endometrial cancer is one of the most frequent malignancies of women in developed countries [1]. The prevalence of cervical involvement by primary endometrial cancer lies between 8% and 10% (FIGO Annual Report 2003) [2]. Extension to the cervix (FIGO Stage IIa or IIb disease) has implications for the prognosis [3], planning surgery [4, 5] and adjuvant treatment. There are few data in the literature on whether cervical involvement in women with endometrial cancer can be detected clinically.

We reviewed whether findings at preoperative clinical exam including cervical cytology, colposcopy, cervical palpation as well as rectal parametrial assessment in patients with endometrial cancer could predict cervical extension of the disease. The identification of such factors has been suggested to be helpful in the preoperative evaluation of endometrial cancer patients.

Material and Methods

A total of 1,034 patients underwent surgical treatment for epithelial endometrial cancer at our institution between January 1, 1985 and December 31, 2005. One hundred and four of these patients (10%) had cervical involvement based on final histology (Stage II disease). Patients with Stage III or IV disease were excluded even if the cervix was involved. Patients with Stage I disease operated on before and after each study patient were selected as controls (n = 208).

Revised manuscript accepted for publication February 19, 2009

The results of preoperative routine cervical cytology, colposcopy, and rectovaginal bimanual pelvic exam were abstracted from patient records. Clinical exams were performed by experienced staff members.

Pap smears classified as Pap III, IIIG, IV and V were considered indicative of neoplastic cervical involvement. Colposcopic findings of neoplastic ulcus, exophytic tumor and/or irregular external os of the cervical canal [ ] were considered suspicious for or indicative of cervical involvement. Cervical palpation was classified as suspicious or indicative of neoplastic involvement in the case of an exophytic tumor, irregularity/nodularity of the cervical surface and/or irregularity/nodularity of the external os of the cervical canal. Parametrial infiltration was suggested if nodular structures were palpable or the parametria were infiltrated at rectal examination.

Most patients underwent simple abdominal hysterectomy (Table 1). The decision about the type of surgery was mainly based on the presumed extent of the disease as well on the patient's performance status.

Statistical evaluations

The Pearson chi-square test and Fisher's exact test were used to identify significant differences between patient subgroups; p values < 0.05 were considered statistically significant.

Results

The characteristics of the 104 patients with cervical involvement and of the 208 patients with FIGO Stage I endometrial cancer are shown in Table 1. More than two-thirds of patients with cervical involvement had Stage IIb disease. There were no significant differences between

the patient subgroups with Stage I, IIa and IIb disease with regard to age and type of surgery. Patients with Stage II disease had a significantly lower prevalence ($p < 0.001$) of endometrioid carcinomas and a significantly higher ($p < 0.01$) prevalence of G3 tumors compared to the control patients.

The rate of abnormal Pap smears, suspicious colposcopy, suspicious cervical palpation and suspicious rectal parametrial assessment was significantly higher in patients with Stage II than in those with Stage I disease (Table 2). Pap smears were abnormal in 39% of patients with Stage II and 9% of those with Stage I disease, respectively ($p < 0.0001$). Even in Stage IIa disease, a statistically higher number of positive test results ($p < 0.0001$) was found compared to the control group with Stage I disease. Among the 208 patients with FIGO Stage I disease, only 9% of patients had a suspicious Pap smear (Table 2). Four, seven and seven patients of these had grade 1, grade 2 or grade 3 tumors at final histology, respectively. Forty-one of the 104 patients with FIGO Stage II disease (39 %) had a positive preoperative Pap smear. Six of these women showed a grade 1 tumor, 15 a grade 2 tumor and 20 a grade 3 tumor at final histology, respectively (Table 3).

The number of positive preoperative tests suggestive of cervical involvement including cervical Pap smear, findings at colposcopy, cervical palpation as well as rectal parametrial examination are shown in Table 4. None of the preoperative tests was suggestive of or indicative of cervical involvement in 87% of patients with Stage I disease, but only in 38% of patients with Stage II disease ($p < 0.001$). The majority of patients with Stage II disease had at least one of these tests positive.

Discussion

Our study reviewed findings routinely obtained during preoperative clinical evaluation of patients with endometrial cancer associated with the histological diagnosis of cervical involvement by primary endometrial cancer. These parameters were uniformly evaluated in all patients with primary endometrial cancer at our institution. In this paper the role of preoperative imaging studies, hysteroscopy or dilatation & curettage is not discussed.

Significantly more patients with Stage II disease than with Stage I disease had a positive cervical Pap smear ($p < 0.0001$), suspicious or cancerous findings at colposcopy ($p < 0.0001$), pathological cervical palpation ($p < 0.0001$) or suspicious rectal parametrial examination ($p < 0.0005$). However, all four preoperative tests evaluated were negative in 38% of patients with Stage II endometrial cancer.

In patients with Stage II disease grade 3 tumors were significant more prevalent than in Stage I disease (Table 1). A higher prevalence of pathological cervical Pap smears was found in Stage II cancer patients of whom the majority had undifferentiated cancers. Our findings are in accordance with the data of Larson *et al*. [7], Eddy *et al*. [8] and Uyar *et al*. [9] who described a higher rate of pathological Pap smears in patients with high-grade carcinomas.

Table 1. — *Characteristics of the 104 patients with Stage II primary endometrial cancer and exclusive spread to the cervix based on final histology (study group) compared with 208 patients with endometrial cancer without cervical spread (control group).*

Variable	No. of patients (%)		
	FIGO Stage I* (Control group)	FIGO Stage IIa	FIGO Stage IIb
Total	208	28 (27)	76 (73)
Mean age; years (range)	65 (42-94)	66 (42-78)	65 (44-81)
Histology			
Endometrioid adenocarcinoma	192 (93)[a, b]	17 (61)[a]	43 (57)[b]
Serous papillary adenocarcinoma	7 (3)	7 (25)	18 (24)
Clear cell carcinoma	7 (3)	4 (14)	11 (14)
Carcinosarcoma	2 (1)	–	4 (5)
Grading			
G1	82 (40)	7 (25)	21 (28)
G2	71 (34)	9 (32)	24 (32)
G3	55 (26)[c, d]	12 (43)[c]	31 (41)[d]
Type of Surgery			
Radical hysterectomy	–	5 (18)	14 (18)
Hysterectomy	208 (100)	23 (82)	62 (82)

*FIGO Ia: n = 40; FIGO Ib: n = 110; FIGO Ic: n = 58; [a, b] $p < 0.001$; [c, d] $p < 0.01$.

The prevalence of a positive cervical Pap smear was significantly higher in Stage IIb disease than in Stage IIa disease ($p < 0.001$) (Table 2). Previous studies have found a positive cervical smear in up to 48% of patients [10] with Stage I endometrial cancer. In two studies, positive Pap smear findings were correlated with adverse histological subtypes of endometrial cancer. Similarly to our results, the authors reported a higher prevalence of abnormal Pap smears among patients with Stage II-IV endometrial cancer compared to Stage I disease [7, 9].

Suspicious or grossly malignant findings at colposcopy ($p < 0.05$) were significantly higher in patients with Stage IIb disease than in those with Stage IIa disease and about four times higher overall than in the control group (Table 2). Although our study found somewhat higher numbers, Scurry *et al*. [11] identified gross cervical tumors in 23% of patients with Stage II endometrial cancer. In the latter almost one-third of patients had Stage IIa disease. Another study failed to detect cervical involvement by inspection [12].

Currently, the FIGO staging committee plans to omit substaging in Stage II disease. Only stromal invasion (now FIGO Stage IIb) should be classified as Stage II disease in the future (S. Pecorelli, personal communication). However, our clinical findings indicate that in Stage IIa disease at least preoperative parameters are considerably different from those in Stage I disease (Table 2).

For patients with FIGO Stage II disease, radical abdominal hysterectomy, bilateral salpingo-oophorectomy and lymphadenectomy are recommended [13, 14] . Since results from the SEER database [15] indicated radical hysterectomy to be superior to simple extrafascial hysterectomy with regard to overall survival, our data with the identification of simple routine gynecologic examination parameters may contribute to the identification of candidates for more radical surgery.

Table 2. — *Preoperative test results of the cervical Pap smear, findings at colposcopy, cervical palpation and rectal parametrial assessment in 104 patients with primary endometrial cancer and exclusive spread to the cervix (study group) compared to 208 patients with Stage I disease (control group).*

	FIGO Stage I* (control group) Suspicious/indicative of cancer No. of patients (%)	FIGO Stage IIa (n = 28) Suspicious/indicative of cancer No. of patients (%)	FIGO Stage IIb (n = 76) Suspicious/indicative of cancer No. of patients (%)	FIGO Stage II (total) (n = 104) Suspicious/indicative of cancer No. of patients (%)
Cervical Pap smear	18 (9) [a, b, c]	5 (18) [a, e]	36 (47) [b, e]	41 (39) [c]
Colposcopy	20 (10) [a, b, c]	6 (21) [a, f]	35 (46) [b, f]	41 (39) [c]
Cervical palpation	8 (4) [a, b, c]	8 (29) [a]	36 (47) [b]	44 (42) [c]
Parametrial assessment	0 (0) [a, b, d]	3 (11) [a]	14 (18) [b]	17 (16) [d]

[a, b, c] $p < 0.0001$; [d] $p < 0.005$; [e] $p < 0.001$; [f] $p < 0.05$.

Table 3. — *Number of preoperative test results including cervical Pap smear, findings at colposcopy, cervical palpation and rectal parametrial examination suggesting cervical involvement in the 104 patients with primary endometrial cancer depending on grading of final histology.*

	Pathological findings			
Grading (patients)	Pap smear	Colposcopy	Cervical palpation	Rectal palpation
G1 (28)	6 (21%)	8 (29%)	11 (39%)	2 (7%)
G2 (33)	15 (45%)	14 (42%)	11 (33%)	6 (18%)
G3 (43)	20 (46%)	19 (44%)	22 (51%)	9 (21%)

Table 4. — *Number of preoperative test results including cervical Pap smear, findings at colposcopy, cervical palpation and rectal parametrial examination suggesting cervical involvement in the 104 patients with primary endometrial cancer depending on grading of final histology.*

	FIGO Stage I (control group) No. of patients (%)	FIGO Stage II (study group) No. of patients (%)
Total	208 (100)[a]	104 (100)
Four negative test results	181 (87)[a]	39 (38)[a]
Positive test results	27 (13)	65 (62)
One test result suggestive/indicative	12 (6)	20 (19)
Two test results suggestive/indicative	14 (7)	19 (18)
Three test results suggestive/indicative	1 (0)	17 (16)
Four test results suggestive/indicative	0 (0)	9 (9)

[a] $p < 0.001$.

Conclusion

Reliable preoperative detection of cervical involvement might improve the planning of surgery by selecting patients for extended hysterectomy. The four routine clinical parameters Pap smear, colposcopy, cervical palpation and rectal parametrial examination are significantly more often pathologic in patients with Stage II disease than in Stage I disease. The majority of patients with Stage II disease had at least one of these tests positive. Besides cervical curettage, hysteroscopy, vaginal ultrasound and probably pelvic MRT [16, 17] the four routine clinical parameters may be useful to preoperatively detect cervical involvement by primary endometrial cancer. Particularly patients in which G3 tumors are diagnosed preoperatively, should undergo careful evaluation of the Pap smear, colposcopy and cervical palpation.

References

[1] Creasman W., Odicino F., Maisonneuve F., Beller U., Benedet J.L., Heintz A.P. *et al*.: "Carcinoma of the corpus uteri". In: "Annual Report of Treatment in Gynecological Cancer". *J. Epidemiol. Biostat*, 2001, *6*, 45.

[2] Annual Figo Report 2003 (http://www.figo.org).

[3] Eltabbakh G.H., Moore A.D.: "Survival of women with surgical Stage II endometrial cancer". *Gynecol. Oncol.,* 1999, *74,* 80.

[4] Mariani A., Webb M.J., Keeney G.L., Podratz K.C.: "Role of wide/radical hysterectomy and pelvic lymph node dissection in endometrial cancer with cervical involvement". *Gynecol. Oncol.,* 2001, *83,* 72.

[5] Tamussino K.F., Reich O., Gücer F. *et al*.: "Parametrial spread in patients with endometrial carcinoma undergoing radical hysterectomy". *Int. J. Gynecol. Cancer,* 2000, *10*, 313.

[6] Burghardt E., Pickel H., Giradi F.: "Colposcopy, Cervical Pathology: Textbook and Atlas". Stuttgart, Thieme, 1998.

[7] Larson D.M., Johnson K.K., Reyes C.N. Jr., Broste S.K.: "Prognostic significance of malignant cervical cytology in patients with endometrial cancer". *Obstet. Gynecol*., 1994, *84*, 399.

[8] Eddy G.L., Wojtowycz M.A., Piraino P.S., Mazur M.T.: "Papanicolaou smears by the Bethesda system in endometrial malignancy: utility and prognostic importance". *Obstet. Gynecol.,* 1997, *90*, 999.

[9] Uyar D.S., Eltabbakh G.H., Mount S.L.: "Positive predictive value of liquid-based and conventional cervical Papanicolaou smears reported as malignant". *Gynecol. Oncol*., 2003, *89,* 227.

[10] Gu M., Shi W., Barakat R.R., Thaler H.T., Saigo P.E.: "Pap smears in women with endometrial carcinoma". *Acta Cytol*., 2001, *45,* 555.

[11] Scurry J., Craighead P., Duggan M.: "Histologic study of patterns of cervical involvement in FIGO Stage II endometrial carcinoma". *Int. J. Gynecol. Cancer,* 2000, *10,* 497.

[12] Almog B., Gutman G., Lessing J.B., Grisaru D.: "Prediction of cervical involvement in endometrial cancer by hysteroscopy". *Arch. Gynecol. Obstet*., 2007, *275,* 45.

[13] Morrow C.P., Curtin J.P.: "Management of uterine neoplasia". In: Morrow C.P., Curtin J.P. (eds.). Gynecologic Cancer Surgery, New York: Churchill Livingstone, 1996, 569.

[14] Boente M.P., Yordan E.L., McIntosh D.G., Grendys E.C. Jr., Orandi Y.A., Davies S. *et al*.: "Prognostic factors and long-term survival in endometrial adenocarcinoma with cervical involvement". *Gynecol. Oncol.,* 1993, *51*, 316 22.10.1006/gyno.1993.1297.

[15] Cornelison T.L., Trimble E.L., Kosary C.L.: "SEER data, corpus uteri cancer: treatment trends versus survival for FIGO Stage II, 1988-1994". *Gynecol. Oncol*., 1999, *74,* 350.

[16] Nagar H., Dobbs S., McClelland H.R., McCluggage W.G., Grey A.: "The diagnostic accuracy of magnetic resonance imaging in detecting cervical involvement in endometrial cancer". *Gynecol. Oncol*., 2006, *103*, 431.

[17] Kietlinska Z., Stelmachow J., Antczak-Judycka A., Timorek A., Sawicki W., Tymińska B.: "Fractional curettage, hysteroscopy and imaging techniques: transvaginal sonography (TVS), magnetic resonance imaging (MRI) and computed tomography (CT) in the diagnosis of cervical canal involvement in cases of endometrial carcinoma". *Eur. J. Gynaecol. Oncol.,* 1998, *19,* 561.

Address reprint requests to:
G. PRISTAUZ, M.D.
Department of Obstetrics & Gynecology
Medical University of Graz
Auenbruggerplatz 14 - 8036 Graz (Austria)
e-mail: gunda.pristauz@klinikum-graz.at