

PERITONEAL CYTOLOGY IN STAGE I ENDOMETRIAL CANCER

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Peritoneal lavage fluid for cytologic study was obtained in 73 patients undergoing primary surgery for stage I endometrial adenocarcinoma. Preoperative irradiation was not used. Malignant cells consistent with endometrial adenocarcinoma were present in eight (11 percent) cases. There was no significant difference in the proportion of patients with "positive peritoneal cytology" when patients with grade 1 and 2 tumors, five of 45 (11 percent), were compared with those with grade 3 and adenosquamous tumors, three of 28 (10.7 percent), between deeply invasive tumors, two of 20 (10 percent), and those with superficial or no invasion, six of 52 (11.5 percent), between stage IA, six of 42 (14.5 percent) and stage IB disease, two of 31 (6.5 percent). The prevalence of positive peritoneal

cytology in this series of 73 patients who received no preoperative irradiation is similar to that reported in other series where preoperative irradiation was used. No correlation between positive peritoneal cytology and other reported poor prognostic indicators in stage I endometrial adenocarcinoma was found.

The role of peritoneal cytology in ovarian cancer is well established, while its role in endometrial cancer is still being defined. In 1971, Creasman and Rutledge¹ reported on 183 patients with cancer of the uterine corpus who underwent hysterectomy after radiation. Class IV and V peritoneal cytology was reported in 21 (11.5 percent) patients, with 12 of the 21 patients having gross disease outside of the uterus. Of 39 patients with stage I endometrial cancer without extrauterine spread studied by Keettel et al² five (12 percent) had cytopathologic findings of peritoneal washings reported as "atypical or abnormal, probably malignant." More recently, in a report of two study populations, 26 of 167 (16 percent) and 23 of 175 (13 percent) patients with clinical stage I

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endometrial cancer had "positive peritoneal cytology."³ The finding of malignant cells in the peritoneal lavage was associated with deep myometrial invasion, adnexal involvement, nodal metastases, and tumor in the lower uterine segment or endocervix. In a report from the Roswell Park Memorial Institute, 10 of 93 (11 percent) patients with histologically confirmed stage I endometrial adenocarcinoma had malignant cells in the peritoneal lavage fluid.⁴ They found no statistically significant differences in the prevalence of malignant peritoneal cytology between patients with stage IA and IB disease, FIGO* grade 1, 2, and 3 tumors, and patients with deep myometrial invasion and those with superficial or no invasion.

The use of preoperative intracavitary radium¹⁻⁴ and the evaluation of the cytopathologic material by pathologists from different institutions³ confuse the interpretation of these reports. The authors investigated the prevalence of malignant cells in the peritoneal lavage fluid of patients with clinical stage I endometrial cancer undergoing primary surgical treatment. Preoperative irradiation was not used. The possible association between positive peritoneal cytology and other prognostic indicators in stage I endometrial cancer is evaluated.

MATERIALS AND METHODS

From 1976 to 1982 peritoneal lavage for cytologic study was obtained from 73 patients undergoing total abdominal hysterectomy and bilateral salpingo-oophorectomy for stage I endometrial adenocarcinoma. Preoperative irradiation was not used.

Upon entering the peritoneal cavity, the uterus was identified, elevated, and long Kelly clamps applied to the specimen, thereby occluding the fallopian tubes at the cornua. The pelvis was then lavaged with 200 mL of normal saline solution. This fluid was aspirated, 5,000 units of heparin added, and it was sent for cytopathologic analysis. The material was processed and stained by the Papanicolaou method. All cytologic specimens

and histologic sections were reviewed by the staff of the Division of Cytopathology and by the Gynecologic Pathology Laboratory of The Johns Hopkins Hospital.

The paraaortic and pelvic nodes were palpated in all cases. Paraaortic node sampling was performed in 26 of the 73 patients. Selective pelvic lymphadenectomy was done in 23 patients.

The peritoneal lavage cytology was classified as positive, suspicious, or negative. A "positive" diagnosis was made when malignant cells consistent with endometrial adenocarcinoma were present in the lavage fluid. When atypical cells were present, but a definitive diagnosis of malignancy could not be made, a diagnosis of "suspicious" was rendered.

The surgical specimens were processed by the Gynecologic Pathology Laboratory. The histologic diagnoses included adenocarcinoma, FIGO grades 1 through 3, and adenosquamous. Adenosquamous tumors were considered in the same category as grade 3 adenocarcinomas. The depth of myometrial invasion was classified as none when the disease was limited to the endometrium. Superficial invasion represented invasion to less than 50 percent of the myometrium. Deep invasion was diagnosed when the tumor penetrated over 50 percent of the myometrium.

The association between positive peritoneal lavage cytology and other established prognostic indicators in stage I endometrial cancer, ie, substage, histologic grade, and myometrial invasion were investigated. The data was analyzed by use of Fisher's exact test or simple analysis of variance where appropriate.

RESULTS

The patients' ages ranged from 39 to 88 years with a mean of 61.8 years. There were 42 (57.5 percent) clinical stage IA tumors and 31 (42.5 percent) stage IB. The histologic grade of the endometrial neoplasm was: grade 1, 32 (44 percent), grade 2, 13 (18 percent), grade 3, 11 (15 percent), and adenosquamous, 17 (23 percent). Histologic evaluation of depth of myometrial invasion showed no invasion in 17 cases (23 percent), superficial in 35 (48 percent) and deep in 20

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TABLE 1. CLINICO-PATHOLOGIC CHARACTERISTICS OF PATIENTS WITH CERVICAL, OVARIAN, OR NODAL TUMOR INVOLVEMENT

Site With Tumor Involvement	Age	Stage	Grade	Myometrial Invasion (%)	Peritoneal Cytology	Paraortic Nodes	Pelvic Nodes
Cervix	57	IB	AS*	None	Suspicious	ND**	Negative
	63	IB	AS	≥50	Negative	Positive	Negative
Ovary	46	IB	2	<50	Suspicious	Negative	ND
	78	IB	3	?	Negative	Negative	ND
Paraortic nodes	54	IB	3	≥50	Negative	Positive	ND
	62	IA	3	≥50	Positive	Positive	Positive
	63	IB	3	≥50	Negative	Positive	Negative
	63	IB	AS	≥50	Negative	Positive	Negative
Pelvic nodes	62	IA	3	≥50	Positive	Positive	Positive

*Adenosquamous

**Not done

(28 percent). In one instance, the depth of invasion could not be determined. Occult cervical involvement was present in two (2.7 percent) of the 73 specimens. The involvement was deep in the cervical stroma in both instances. Microscopic adnexal involvement was found in two (2.7 percent) of the 73 specimens. The involvement was deep. Tumors in the paraortic nodes were found in four (15.4 percent) of the 26 patients who had paraortic node sampling. Pelvic node involvement was present in one (4 percent) of the 23 patients who had pelvic nodes samples, and this patient also had a tumor in the paraortic nodes. The clinical characteristics of the patients with ovarian, cervical, or nodal involvement are presented in Table 1.

The peritoneal lavage cytology was reported as positive in eight (11 percent) cases, suspicious in 11 (15 percent), and negative in 54 (74 percent). The relationship between peritoneal lavage cytopathologic findings and histopathologic findings is presented in Table 2. There was no statistically significant difference in the mean age of patients with negative, positive, or suspicious cytology ($P < 0.06$). The prevalence of "negative" peritoneal cytology is similar for stage IA and IB, for all tumor grades, for all levels of myometrial invasion, and for the presence or absence of tumor in the paraortic nodes. No difference was found between the proportion of cases with "positive"

cytology when cases with deep myometrial invasion (two of 21, 9.5 percent) are compared with those with superficial or no invasion (six of 52, 11.5 percent), ($P = 0.58$). No difference in the proportion of cases with positive cytology was found when comparing grade 1 and 2 tumors (five of 45, 11 percent) against grade 3 and adenosquamous (three of 28, 10.7 percent), ($P = 0.64$). A positive diagnosis on the peritoneal lavage cytology was rendered in 14.3 percent of stage IA cases and 6.5 percent of stage IB ($P = 0.25$). No statistically significant differences were seen in the prevalence of suspicious and positive cytology between stage IA and IB cases, grade 1 and 2 vs grade 3 and adenosquamous and cases with superficial vs those with deep myometrial invasion (Table 3).

DISCUSSION

The clinical significance of malignant cells in peritoneal lavage fluid of patients with stage I endometrial adenocarcinoma has not yet been defined. Malignant cells are reported to be found in the peritoneal lavage fluid of 11 to 16 percent of patients undergoing surgery for stage I endometrial adenocarcinoma.¹⁻⁴ It has been postulated that the presence of malignant cells in the peritoneal

TABLE 2. PATIENT'S AGE, STAGE, AND HISTOPATHOLOGIC FINDINGS VS PERITONEAL LAVAGE CYTOLOGY FINDINGS

	Peritoneal Cytology		
	Negative (%)	Positive (%)	Suspicious (%)
Age (Years)			
Range	40-88	52-79	39-68
Mean	61.9	65	56.4
Stage			
IA	30 (71.4)	6 (14.3)	6 (14.3)
IB	24 (77.4)	2 (6.5)	5 (16.1)
Grade			
1	23 (71.9)	4 (12.5)	5 (15.6)
2	10 (76.9)	1 (7.7)	2 (15.4)
3	7 (63.7)	3 (27.3)	1 (9)
Adenosquamous	14 (82.35)	0	3 (17.65)
Myometrial Invasion			
none	12 (70.6)	2 (11.8)	3 (17.6)
<50%	26 (74.3)	4 (11.4)	5 (14.3)
≥50%	15 (75)	2 (10)	3 (15)
Cervical Involvement			
Yes	1 (50)	0	1 (50)
No	53 (74.7)	8 (11.3)	10 (14)
Adnexal Involvement			
Yes	1 (50)	0	1 (50)
No	53 (74.7)	8 (11.3)	10 (14)
Positive Pelvic Nodes			
Yes	0	1 (100)	0
No	16 (72.8)	2 (9)	4 (18.2)
Positive Paraortic Nodes			
Yes	3 (75)	1 (25)	0
No	16 (72.7)	2 (9.1)	4 (18.2)

cavity of patients with endometrial adenocarcinoma in the absence of extrauterine disease can be due to transtubal transport.⁵⁻⁶ Creasman and Rutledge¹ and Keetel et al² explained the low incidence of positive peritoneal lavage cytology in their series as being due to preoperative irradiation sealing the uterine cornua. Preoperative irradiation was not utilized in the present series, and the percentage of patients with malignant cells in the peritoneal lavage fluid (11 percent) is similar to that reported by other investigators. Yazigi et al⁴ reported on 93 patients with histologically confirmed stage I endometrial adenocarcinoma. Treatment consisted of intracavitary irradiation

followed by hysterectomy in 50 (53.7 percent) patients. Their findings were similar to this study. Malignant cells were present in 11 percent of the cytology specimens. Other mechanisms besides transtubal transport must be entertained in trying to explain the presence of malignant cells in the peritoneal lavage of patients with early uterine cancer.

Another possible explanation is the presence of multifocal disease. The peritoneal mesothelium and genital tract mesoderm being simultaneously exposed to an agent or agents capable of producing malignant changes in different but embryologically related anatomic sites.

TABLE 3. STAGE, GRADE, AND DEPTH OF MYOMETRIAL INVASION VS PERITONEAL LAVAGE CYTOLOGY FINDINGS

	Peritoneal Cytology		
	Negative (%)	Positive and Suspicious (%)	
Stage			
IA	30 (71)	12 (29)	P = .38
IB	24 (77)	7 (23)	
Grade			
1 & 2	33 (73)	12 (27)	P = .55
3 & AS*	21 (75)	7 (25)	
Invasion			
<50*	38 (73)	14 (27)	P = .56
≥50*	15 (75)	5 (25)	

*Adenosquamous

There also exists the possibility of a misinterpretation of the cytopathologic findings. It has been reported that 4.5 percent of laparotomies done for benign disease will have markedly abnormal cells, "class IV and V," and an additional 3 percent have cells classified as "class III."¹ In another series of 203 "positive peritoneal lavages," 17 were associated with benign disease.² The diagnosis of well-differentiated endometrial carcinoma in peritoneal lavage fluid is especially difficult because of the lack of significant cellular atypia.

Endometrial cancer cells may gain access to the peritoneal cavity by direct extension of the tumor through the myometrium. In cases of deep myometrial invasion, the tumor may reach the uterine serosa or be present in the serosal lymphatics and be shed into the peritoneal cavity. This is supported by the reported association of deep myometrial invasions and "positive peritoneal washings."^{3,7} This association could not be corroborated in this series. A diagnosis of positive peritoneal cytology was made in 10 percent of patients with deep myometrial invasion and in 11.5 percent of those with superficial or no invasion.

No association was found between positive peritoneal cytology and tumor grade or between positive peritoneal cytology and substage in this series.

The significance of abnormal cytopathologic findings in peritoneal lavage fluid in endometrial

adenocarcinoma should be judged with caution. Therapeutic implications must be carefully weighed. Larger series and long-term follow-up of patients with positive peritoneal cytology (as the only possible poor prognostic indicator) are needed to elucidate the prognostic significance of this finding.

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