Is adjuvant therapy necessary for peritoneal cytology-positive surgical-pathologic Stage I endometrial cancer? Preliminary results

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Summary

Objective: To compare the clinical and laboratory findings between adjuvant therapy performed and not performed on peritoneal cytology-positive patients with cytology-negative cases of surgical-pathologic Stage I endometrial cancer.

Methods: Twelve peritoneal cytology-positive and 12 negative surgical-pathologic Stage I endometrial cancer cases were used in the study. Adjuvant radiotherapy was performed for six cytology-positive patients (group I); no adjuvant therapy was performed for six cytology-positive (group II) and 12 cytology-negative patients (control group). Pelvic examination, vaginal cytology, serum CA125 levels and routine blood tests were checked at two-month intervals for two years and at six-month intervals for the third year. Abdominopelvic computerized tomography was planned annually.

Results: There was no statistically significant difference among the three groups and no recurrence in any group.

Conclusion: We do not recommend adjuvant therapy for cytology-positive patients if the tumor is confined to the uterus.

Key words: Endometrial cancer; Peritoneal cytology; Adjuvant therapy.

Introduction

Adenocarcinoma of the endometrium is the most common gynecologic malignancy of the female genital tract. Over 75% of the patients have early stage disease [1, 2]. In 1988 the International Federation of Gynecology and Obstetrics (FIGO) adopted a surgical staging system for endometrial carcinoma to replace clinical staging [3]. Patients with metastasis to the adnexa and/or with uterine serosal invasion and/or positive peritoneal cytology were included in Stage IIIA.

The patient is classified in Stage IIIA when the peritoneal cytology is positive even if the tumor is limited to the uterine corpus according to the FIGO staging system. The management of patients is quite different in Stage I and Stage III cases. Thus peritoneal cytology positivity has great importance in the management of these cases. However, the prognostic significance of positive peritoneal cytology is still controversial. Several authors have concluded that positive peritoneal cytology is a significant prognostic indicator [4, 5], but others have not confirmed these findings [6, 7].

We conducted this study to determine whether positive peritoneal cytology can be a prognostic factor for patients if the tumor is confined to the uterus.

Materials and Methods

The study was designed as a prospective, randomized, case-controlled clinical trial.

Between September 1993 and September 1998, 184 women with endometrial carcinoma, who had been diagnosed by endometrial biopsy, were treated surgically and examined for peritoneal cytology intraoperatively at the Obstetrics and Gynecology Department of Gülhane Military Medical Academy in Ankara, Turkey. A surgical staging procedure was performed (total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, appendectomy, pelvic and para-aortic lymphadenectomy) for these patients. Peritoneal washing was carried out preceeding laparotomy.

Twelve cytology-positive surgical-pathologic Stage I endometrial cancer cases were used as the study group, and 12 negative cases as the control group.

The demographic parameters of the two groups resembled each other and are summarized in Table 1. Pathologic grading of the cases is summarized in Table 2. The cytology-positive group was randomized according to time of surgery and staging. Adjuvant radiotherapy was performed for six patients (Group I). Totally 5000 cGy external radiotherapy was performed by 6 MV photon, in 25 fraxionated doses to the pelvic and peripheral lymphatic areas. No adjuvant therapy was used for the six cytology-positive (Group II) and 12 cytology-negative (Group III) cases. The study protocol was explained and informed consents were signed by all patients.

Pelvic examination, vaginal cytology, serum CA125 levels and routine blood tests were done at two-month intervals for two years and at six-month intervals for the third year, according to our clinical follow-up protocol. The results were the same for the three-year period, although the follow-up procedure is still going on and will be reported in the future. Abdominopelvic CT was planned annually. The results were analysed by the Wilcoxon signed rank test, Mann-Whitney U test, Friedmann and Kruskal Wallis analysis and Bonferroni t procedure.

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Table 1. — *Demographic data.*

	Group I	Group II	Control Group	p
Age	52.5 ± 12.5	55.0 ± 12.8	56.4 ± 8.3	NS
Parity	3.3 ± 2.3	3.3 ± 2.0	2.8 ± 1.4	NS
BMI	26.8 ± 3.7	28.0 ± 4.7	26.3 ± 2.0	NS
Nulliparity	1	–	2	NS
Diabetes Mellitus	2	3	4	NS
Hypertension	–	1	1	NS
Use of Tamoxifen	1	–	2	NS
Endometrial hyperplasia	1 Atypic Complex	1 Complex	1 Complex, 1 Atypic Complex	NS
Late Menopause	2	1	2	NS

Table 2. — *Stage and grade of groups.*

	Group I	Group II	Control Group
Stage 1A G1	–	1	1
Stage 1A G2	4	4	2
Stage 1A G3	2	1	1
Stage 1B G1	–	1	2
Stage 1B G2	–	1	3
Stage 1B G3	–	1	1
Stage 1C G1	–	1	2

Results

There were no findings related to recurrence at pelvic examination, vaginal cytology and abdomino-pelvic CT in either study group or the control group during the three-year follow-up period. CA125 levels are summarized in Table 3. The results were below cut-off (35 IU/ml) in all groups for the 12th, 24th and 36th month. There were no statistically significant differences in all three groups during the three-year follow-up. The side-effects of adjuvant radiotherapy were grade 1 diarrhea in two patients and rectitis in one patient. Rectitis resolved spontaneously and diarrhea was treated by Lomotil tablets (diphenoxylat HCl 2.5 mg + atrophine sulphate 0.0025 mg). Clinical findings and cytologic, radiologic and biochemical results indicated no recurrence in study and control groups.

Table 3. — *CA125 levels.*

	Initial	12 months	24 months	36 months	p
Group I	24.00 ± 24.51	18.00 ± 6.21	19.50 ± 3.02	17.00 ± 6.57	0.896
Group II	29.50 ± 22.54	14.00 ± 6.36	12.50 ± 10.31	14.00 ± 6.10	0.035*
Control Group	12.00 ± 19.04	10.50 ± 5.59	11.00 ± 5.63	9.50 ± 5.20	0.420
p	0.107	0.063	0.0016	0.031	

*The difference is statistically significant but should not be considered important because the results are below the cut-off value of 35 IU/ml. and in further statistical analysis by Friedmann or Kruskal Wallis there was no statistical significance.

Discussion

There was no statistically significant difference between three groups and no recurrence in any group in our study. The results demonstrated that positive peritoneal cytology had no impact on survival in surgical-pathologic Stage I endometrial cancer.

The study of peritoneal washing cytology originated in 1956, when it was reported on by Keettel and Elkins [8].The significance and correlation of positive results with histology remains controversial, and the incidence of abnormal peritoneal washing (PW) varies widely in the literature.

Creasman and Rutledge reported that the incidence of positive PW in patients with endometrial carcinoma was 11.5% in 1971 [9]. The prognosis was reported to be poorer for these patients in that study. The Gynecologic Oncology Group evaluated 1,180 women with endometrial cancer who underwent surgical staging procedures in 1990 [10]. Twelve percent of these patients had positive peritoneal cytology; 29% of these patients who had positive PW had recurrence of their tumor compared with 10.5% of those with negative cytology, and positive cytology was accepted as a poor prognostic factor in that study. However the patients were not classified by means of staging so the data reported in the study had little importance for survival projection in surgical-pathologic Stage I patients.

Several subsequent reports supported or did not support the prognostic significance of positive peritoneal cytology [11-17]. The incidence of positive PW was found to be higher in advanced stage with higher histologic grade, deeper myometrial invasion and extrauterine spread [5, 18]. The prognostic significance of cytology was still controversial in these studies. The five-year survival rate for patients with positive or negative PW was 80 or 92% in clinical Stage I endometrial cancer, respectively. (5)

Most studies published since 1990 have reported the poor prognostic value of positive peritoneal cytology in Stage I endometrial cancer [17, 18]. In contrast most studies published up to 1990 reported that PW was not significantly associated with clinical outcome.

Obermair *et al.* reported that the probability of being disease-free at 36 months was 96% for patients with negative cytology and 67% for patients with positive cytology in Stage I endometrial cancer [19]. They remarked that positive PW should be considered an adverse prognostic factor for these patients. Peritoneal cytology was independent of the depth of myometrial invasion and the grade of tumor differentiation in the study. They reported three recurrences in the group of 13 patients with positive peritoneal cytology. Two of three cases had vaginal vault recurrences who had not received brachytherapy postoperatively.

The mechanism of expressing peritoneal malignant cells in washing solutions is also controversial. There is an increasing number of case reports assuming abdominal dissemination during hysteroscopy [20, 21, 23, 24]. Egarter *et al.* have demonstrated this phenomenon using intraoperative hysteroscopy [22]. Obermair *et al.* compared the incidence of positive peritoneal washings in patients who underwent fluid hysteroscopy plus dilatation and curettage with that in patients who underwent only dilatation and curettage before surgical staging. The results strongly suggested that dissemination occurred during hysteroscopy [23]. Yasuo *et al.* reported that endometrial cancer cells found in the peritoneal cavity usually appear within a short time and seem to have low malignant potential. Only malignant cells from special

cases such as adnexal metastasis may be capable of independent spread and are possibly associated with intraperitoneal recurrences [24].

Sonoda *et al.* reported a significantly higher incidence of positive peritoneal cytology in patients treated by LAVH (laparoscopy assisted vaginal hysterectomy) for low-risk endometrial cancer. They thought this might be due to retrograde dissemination of cancer cells during uterine manipulation [25]. Nobuhiro *et al.* have pointed out that positive peritoneal cytology does not imply a worse prognosis but does indicate greater tumor aggressiveness and positive PW does not require upstaging in the absence of other adverse prognostic indicators [26].

There are controversial opinions and suggestions on the prognostic significance of positive peritoneal cytology. However there is little controversy on the mechanism of malignant tumor cell dissemination, trans-tubal spread of cells from the endometrial cavity during diagnostic approaches, which is accepted as the main way of dissemination.

Kasamatsu *et al.* concluded that the presence of positive peritoneal cytology was not an indicative factor on survival rates in patients with positive PW in a retrospective analysis of 280 endometrial carcinoma cases [27].

Conclusion

Our study is the first randomized case-controlled clinical trial in the literature. According to the preliminary results of this on-going study, we suggest that positive peritoneal cytology has no prognostic significance in clinical Stage I endometrial cancer cases. We do not recommend adjuvant therapy for patients with positive PW so that the morbidity of radiotherapy can be avoided. More studies with more cases series are needed to clarify the prognostic value of positive PW on survival rates and clinical management protocols for clinical Stage I endometrial cancer patients in the future.

If the tumor is confined to the uterus with only PW positivity it should be classified in another way in the FIGO staging system.

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