PROGNOSTIC INFLUENCE OF PERITONEAL CYTOLOGY IN ENDOMETRIAL CANCER

F. Teksen Çamlıbel, M.D. *

* *Pasteur French Hospital, İstanbul, Turkey.*

SUMMARY

Importance of peritoneal cytologic washings in endometrial cancer is newly recognized. In a series of 60 patients, 16 (27 %) had malignant cells in the peritoneum. Grade of tumor, depth of myometrial invasion, and stage of disease correlated with presence of cancer cells in the pelvis ($p < 0.001$, $p < 0.01$, $p < 0.05$ respectively). Lymph node involvement versus cytology did not correlate however ($p > 0.10$). One year survival of patients with positive cytology was significantly lower ($p = 0.016$).

All patients with endometrial cancer, especially in Stage I, should have cytologic evaluation of peritoneal washings during TAH BSO. P^{32} instillation and/or progestational agents can be used as adjunctive therapy in these cases.

Key Words: Peritoneal Cytology, Endometrial Cancer.

INTRODUCTION

Endometrial cancer is now the most common gynecologic malignancy in USA and American Cancer Society predicted that in the decade of 1970's incidence of this cancer will increase one and a half fold (1). In 1983, 39,000 new cases and 3,000 cancer deaths were expected. Other developed Western countries also have this increased incidence (2). In Turkey, although there are no valid statistics about the absolute and relative incidence of this cancer, more frequent occurrence in recent years became evident (3).

Endometrial cancer is not like its cervical counterpart which can be diagnosed early by mass PAP smear screening. However, bleeding symptoms begin early and patients come to the hospitals in operable and early stage (about 75 %, Stage I). It is therefore physcian's duty not to waste any time with hormone preparations in these patients with "abnormal bleeding" but to take endometrial biopsy and establish the diagnosis immediately.

In Stage I endometrial cancer (according to FIGO) only uterine corpus is involved, there is no extention to cervix or any other area in pelvis. In this stage, 5 yr survival is about 75 %. In Grade I this is 81 %, in Grade II,74 % and in Grade III,50 % (4).

Why is in Stage I Grade I disease, 5 yr survival is about 80 % and not better? Gynecologic oncologists have been trying to answer this question for a long time. Some of these patients found to have more advanced disease in surgery, but what about the majority who have Stage I disease surgico-pathologically as well?

It is noted that some Stage I patients, following TAH BSO, come back to hospitals with abdominal distention, presence of ascites and die shortly after with ileus and wide spread intraabdominal carcinomatosis picture.

These patients probably have malignant cells in the pelvis at the time of TAH BSO, which disseminate later. These cells may not be noticeable as ascites but if abdominal cavity is irrigated with isotonic saline and this washing is submitted to pathology for cytologic screening, they can be detected. This procedure is becoming rutine for all endometrial cancer patients.

Importance of peritoneal cytologic washings in ovarian cancer is well appreciated. In fact, presence of ascites or positive washings put the patients in stage I and II to substages of I.c and II.c respectively. Can similar prognostic importance be attached to peritoneal washings in endometrial cancer? Are malignant cells in abdomen one of the reasons that even in Stage I Grade I cancers, 10 % of patients die within 5 yrs? If so, what can be done to prevent this? We will discuss these in this paper.

MATERIALS AND METHODS

Between July 1976 and October 1982, total of 60 patients with endometrial cancer had their peritoneal cytology done. Although we had more cases of endometrial cancer, not until recent years that this procedure was rutinely performed.

Upon entering abdominal cavity, tubes were clipped and if there is an ascites, it was collected and fixed in 50 % alcohol. If there is no ascites, culdesac was irrigated with 200 cc of isotonic saline and submitted similarly. This fluid was stained as Papanicolau smear and studied (Fig. 1). Cell blocks were done in some cases as well. Washings with cells having usual

characteristics of malignancy considered positive.

RESULTS

60 patients had their peritoneal cytology results available. Firstly, grade of tumor and status of washings were evaluated (Table I). 11 % of Grade I patients had malignant cells in peritoneal cavity compared to 69 % of those with Grade III cancer. This was statistically highly significant ($p < 0.001$). It is generally accepted that grade of endometrial cancer is a very important prognostic factor.

When we examined the depth of myometrial invasion versus peritoneal cytology, it was appearant that chance of positive cytology increased with myometrial involvement ($p < 0.01$, Table II).

In Table III, comparison between stage of disease and status of cytology was presented. In Stage I, 18 % had positive cytology and this was even more common in later stages ($p < 0.05$).

Our data on lymph node involvement versus cytology did not reveal a positive correlation, however ($p > 0.10$) (Table IV). This might indicate that abnormal cells reach the pelvis cavity by means other than lymph channels.

When we looked at the chance of survival between patients with positive and negative pelvis washings, P value was 0.016 for the first year and 0.046 for the following four years (Table V). This indicates that positive cytology patients die at higher rate. Positive cytology seems to be an important prognostic factor, along with grade of tumor, myometrial invasion, and lymph node involvement.

DISCUSSION

Importance of cytologic washings in ovarian Cancer is so well recognized that FIGO has included this parameter in its Stage I and II classification. Stage I-c ovarian cancer is treated by TAH BSO and adjuvant chemotherapy or P^{32} instillation.

Peritoneal cytology has been obtained and results were published by several authors (Table VI). Incidence of positive cytology was surprisingly high, even in early stages. In recent years, obtaining peritoneal fluid has gained wide acceptance and in USA, Gynecologic Oncology Group included this procedure in evaluating endometrial cancer patients in protocols (10).

Mechanism of malignant cell dissemination into the peritoneal cavity is not well understood. Direct exfoliation from uterine serosal surface in deeply invading tumors may explain some cases (Table II). Transport of cells via lymhatic channels is another possibility. However, direct communication between uterine lymphatic drainage and pelvic cavity was not shown, and in our study, peritoneal cytology did not correlate with extent of lymphatic involvement.

The third and most likely theory is the transport of endometrial cells through fallopian tubes. Sampson championed and demonstrated this regurgitation process in 1920's to explain endometriosis. It was noted that during endometrial biopsy procedure, some cells may enter pelvic cavity (11). It is our rutine to ligate tubes prior to TAH BSO done for endometrial cancer, to prevent spillage during uterine manipulation. Preoperative radiotherapy was thought to seal off fallopian tubes and prevent regurgitation. However, in GOG study where no preoperative radiation was used, incidence of positive cytology was 9.9 %, similar or less than the incidence reported by others who used radiation (Table VI). In our series, only 3 of 16 patients in Stage I had preoperative radiation. Regurgitation theory was also disputed in a case of Creasman and Lukeman (7) who had positive cytology and bilateral salpingectomy.

Prognostic significance of positive cytology has been demonstrated in our study as well as in others (6,9) Creasman et al (9) have reported on 167 patients with Stage I disease who had surgery and peritoneal washings. 26/167 patients had (+) washings and 10 of these 26 had recurrence (34 %). In contrast, 141 patients with (−) cytology, only 14 had recurrence (9.9 %). In this study, other high risk factors were evaluated against cytology and was found that positive cytology increases recurrence rate only in the absence of other poor prognostic factors (high grade, deep myometrial invasion, involvement of cervix and / or adnexa and lymph nodes). Therefore, patients who are in otherwise low risk category are pushed into high risk category if their cytology was positive. Patients with already high risk factors are not affected significantly by the status of cytology. Not all studies agree with this conclusion however (12).

This is a very important finding since Stage I and low risk patients are not given any adjuvent treatment in general. Presence of (+) cytology needs to be treated in these group of patients. It was also shown that concentration of cancer cells can better predict the outcome than mere presence of cells. In one study,(8) if there were >1000 cells in 100 cc recurrence rate was 100 %, whereas patients with < 1000 cells per 100 cc had no evidence of recurrence after 3 yrs.

Recurrence site of patients with (+) cytology is usually intraabdominal. The picture resembles intraabdominal carcinomatosis seen in ovarian cancer. Once recurrence developed, survival is very short. Clearly more than TAH BSO is needed in these patients in Stage I–C Ovarian Cancer, instillation of P^{32} intraperitoneally or adjuvant chemotherapy has improved 5 year survival. Creasman and associates (9)have instilled P^{32} in 23 patients and only 3 had recurrent cancer, all outside the treatment field. These results are very encouraging. Another way of management would be to use progestational agents.Its simple use, relatively few side effects and demonstrated ability to treat some endometrial

TABLE I
FREQUENCY DISTRIBUTION OF 60 PATIENTS WITH CANCER OF THE ENDOMETRIUM BY GRADE OF DIFFERENTIATION AND CYTOLOGY OF PELVIC WASHINGS

Cytology/Grade	Grade I N:	%	Grade II N:	%	Grade III N:	%	Total Cases N:	%
Negative cytology	25	89	15	79	4	31	44	73
Positive cytology	3	11	4	21	9	69	16	27
Total cases	28	100	19	100	13	100	60	100

$X^2_2 = 20.25$ $P < 0.001$

TABLE II
FREQUENCY DISTRIBUTION OF 60 PATIENTS WITH CANCER OF THE ENDOMETRIUM BY DEPTH OF MYOMETRIAL INVASION AND CYTOLOGY OF PELVIC WASHINGS

Cytology/Invasion	No Disease N:	%	Inner Third. N:	%	Two Thirds N:	%	Outer Third N:	%	Total N:	%
Negative Cytology	5	100	19	86	13	81	7	41	44	73
Positive Cytology	0	0	3	14	3	19	10	59	16	27
Total Cases	5	100	22	100	16	100	17	100	60	100

$X^2_3 = 13.46$ $P < 0.01$

TABLE III
FREQUENCY DISTRIBUTION OF 60 PATIENTS WITH CANCER OF THE ENDOMETRIUM BY CLINICAL STAGE AND CYTOLOGY OF PELVIC WASHINGS

Cytology/Stage	I N:	%	II N:	%	More Than II N:	%	Total N:	%
Negative Cytology	37	82	7	58	0	0	44	73
Positive Cytology	8	18	5	42	3	100	16	27
Total Cases	45	100	12	100	3	100	60	100

$X^2_2 = 7.6$ $P < 0.05$

TABLE IV
FREQUENCY DISTRIBUTION OF 34 PATIENTS WITH CANCER OF THE ENDOMETRIUM AND LYMPH NODE DISSECTION BY LYMPH NODE INVOLVEMENT AND CYTOLOGY OF PELVIC WASHINGS

Cytology/Lymph Node	Positive N:	%	Negative N:	%	Total Cases N:	%
Negative Cytology	4	50	18	69	22	65
Positive Cytology	4	50	8	31	12	35
Total Cases	8	100	26	100	34	100

$X^2_1 = 0.17$ $P > 0,10$

TABLE V
COMPARISON OF CUMULATIVE CHANCE OF SURVIVING FOR PATIENTS WITH POSITIVE PELVIC WASHINGS AND THOSE WITH NEGATIVE PELVIC WASHINGS

Year Since entry to study	Patients with positive pelvic washings		Patients with negative pelvic washings		Z value $\frac{Px - P'x}{\sqrt{SE(Px)^2+SE(P'x)^2}}$	P value
	P (x)	SE (Px)	Px	SE (P' x)		
0–1	0.68	0.132	0.97	0.027	2.15	P=0.016
1–2	0.68	0.132	0.92	0.052	1.69	P=0.046
2–3	0.68	0.132	0.92	0.052	1.69	P=0.046
3–4	0.68	0.132	0.92	0.052	1.69	P=0.046
4–5	0.68	0.132	0.92	0.052	1.69	P=0.046
5–6	0.00	∞	0.92	0.052		

TABLE VI.
FREQUENCY OF POSITIVE WASHINGS IN ENDOMETRIAL CANCER

Author	N	Radiation Therapy (RT)
Keettel et al 1974	5/39 (12.8%)	All Preop RT
Creasman et al 1971	3/44 (2%)	All Preop RT
Creasman et al 1971	21/183 (11.5%)	All Preop RT
Szpah et al 1981	12/54 (22%)	Recent Preop Cesium in 7/12
Creasman et al 1981	26/157 (15.5%)	Occ Preop Cesium
Gog 1981	50/505 (9.9%)	No Preop RT

cancer metastasis make them reasonable adjuvant agents. In our center, we use medroxyprogesterone acetate or megestrol acetate for approximately 2 years postoperatively. Other progestins such as the ones in oral contraceptives (Norgestrel etc) are not recommended since they also have weak estrogenic activity.

In the future, controlled trials with P^{32},intraperitoneal sitostatic agents, adjuvent chemotherapy and immunotherapy will be needed. Also, putting Stage I patients with positive cytology in a substage of I-c should be considered.

CONCLUSION

As in ovarian cancer, peritoneal cytologic testing should rutinely be done in all endometrial cancer patients, especially in early stages. Positive pelvic washings are proven to be a poor prognostic sign, and needs to be treated. P^{32} instillation and progestins are currently employed.

Establishing Substage of I–C for Stage I patients with positive cytology should be considered.

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