

## The Contribution of Rapid Intraoperative Cytology in the Evaluation of Endometrial Cancer Spread

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### Abstract

**Introduction:** Peritoneal washing cytology and imprint cytology of pelvic lymph nodes samples were used to evaluate the rapid cytologic detection of peritoneal and retroperitoneal spread of endometrial cancer. **Materials and Methods:** We undertook a study on 194 endometrial cancer patients who underwent primary treatment in the Gynecologic Clinic, Democritus University of Thrace. All patients were subjected to peritoneal washing (PW) cytology and imprint cytology performed on lymph node sampling. The cytologic specimens were stained by May-Grünwald Giemsa (MGG) and Haematoxylin eosin (HE) techniques. Cell-blocks prepared from peritoneal washings (PWs) and the lymph node samples were sent for histologic examination. The cytologic findings were correlated to histologic results. **Results:** Rapid intraoperative cytology provides a useful diagnostic technique for the assessment of endometrial cancer spread. HE and MGG stain presented different values of sensitivity and specificity in the detection of peritoneal and retroperitoneal spread of endometrial cancer. **Conclusion:** Cytologic assessment of intraperitoneal and retroperitoneal spread of endometrial cancer is a rapid, intraoperative procedure, which provides the surgeon with useful information regarding the stage of the disease and the subsequent therapeutic approach.

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**Key words:** Endometrial cancer, Imprint cytology, Lymph node dissection, Peritoneal washing cytology

### Introduction

Tumour staging is of great importance to the treatment of patients with oncological diseases. The therapeutic approach of the patient largely depends on the extension of the disease. Misclassification of stage may thus result in suboptimal treatment strategies. The International Federation of Gynecology and Obstetrics (FIGO) adopted its first staging system for endometrial cancer in 1971. This clinical staging system used information obtained from routine pretreatment laboratory and diagnostic studies, careful pelvic examination, uterine sounding and fractional histologic sampling from the endocervical canal and endometrial cavity. When a number of studies showed on the basis of surgical findings that clinical staging was subjected to a high rate of error, the Cancer Committee for FIGO established a surgical staging system in 1988. This system recognised a number of prognostic features that were shown to have

significant impact on the risk of recurrence and survival. While histologic grade, depth of myometrial invasion and extension to the cervix are important prognostic features associated with the primary uterine tumour, endometrial cancers that have spread to retroperitoneal lymph nodes or to sites within the peritoneal cavity are at especially high-risk for recurrence. Survival rates for patients with extrauterine disease are less than 50%.<sup>1,3</sup>

According to the surgical staging system, patients with positive peritoneal cytology and pelvic and/or para-aortic lymph node involvement are assigned to stages III A and III C, respectively. Several reports revealed conflicting results on the prognostic significance of peritoneal cytology in endometrial cancer. However, the incidence of positive peritoneal cytology in endometrial cancer varies from 2% to 30%.<sup>4-14</sup>

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The incidence of pelvic lymph node metastases in FIGO stage I endometrial cancer has been reported to be 4% to 20%, while some authors have reported a 7% to 10% recurrence rate in endometrial cancer with no myometrial invasion due, possibly, to lymph node involvement.<sup>15-21</sup>

Since the type, the timing and the duration of therapy in endometrial cancer vary considerably depending on the magnitude of the anticipated risk and the biases of the treating physician, the early and accurate assessment of cancer's spread could provide the patient with optimal therapeutic management. The intraoperative cytologic assessment of intraperitoneal and retroperitoneal spread of the disease offers a rapid diagnostic procedure, which could probably act as an alternative to frozen section, as well as be incorporated in the staging modalities in order to minimise the delay in therapeutic management.

In the present study, we used peritoneal washing cytology and imprint cytology of pelvic lymph nodes, in order to evaluate the rapid cytologic detection of peritoneal and retroperitoneal spread of endometrial cancer.

## Materials and Methods

One hundred and ninety four patients with uterine corpus cancers (Fig. 1) underwent primary surgical therapy at the Gynecologic Clinic, Democritus University of Thrace. All inoperable cases with advanced endometrial cancer were not included in the above-mentioned number. The patients underwent a standard preoperative evaluation to assess the clinical extent of disease and operative risk. This consisted of history and physical examination, Papanicolaou smear, study of endometrial biopsy report and laboratory studies. Additional laboratory and diagnostic studies, as well as medical consultation were done as indicated by the clinical situation.

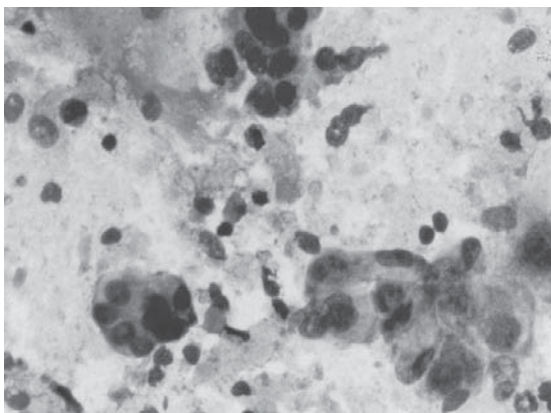


Fig. 1. Imprint cytology of endometrial carcinoma. Malignant glandular cells in clusters with loss of cohesion, abnormal pleomorphic nuclei and nucleoli, (HE, X40).

Simple hysterectomy with bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node dissection was performed on patients with stage I endometrial cancer. Radical hysterectomy with bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node dissection was performed on patients with stage II endometrial cancer. Palliative simple hysterectomy, lymph node biopsy and adjuvant radiotherapy and/or chemotherapy were performed on patients with stage III and IV endometrial cancer.

All patients underwent peritoneal washing cytology (Fig. 2). Imprint cytology was also performed on lymph node biopsy specimens (Fig. 3) prior to the lymph node dissection.

The peritoneal cytology specimens were obtained at the time of abdominal entry by the use of 200 cc washings of sterile normal saline. The 200 cc of fluid was instilled and

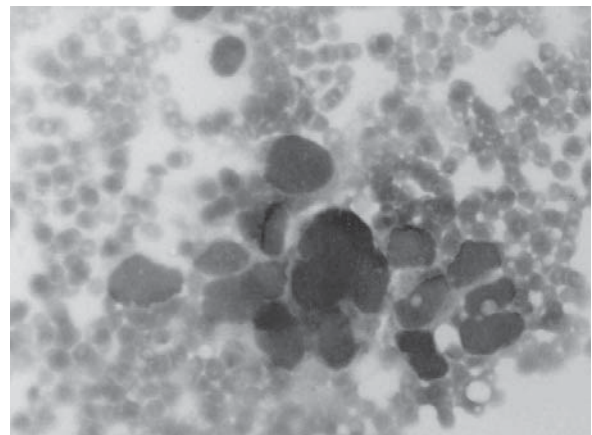


Fig. 2. Peritoneal washing cytology of endometrial carcinoma. Pleomorphic malignant cells with anisonucleosis, overlapping, loss of polarity and polychromasia, (HE, X40).

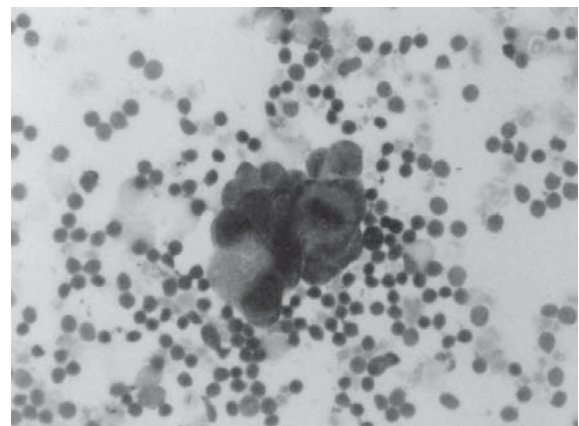


Fig. 3. Lymph node metastasis of endometrial carcinoma, imprint cytology. A 3-dimensional cluster of malignant cells, one of them with mitotic activity, against a background of lymphoid cells, (MGG, X20).

allowed to wash the uterus, tubes, ovaries and cul-de-sac. The fluid was then aspirated, mixed with 1000 units of heparin, and sent to the cytology laboratory next to the theatre room. The peritoneal fluids were centrifuged at 1500 rpm for 5 minutes. Four slides were prepared from each washing. They were air-dried and subsequently stained by the May-Grünwald Giemsa (MGG) and Haematoxylin eosin (HE) technique. If the material was bloody, it was lysed with a haemolytic agent and then recentrifuged. A control slide of the bloody specimen was made prior to haemolysis to provide an accurate impression of cellularity. The evaluation of the cytologic specimens was performed according to the following criteria: Cells considered to be malignant should be present both singly and in groups and should be malignant by the usual cytologic criteria. They should also be different from and not confused with reactive mesothelial cells.

In addition, a cell-block was prepared from all peritoneal washings. The cell pellet obtained from the centrifuged PWs was transferred into 10% neutral buffered formalin and processed routinely in paraffin. The cellblocks were sectioned at 3 µm in thickness and the histologic sections were stained with HE.

The biopsy specimen consisted of an average of 4 lymph nodes per patient. All enlarged, palpable or hard nodes were excised without disruption and sent immediately to the cytology laboratory. Sample nodes were bisected and the cut surface of each half-node was imprinted on 2 clean and dry slides. The slides were air-dried, and stained by the MGG and HE techniques. Sample nodes were also subjected to histologic examination separately from the contents of the complete lymph node dissection.

All cytologic results from PWs were correlated with the histologic results of the cellblocks. Cytologic results from lymph node imprints were compared to the histologic ones from the sample biopsies.

## Results

Peritoneal washing cytology results were positive in 33 cases (with either stain methods) out of 194 (17%), while the histologic examination of the centrifuged cell blocks revealed neoplastic cells in 36 cases (18.5%). Imprint cytology from the lymph node biopsies was positive in 45 cases (with either stain methods) out of 194 (23%). Histologic examination of the lymph node samples was positive in 51 cases out of 194 (26.2%).

Table 1 describes in detail the results of PW cytology for each of the 2 stain methods compared to the histologic results of the centrifuged cell-blocks. It is easily perceived that HE stain presents greater values for sensitivity and specificity in the evaluation of PWs (97.2% and 99.3%,

respectively) compared to the ones obtained from the MGG stain (91.6% and 98.1%, respectively).

Table 2 correlates the cytologic findings gained from the lymph node imprints for each stain method separately, with the histologic findings of the sample biopsies. We notice that sensitivity and specificity of MGG stain in the detection of neoplastic cells (94.1% and 97.9%, respectively) exceed the ones of HE stain (88.2% and 97.9%, respectively).

## Discussion

The inaccuracies of clinical staging, coupled with a greater emphasis on treatment tailored to the patient's risk assessment, led FIGO to adopt the surgical staging system for endometrial cancer in 1988,<sup>3</sup> which incorporates certain prognostic factors such as peritoneal cytology and lymph node spread. However, the staging criteria do not specify a required set of minimum procedures needed to adequately determine stage. Consequently, the precise details of what constitutes a staging operation are left to the discretion of the surgeon.<sup>2</sup> Surgical staging is most applicable to patients with tumours clinically confined to the uterus. Detection of small-volume sub-clinical extrauterine disease in this setting is helpful in establishing the need for further treatment as well as in selecting the appropriate adjunctive approach.<sup>1</sup> Furthermore, patients with additional surgical risk associated with obesity, diabetes mellitus, and other concomitant medical illnesses, might benefit from a more limited staging operation minimising the immediate or delayed complications attributable to major surgery.

PW cytology in endometrial cancer raised controversial opinions. The prognostic significance of peritoneal cytology in low-stage endometrial cancer varies considerably and the incidence of positive peritoneal cytology in these patients ranges from 2% to 30%.<sup>4,10,12-14</sup> Kashimura et al<sup>4</sup> report that 9% of patients with clinical stage I, 25% of patients with clinical stage II, 11% of patients with grade 1 tumours and 5% of patients with no myometrial invasion were upstaged by consideration of PW cytology.

Less controversy exists over the prognostic value of lymph node involvement in low-stage endometrial cancer. Most authors agree that the impact of lymph node metastases on the survival of these patients remains crucial.<sup>15-21</sup> Takeshima et al<sup>15</sup> report that pelvic lymph node metastases in endometrial cancer with no myometrial invasion is not rare, even with grade 1 tumours. They suggest that lymphadenectomies might be necessary in all patients with endometrial cancer, except when clinical or operative factors increase the procedure's risk for morbidity. According to our study results imprint cytology from lymph node samples selects accurately enough (according to the method's sensitivity and specificity obtained from both stain techniques) a

considerable number of patients that should undergo further lymph node dissection or should be subjected to adjuvant therapy if major surgery is not indicated. In conclusion, cytologic assessment of intraperitoneal and retroperitoneal spread of endometrial cancer, is a rapid intraoperative procedure, which provides the surgeon with useful information regarding the stage of the disease and the subsequent therapeutic approach.

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