Peritoneal cytology in endometrial cancer
Minireview

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Received July 12, 2004

The results as well as prognostic interpretation of peritoneal washing cytology in endometrial cancer cases is still controversial. The incidence rate of positive cytology varies widely and the clinical significance of the positive results, especially in patients with early stage of endometrial cancer remains also controversial. Prognostic significance of malignant peritoneal cytology in endometrial cancer patients in comparison with those with ovarian cancer has been less well defined. At present, positive peritoneal cytology is not a negative prognostic factor itself, but it enhance other negative prognostic indicators. Literature regarding the significance of peritoneal cytology in endometrial cancer was reviewed in order to draw conclusions for possible therapeutic implications in patients with positive cytologic findings.

Key words: endometrial carcinoma, peritoneal cytology, prognosis, risk factors

The traditional prognostic factors of endometrial carcinoma include clinical stage, histological subtype, grade of differentiation, depth of myometrial invasion and lymph node spread [25, 29].

In 1985, the International Federation of Gynecology and Obstetrics (FIGO) incorporated the results of peritoneal washings into the staging classification for ovarian carcinoma followed by the incorporation of the same results into the FIGO staging system for endometrial carcinoma in 1989 [5, 7].

Characteristics of peritoneal cytology in ovarian cancer cases was first described in 1956 by KEETEL and ELKINS [21].

Sources of malignant cells in peritoneal cytology

The sources of malignant peritoneal cytology in patients with early endometrial adenocarcinoma have not yet been completely defined. It has been postulated that the presence of malignant cells within the peritoneal cavity of patients with endometrial cancer in the absence of extrauterine disease may be the result of transtubal transport, multifocal disease arising from peritoneal mesothelium, or direct extension of tumor through the myometrium or via serosal lymphatics into the peritoneal cavity in patients with deep myometrial invasion. Each of these mentioned mechanisms of spread may have far different prognostic and therapeutic implications. With increasing depth of myometrial invasion in an increasing percentage of patients with endometrial adenocarcinoma, cancer cells in the pouch of Douglas are found [15].

The presence of malignant cells in the peritoneal washings from some patients having no myometrial invasion and high incidence of lymph node metastases in patients with positive peritoneal cytology suggest that malignant cells gain access to the peritoneal cavity in a variety of ways. The high incidence of lymph node metastasis in such patients suggests that lymphatic dissemination of malignant cells play a significant role in the development of positive peritoneal cytology in the patients with endometrial cancer [28].

Incidence of positive peritoneal cytology and its significance

The incidence of positive peritoneal cytology in all stages of endometrial cancer is very different, from 4.9 % to 68.0 % [4, 6, 11, 13, 43, 44]. Among patients with FIGO stage I endometrial cancer the incidence of positive peritoneal cytology is in between 2.9 to 29.8 % [31].

There have been a number of studies concerning prognostic significance of peritoneal washing cytology and their results are controversial.

CREASMAN et al. identified in a study of 161 patients with clinical stage I 15.5 % malignant cells in cytologic peritoneal

washings and concluded that peritoneal cytologic examination seems to be an important factor in the prognosis of endometrial cancer [3]. In the study from Roswell Park Memorial Institute there were no significant survival differences between eighty-three patients with negative and ten patients with positive peritoneal cytology. The 5-year survival rate was 93.9 % versus 87.5 %, respectively. No patient received specific treatment for positive cytology. The authors suggest that malignant peritoneal cytology does not seem to be a prognostic indicator in stage I endometrial cancer [48].

There was no difference in disease-free survival between the negative and positive cytology in stage I patients who had one-third or less myometrial invasion in the group of 243 patients [12].

In a retrospective study of 567 patients treated for surgical stage I endometrial cancer twenty-eight women (4.9 %) had peritoneal cytology positive for malignant cells. Forty-nine women (8.6 %) developed recurrent tumor, 7 % of the negative-cytology group and 32 % of the positive-cytology group. Patients with negative peritoneal cytology had a significantly better 5-year survival rate, 96 % versus 84 % ($p=0.001$). Based on these results TURNER et al suggest that positive peritoneal cytology is a poor prognostic factor for patients with surgical stage I endometrial cancer [43]. In SUTTON's study of 615 patients with endometrial carcinoma clinical stage, histologic grade, age of patients, and the results of peritoneal cytology were most reliable prognostic factors. Survival of clinical stage I patients with negative peritoneal cytology was superior to those with malignant cytology [40].

In the study at the Dalhousie University in Canada, 16 of 323 (5.0 %) patients in clinical stage I, had positive peritoneal cytology. There was no significant difference in 5-year survival between groups with positive and negative cytology (80 % versus 86.3 %). The majority (70.8 %) of patients with endometrial cancer and positive peritoneal cytology have already extrauterine spread of the disease at the time of surgery. Although values of overall 5-year survival are lower for patients with positive cytology when other negative prognostic factors are present, there is no difference in survival for patients with no demonstrable extrauterine disease despite positive cytology. The authors concluded that positive peritoneal cytology is not an independent prognostic indicator for patients with endometrial cancer [8].

Positive peritoneal cytology rates compared with histological differentiations were 28 % for grade 1, 36 % for grade 2 and 46 % for grade 3. Positive cytological results were found in 28 % of cases of less than one third of intramuscular infiltration and 37 % in cases of one third and more myometrial invasion. An analysis of the data indicated that the influence of positive peritoneal cytology on the recurrence superceded that of other known risk factors, such as grade, myometrial invasion, extrauterine spread of the disease, and lymph node metastasis [16]. GU et al concluded in their series of 298 patients from the Memorial Sloan-Kettering Cancer Institute that abnormal peritoneal washings did not correlate with histologic subtypes (endometrioid adenocarcinoma, papillary serous carcinoma, clear cell carcinoma, adenosquamous carcinoma), grade, depth of myometrial invasion, vascular invasion and abnormal Pap smears. A significantly higher incidence of abnormal peritoneal washings is associated with stage III/IV disease [9]. Malignant cells in the peritoneal washing were found in the study from University in Zagreb in 6.5 % patients with stage I, in 9.1 % patients with stage II and in those in whom disease had spread outside the uterus (stage III and IV) in 68 %. Positive peritoneal cytology was found significantly more frequently in patients with tumor localized in uterine horns and in those patients with low values of steroid receptors. Regardless of the stage of the disease, the frequency of recurrence and 5-year survival did not correlate with the finding of malignant cells in the peritoneal lavage. The authors concluded that the finding of positive peritoneal cytology as an isolated prognostic factor does not play an important role in the prognosis of patients with endometrial cancer, particularly those in whom the tumor is localized only in the uterus [44].

From 369 patients with clinical stage I endometrioid adenocarcinoma from Queensland Centre for Gynaecological Cancer positive cytology was found in 13 (3.5 %) cases. Patients with negative cytology had disease-free survival of 96 % at 36 months compared with 67 % for patients with positive cytology ($p<0.001$). The presence of positive peritoneal cytology in patients with clinical stage I endometrioid adenocarcinoma of the endometrium was considered in their series as an adverse prognostic factor [33]. KASAMATSU et al concluded that the presence of positive peritoneal cytology is not an independent prognostic factor in patients with endometrial carcinoma confined to the uterus, and adjuvant therapy does not appear to be beneficial in these patients. In their series of 280 patients with surgically staged endometrial carcinoma histologically confined to the uterus, 48 patients, (17 %), had positive peritoneal cytology. The 5-year survival rate among patients with positive or negative peritoneal cytology was 91 and 95 %, respectively, showing no significant difference [18]. SANTALA et al suggest that peritoneal cytology and preoperative serum CA 125 levels are important independent prognostic factors in stage II/IV endometrial cancer and they could be used in the management of this disease [36]. In the study from Mayo Clinic cervical stromal invasion, adnexal spread of the disease, myometrial invasion >50 %, positive lymph nodes, positive peritoneal cytology, lymphovascular invasion, grade 3 histology, nonendometrioid subtype, p53>33 %, strong HER-2/neu membranous staining, aneuploidy, S-phase fraction ≥9 %, proliferative index ≥14 %, and DNA index ≥1.5 significantly ($p<0.05$) predicted reliably even distant failures [30].

Stage IIIA endometrial cancer includes patients with serosal or adnexal invasion and patients with positive peritoneal cytology only. TEBEU et al categorized stage IIIA into 'cytological' stage IIIA (only peritoneal cytology posi-

tive) and 'histological' stage IIIA (serosal or adnexal infiltration). They found in the series of 170 endometrial cancer that cytological stage IIIA has similar prognosis as stage I (the 5-year survival 94 vs 88 %, respectively, p=0.5) and better prognosis than histological stage IIIA (5-year survival 94 vs 51 %, respectively, p<0.01). Additional research, definitively separating stage and cytology is warranted [42].

TAKESHIMA et al from the Cancer Institute Hospital in Tokyo concluded in their series of 534 patients that positive peritoneal cytology is not a negative prognostic indicator itself, but potentiates other negative prognostic indicators in endometrial cancer [41].

Dissemination of malignant cells during invasive procedures

The results of several studies on dissemination of malignant cells during invasive procedures are controversial.

LEVEQUE at al postulated that the endoscopic procedures may have facilitated the transtubal malignant cell dissemination [26]. SAGAWA et al suggested that leakage of endometrial cancer cells into the peritoneal cavity can be induced by hysteroscopy and by endometrial biopsy [35].

According to GU et al the diagnostic procedures, including hysteroscopy, does not appear to be associated with a higher incidence rate of abnormal peritoneal washings [10]. In a multicentric retrospective analysis involving seven Austrian hospitals between 1996 and 1997, on 113 consecutive patients with endometrial carcinoma limited to the the inner half or less of the myometrium, the only factor significantly associated with positive peritoneal cytology was the hysteroscopic examination (p=0.04). The authors concluded that fluid hysteroscopy facilitates intraabdominal dissemination of endometrial cancer cells [32].

KUZEL et al evaluated peritoneal washing cytology of the pouch of Douglas prior to hysteroscopy, after fluid hysteroscopy with target biopsy and after curettage in 42 patients. Slides from the patients with carcinoma of the endometrium in peritoneal washing cytology did not deteriorate after hysteroscopy with target biopsy of the endometrium, but tumor cells appeared in the pouch of Douglas after curettage in 88.9 % women [24]. Under SELVAGGI et al fluid hysteroscopy does not increase the risk of microscopic intraperitoneal spread in endometrial cancer patients as compared to dilatation and curretage [37].

Whether iatrogenically disseminated malignant cells have the same prognostic implications as positive peritoneal cytology in patients who did not undergo hysteroscopy is unknown. A good answer to this question would require a randomized trial, which in this setting would be unethical. The same problems could be associated also with other uterine manipulations, such as laparoscopically assisted vaginal hysterectomy or saline infusion sonography, that have also been associated with dispersion of tumor cells into the abdominal cavity [1, 38].

Potential for implantation of positive malignant cells in the peritoneal cavity

The biological potential of malignant cells in the peritoneal cavity for metastatic implantation into the peritoneum is the subject for discussions.

In the study of KATO et al was demonstrated that malignant cells in the peritoneal cavity appear to have a very low potential for implantation into the peritoneum. The authors inserted a tube in the abdominal cavity before the closure of the abdomen in twelve patients with endometrioid adenocarcinoma with positive intraoperative peritoneal cytology. The peritoneal cavity was washed with 500 ml of physiological saline through the tube 14 days after the surgery. The cytology of these recovered washings was negative in all cases [20]. In the study at the Cancer Institute Hospital in Tokyo the peritoneal cavity was irigated with physiologic saline, and washings were obtained through the tube 7 and 14 days after the surgery for endometrial cancer in fifty patients. Persistence of positive peritoneal cytology was observed only in five (10 %) patients with clinical stage I–II. It seems that endometrial cancer cells found in the peritoneal cavity usually disappear within a short time and seem to have a low malignant potential. It also seems that only malignant cells from special cases, such as adnexal metastasis, may be capable of independent growth, and are possibly associated with intraperitoneal recurrence [14]. The presence of malignant cells in the peritoneal washings from some patients with no myometrial invasion and high incidence of lymph node metastases in other patients with positive peritoneal cytology suggest that malignant cells gain access to the peritoneal cavity in a variety of ways. It is not clear whether each of these modes of access could result in penetration of viable tumor cells having even metastatic capacity [28].

Cytologic interpretation of peritoneal washing

To evaluate peritoneal cytology as a reliable test for the detection of malignant cells in the peritoneal cavity is limited by great variation of the study populations, variability in approaches of preoperative radiation in older studies, the lack of consistent methodology for specimen and even possible subjectivity of cytologic interpretation [31].

Atypical reactive mesothelial cells can simulate malignant cells. Experienced cytologic evaluation is important [45]. A standardized methodology for retrieval and processing of peritoneal cytologic specimens should be developped to allow meaningful comparisons of the studies. Noncancerous cells simulating adenocarcinoma cells may interfere in the analysis of peritoneal cytology. Immunocytochemistry may improve the diagnosis with comparison of conventional Papanicolaou staining [2, 27].

The finding of endometrial adenocarcinoma cells exhibiting high cellularity, scalloped edge of cell clusters and isolated cells in smears from peritoneal fluid is associated with

the presence of intraabdominal macroscopic metastatic lesions and could be regarded as a risk factor for intraabdominal recurrence of carcinoma [46]. The same authors divided 54 stage IIIA endometrial cancer patients with positive peritoneal cytology into two groups based on the cytological pattern of their peritoneal smears. In group A, malignant cell clusters had well-defined edges, and in group B tumor cell clusters with scalloped edges. The 5-year disease-free survival rate was 97.5 % in group A versus 50 % in group B. Multivariate analysis confirmed that cytologic pattern had an independent influence on survival. YANOH et al concluded that positive peritoneal cytology composed of malignant cell clusters with well-defined edges has no impact on survival and only endometrial cancer patients who have tumor cell clusters with scallope edges in peritoneal smears are worth considering for upstaging [47].

Therapeutic conclusions of positive peritoneal cytological findings

The significance and consequence of positive peritoneal cytology for the management of endometrial cancer patients is still not well-defined [39].

In the study from 1981 CREASMAN et al concluded that peritoneal cytologic examination appears to be an important factor in the prognosis of endometrial cancer and, when the washings are positive for malignant cells, intraperitoneal chromic phosphate therapy appears to be efficacious [3]. Positive cytology in endometrial cancer was not an independent prognostic factor and whole abdominal irradiation did not influence survival in the non-randomized study from Rochester Cancer Center in the series of 132 patients with clinical stage I [23]. PIVER et al treated forty-five patients with endometrial carcinoma confined to the uterus only and positive endometrial cytology with 1 year of progesterone therapy. Only two patients had persistent malignant cytology during second-look laparoscopy [34].

At present neither intraperitoneal chromic phosphate nor progesterone are standard treatment of the endometrial cancer patients with positive peritoneal cytology when the disease is limited to the uterus. Conclusions regarding effective adjuvant therapy in positive cytology cases could not be drawn due to the smaller number of patients with abnormal results and the variety of treatment applied [19, 22].

Patients with extrauterine spread of the disease and positive cytology have a very poor prognosis with a probability for distant spread and should receive systemic therapy [17]. These patients may be candidates for innovative clinical trials.

Conclusions

The following conclusions regarding positive peritoneal cytology can be drawn:

In all patients with endometrial carcinoma should be performed precise surgical-pathological staging of the disease.

Positive peritoneal cytology is associated with other known poor prognostic factors (grade 3 histology, deep myoinvasion, and other evidence of extrauterine disease spread).

Positive peritoneal cytology without other evidence of disease spread outside of the uterus and/or in the absence of other poor prognostic factors probably has no significant effect on recurrence and survival.

Positive peritoneal cytology when associated with other poor prognostic factors and/or extrauterine spread of the disease increases the likelihood for distant as well as intraabdominal disease recurrence and has a significant adverse effect on survival.

Use of several different therapeutic modalities has not resulted in any proven benefit to patients with endometrial cancer limited to the uterus and positive peritoneal cytology. At this time there is no benefit for treating positive cytology in the absence of other evidence of extrauterine disease.

Patients with extrauterine spread of the disease and positive cytology should receive systemic therapy because their prognosis is very poor.

The exact role of peritoneal cytology in the management of endometrial cancer patients needs futher investigations in randomized studies.

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