

RESEARCH ARTICLE

Prognostic Value of Peritoneal Washing Cytology in Gynecologic Malignancies: a Controversial Issue

Fariba Binesh¹, Ali Akhavan^{2*}, Nasim Behniafard³, Somayeh Zabihi¹, Elhamsadat Hosseinizadeh³

Abstract

Purpose: To evaluate the prognostic impact of peritoneal washing cytology in patients with endometrial and ovarian cancers. **Materials and Methods:** We retrospectively identified 86 individuals with ovarian carcinomas, ovarian borderline tumors and endometrial adenocarcinomas. The patients had been treated at Shahid Sadoughi Hospital and Ramazanzadeh Radiotherapy Center, Yazd, Iran between 2004 and 2012. Survival differences were determined by Kaplan-Meier analysis. Multivariate analysis was performed using the Cox regression method. A $p < 0.05$ value was considered statistically significant. **Results:** There were 36 patients with ovarian carcinomas, 4 with borderline ovarian tumors and 46 with endometrial carcinomas. The mean age of the patients was 53.8 ± 15.2 years. In patients with ovarian carcinoma the overall survival in the negative cytology group was better than the patients with positive cytology although this difference failed to reach statistical significance ($p = 0.30$). At 0 to 50 months the overall survival was better in patients with endometrial adenocarcinoma and negative cytology than the patients with positive cytology but then it decreased ($p = 0.85$). At 15 to 60 months patients with FIGO 2009 stage IA-II endometrial adenocarcinoma and negative peritoneal cytology had a superior survival rate compared to 1988 IIIA and positive cytology only, although this difference failed to reach statistical significance ($p = 0.94$). Multivariate analysis using Cox proportional hazards model showed that stage and peritoneal cytology were predictors of death. **Conclusions:** Our results show good correlation of peritoneal cytology with prognosis in patients with ovarian carcinoma. In endometrial carcinoma it had prognostic importance. Additional research is warranted.

Keywords: Peritoneal washing cytology - endometrial cancer - ovarian cancer - survival - gynecology

Asian Pac J Cancer Prev, 15 (21), 9405-9410

Introduction

In South-Eastern Asia endometrial adenocarcinoma is the third most common gynecological malignancy, following cervical and ovarian carcinomas. It is said that ovarian cancer is the deadliest cancer for the female (Wei-Na et al., 2014). However, in Iran gynecologic cancer account for 7.8% of total female cancers, which is lower in comparison with those of some other countries (Maliheh et al., 2014).

The optimal staging of tumors would reflect their patterns of spread; allowing perfect anticipation, and therapeutic decision. However staging systems are not static, and change with the attainment of new medical science. Surgical staging of gynecologic neoplasms include the collection of peritoneal washings in the abdomen and pelvis. The objective of taking peritoneal washings is to identify occult disease, and peritoneal cytology is supposed to add information on the spread of microscopic peritoneal disease. However, the constraints of peritoneal washing cytology examination are the

possibility of false positivity in benign diseases and false negativity in the early stage of the disease. In the assessment of patients with ovarian carcinoma, peritoneal cytology is an accepted method. Less is known about the prognostic impact of peritoneal cytology in endometrial carcinoma. However, published researches have shown inconsistent results regarding the importance of positive cytology and survival in patients with endometrial carcinoma. As some studies have indicated that cytology is an important prognostic factor, while others did not (Obermair et al., 2001).

(Morrow et al., 1991; Kadar et al., 1992; Preyer et al., 2002; Kasamatsu et al., 2003). The FIGO surgical staging for endometrial cancer was revised in 2009. The FIGO 2009 staging system has amended prediction of prognosis, and is less complicated, compared to earlier issues. Although peritoneal washing in ovarian cancer staging systems stay part of the FIGO staging system, the role of peritoneal washings in staging of endometrial carcinoma has been argumentative and is no longer part of the current FIGO staging system (Lewin et al., 2009). In this study,

¹Department Of Pathology, Shahid Sadoughi University Of Medical Sciences, ²General Practitioner, Yazd, Iran, ³Department Of Radiotherapy, Isfahan University Of Medical Sciences, Isfahan *For correspondence: ali52akhavan@yahoo.com

we evaluated the impact of positive peritoneal cytology on the survival of patients with endometrial and ovarian malignancies. We also analyze the survival of patients with FIGO 2009 stage IA–II endometrial carcinoma and negative peritoneal cytology in comparison to 1988 IIIA with positive cytology only.

Materials and Methods

This research was approved by the university ethics committee. A retrospective chart review was performed on all patients who were diagnosed with endometrial adenocarcinoma, ovarian carcinoma and ovarian borderline tumors treated at Shahid Sadoughi Hospital and Ramazanzadeh Radiotherapy Center, Yazd, Iran. Follow-up information was available for 86 patients with endometrial and ovarian malignancies. These patients had peritoneal washings performed during initial surgery at our center during the period from 2004 to 2012. Staging was defined according to the FIGO surgical staging system 1988 for ovarian tumors and the FIGO surgical staging systems 1988 and 2009 for endometrial carcinoma. Other variables of interest were: age at diagnosis, period of diagnosis, and in the case of endometrial carcinoma, grade (1-3) and degree of myometrial invasion (<50%, 50%). Inoperable patients with advanced stage disease or metastasis and patients with inadequate sample for evaluation and clinically detected ascites were excluded from the study. The final study population included 86 patients. There were 46 patients with endometrial carcinomas, 36 with ovarian carcinomas and 4 with borderline ovarian tumors. Peritoneal washing was performed by rinsing the cavity with 100 cm³ of physiological saline. The liquid was centrifuged and assessed for the presence of malignant cells. The specimen was fixed in 95% ethyl alcohol and stained by the Papanicolaou technique. All cases were reviewed without prior knowledge of the patient's pathological condition. Only cells with unequivocally malignant criteria were considered positive. The median follow-up of the patients was 48 months (range, 1-94.53 months). Postoperative adjuvant therapy was recommended for patients with positive peritoneal cytology. To clarify the confusion regarding the prognostic significance of positive peritoneal cytology in endometrial cancer we divided these patients into three groups as it had been done previously by Takeshima et al. (2001): "low risk, moderate risk, and high risk. The low-risk group consisted of patients whose disease was confined to the uterus, was grade 1, and invaded half or less of the thickness of the myometrium. The moderate-risk group was defined as patients whose disease was confined to the uterus, but was either grade 2 or 3 or involved more than half of the thickness of the myometrium. The high-risk group was defined as patients who had extrauterine spread, such as nodal disease, adnexal metastases, and small sites of peritoneal seeding that could be resected at surgery." Follow-up data were obtained from the Tumor Registry at Shahid Sadoughi University. Overall survival time was defined as the period between primary surgery and death. Patients dying of intercurrent disease were censored.

Survival differences were determined by Kaplan-Meier analysis and were evaluated by two-tailed log rank test, and multivariate analysis was performed using the Cox regression method. A $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS (version 16).

Results

This study includes 86 patients operated for a gynaecologic pathology. There were 36 patients with ovarian cancer, 4 with ovarian borderline tumor and 46 patients with endometrial carcinoma. The mean age of the patients was 53.75 ± 15.18 years.

A total of 35 (40.6%) of 86 patients had identifiable tumor cells in the washings at primary surgery. These patients included 22 (61.1%) of 36 with ovarian cancers, 2 (5.7%) of 4 with borderline ovarian lesions and 11 (23.91%) of 46 patients with endometrial carcinomas. Peritoneal cytology showed specificity of 78.6% and sensitivity of 86.9% when peritoneal histology was used as the standard. While 5.9% of the patients had negative cytology with positive intraperitoneal histology, 37.1% had positive cytology and negative peritoneal histology. Results of the individual primary sites were analyzed as follow: Ovarian Carcinomas: For the 36 patients with ovarian carcinoma, cytology was positive in 22 (61.1%), including 4 patients with stage I disease, 1 patient with stage II disease, 11 patients with stage III disease, and 6 patients with stage IV disease. The median survival for ovarian cancer patients with positive cytology was 42 months. Five-year survival for ovarian cancer patients with negative cytology was 19.3% (95% confidence interval [CI]=3.55%-100%) compared with 9.01% (95% CI=1.43%-56.6%) for those with positive cytology. As it is shown in Figure 1 the overall survival in patients with negative cytology is better than patients with positive cytology, although this difference failed to reach statistical significance ($p=0.30$). Kaplan-Meier survival analysis for the pooled (all stages) population of patients with ovarian carcinomas showed significant differences based on cytologic status after adjustment for stage ($p=0.00$). Significant survival differences were also demonstrated for patients with stage I ($p=0.03$) and IV ($p=0.00$) ovarian cancers, but not for patients with stage II ($p=0.38$) and III

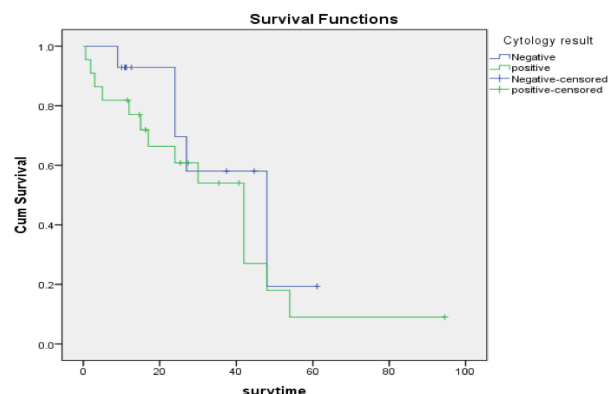


Figure 1. Overall Survival in Patients with Ovarian Carcinoma According to Cytology Result

($p=0.36$) cancers.

Borderline ovarian tumors

Cytology was positive in 2 patients with borderline ovarian tumors. None of the 4 patients with borderline tumors died during a follow-up period.

Endometrial carcinomas

Eleven patients (23.9%) had malignant cytology. These patients included 1 patient with stage I disease, 1 patient with stage II disease, 5 patients with stage III disease, and 4 patients with stage IV disease. Peritoneal histology and cytology results correlated in 37 endometrial cancer patients and 3 patients who had positive cytology had histologic evidence of intraperitoneal tumor. Five patients with endometrial carcinoma and positive cytology died, (median survival, 12 months). As it is shown in Figure

2. At 0 to 50 months the overall survival is better in patients with negative cytology than positive cytology but then it decreased and in patients with positive cytology, because 4 patients were alive, the overall survival seems to be better although this difference failed to reach statistical significance ($p=0.85$). Figure 3, 4, 5 show that there was no difference in overall survival between risk categories and peritoneal washing cytology, however there was significant difference between risk categories and the overall survival ($p=0.03$) (Figure 6). At 15 to 60 months patients with FIGO 2009 stage IA-II and negative peritoneal cytology had superior survival compared to 1988 IIA patients with positive cytology only (Figure 7) although this difference failed to reach statistical significance ($p=0.94$). Multivariate analysis using Cox proportional hazards model was conducted to evaluate the

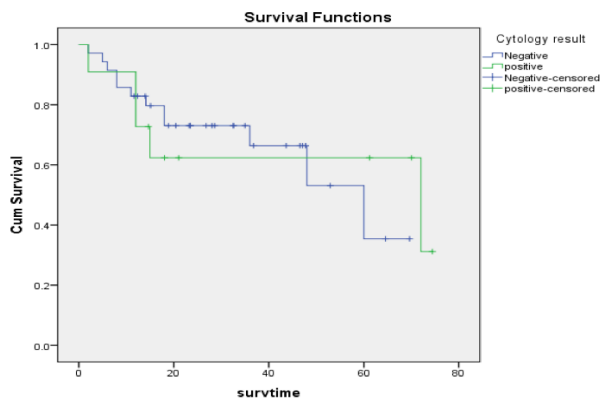


Figure 2. Overall Survival in Patients with Endometrial Carcinoma According to Cytology Result

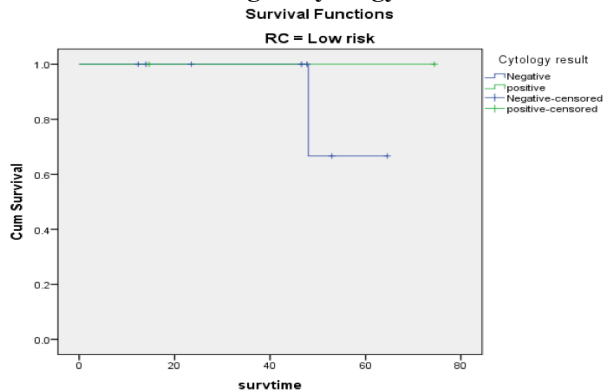


Figure 3. Overall Survival in Patients with Low Risk Endometrial Carcinoma According to Cytology Result

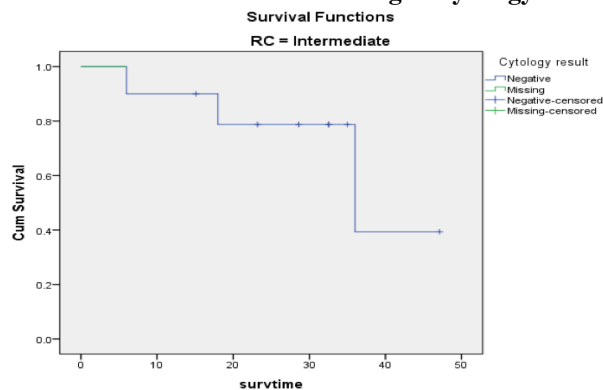


Figure 4. Overall Survival in Patients with Intermediate Risk Endometrial Carcinoma According to Cytology Result

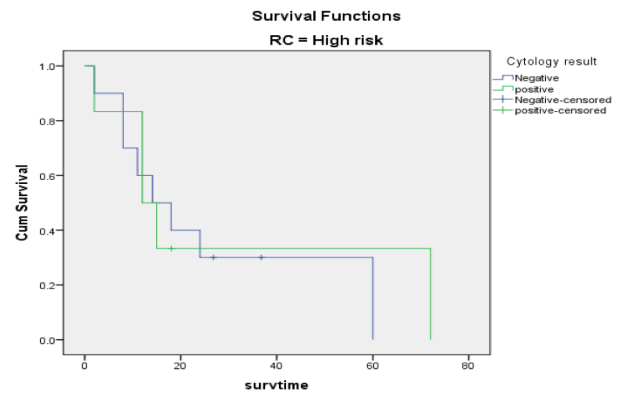


Figure 5. Overall Survival in Patients with High Risk Endometrial Carcinoma According to Cytology Result

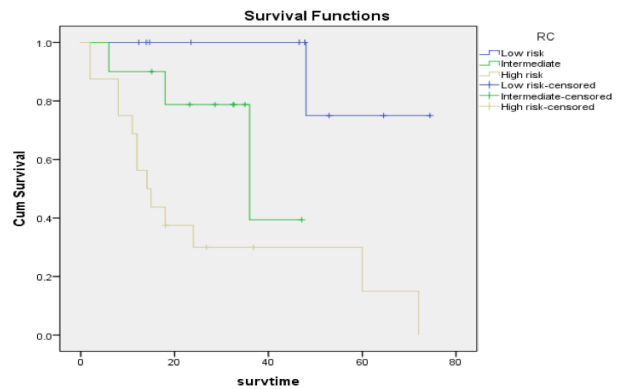


Figure 6. Overall Survival in Patients with Endometrial Carcinoma According to Risk Categories

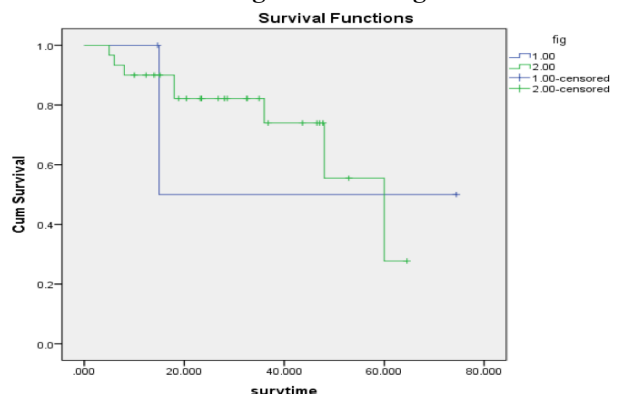


Figure 7. Overall Survival in Patients with FIGO 2009 Stage IA-II Endometrial Carcinoma and Negative Peritoneal Cytology in Comparison to 1988 IIA with Positive Cytology Only

Table 1. Cox Multivariate Survival Analysis with Stage, and Finding of Peritoneal Washing Cytology as Prognostic Factors

Covariate	Hazard ratio (95% CI)	P-Value
FIGO 98 stage		
FIGO 98 stage IV	1	
FIGO 98 stage I	0.039 (0.007-0.215)	0
FIGO 98 stage II	0.11 (0.020-0.61)	0.012
FIGO 98 stage III	0.162 (0.034-0.77)	0.022
Cytology result		
Negative	1	
Positive	4.022 (0.998-16.211)	0.05

effect of grade, stage, and result of peritoneal cytology on the survival (Table 1). It showed that stage and peritoneal cytology were predictors of death.

Discussion

In this report, we appraised the overall clinical utility of peritoneal washing cytology in endometrial and ovarian cancers. We found out that the sensitivity and specificity of peritoneal washing cytology were 86.9% and 78.6% respectively. Since peritoneal washing provides wider sampling of the peritoneum than random staging biopsies, it is a sensitive indicator of peritoneal involvement and can detect occult peritoneal disease in a high proportion of patients (Geza Acs, 2005). Conversely, 16-23% of patients with a positive washing have negative peritoneal biopsies. These discrepancies may be explained by sampling error or the presence of benign process that simulates malignancy (Rodriguez et al., 2013).

The limitations of peritoneal washing cytology examination are the possibility of false positivity in benign conditions and false negativity in the early stage of malignant diseases (Mustafa et al., 2013). Poor distribution of peritoneal washings specimens, infrequent exfoliation of malignant cells, and interpretive errors contribute in this relatively high false negative rate. Cytologic examination of intraoperative peritoneal washings as a means of detecting subclinical metastases was proposed in 1956 by Keettel and Elkins (Keettel WC, Elkins HB, 1956). Subsequently, peritoneal washing cytology has been accepted as part of the surgical work-up of patients with gynecologic malignancies. In 1971, Creasman and Rutledge (Creasman and Rutledge, 1971) explained that peritoneal cytologic results correlated well with prognosis in ovarian, endometrial, and cervical cancers. In the evaluation of patients with carcinoma of the ovary, peritoneal cytology is an admitted method. In this study the overall survival in patients with ovarian carcinoma and negative cytology was better than patients with positive cytology, although this difference failed to reach statistical significance ($p=0.30$).

In concordance with our results in another study positive cytology was related to poor overall survival ($p<0.001$) (Kaoru et al., 2013) and Germana et al. (2013) showed that positive cytology was strongly associated with peritoneal relapses. In addition one study showed that the presence of peritoneal implants in ovarian cancers with a low malignant potential demonstrated a high risk of recurrence (Sneige et al., 2012). In another

research, age, 2009 FIGO stage, histologic type, positive peritoneal cytology, adnexal involvement, nodal status, myometrial invasion, lymphatic/vascular space invasion, and endocervical involvement were significantly involved with recurrence on univariate analysis (Joan et al., 2012). Lazarov et al. (2013) revealed that if the peritoneal washing cytology is positive, the prognosis for female patients with early stage ovarian carcinoma becomes poor, even poorer compared to those in advanced stages.

However, the prognostic importance of positive results of peritoneal cytology in patients with endometrial carcinoma continues to be disputed. Between 3% and 30% of women with clinical early stages of endometrial carcinoma are found to have tumor cells in pelvic washing cytology, but only about 5% to 10% of women with no extra uterine metastases identified pathologically to have positive peritoneal cytology. The reported 5-year survival for those women with positive cytology only varies from about 80% to 90%, whereas the recurrence rate is about 30% (Zaino, 2009). During the past two decades many studies to assess the prognostic value of peritoneal washing cytology in endometrial cancer have been performed. Although some studies report good correlation of peritoneal cytology with outcome, other works do not. It has been declared that studies before 1990 just reported peritoneal washings to be significantly associated with prognosis (Mazurka et al., 1988; Turner et al., 1989). Studies after 1990 indicate different results (Aoki et al., 2001; Hirai et al., 2001; Obermair et al., 2001). As a result, peritoneal washing cytology was dropped from FIGO 2009 staging criteria for endometrial carcinoma.

Furthermore, the use of adjuvant therapy in patients with positive cytology only varies widely, from observation to aggressive management with either pelvic or whole abdominal radiation therapy. Morrow et al. (1991) showed that pelvic radiotherapy or lymphadenectomy might be especially important for patients with positive peritoneal cytology because the presence of positive peritoneal cytology increases the risk of pelvic and para-aortic lymph node invasion. The present study showed that at 0 to 50 months the overall survival is better in patients with negative cytology than positive cytology but then it decreased and in patients with positive cytology, because 4 patients were alive, the overall survival seems to be better, although this difference failed to reach statistical significance ($p=0.85$). We think that it might be treatment related. Anastasiadis et al. (2011) revealed that although the presence of malignant cells in the peritoneal cavity does not change the stage of the disease, it has a prognostic significance. Garg et al. (2013) showed that albeit, no longer a part of the FIGO 2009 staging system, peritoneal cytology condition should still be considered for accurate risk-stratification of these patients. It is shown in one study that peritoneal washing cytology remains a useful method for staging in gynecologic malignancies (Giordano et al., 2014). In another study Ellen reported that contrary to the recent change to the FIGO 2009 staging criteria, which excludes patients with positive cytology only from the IIIA designation, the cause specific survival was not different for patients with IIIA disease because of positive cytology versus patients staged as IIIA for serosal or adnexal

involvement (Ellen et al., 2011). It should be noted that positive peritoneal fluid cytology is frequently associated with other ominous factors such as high histologic grade, deep myometrial invasion, and extrauterine disease. As one reviews the literature, it is obvious that the outcome of endometrial adenocarcinoma is related to a wide variety of aspects, including those innate to the tumor (histologic type and grade of differentiation) those relevant to its growth pattern in the uterus (such as the depth of myometrial invasion and lymphatic offense), and those related to extra uterine extension. Consequently, no single feature seems to represent overcoming prognostic factor. Thus, the prognosis is based on a constellation of characteristic (Zaino, 2009).

To clarify this matter we divided the patients with endometrial cancer into three groups as it had been done previously by Takeshima et al. (2001) Figure 3, 5 shows that there was no difference in overall survival between risk categories and peritoneal washing cytology ,however, there was a significant difference between risk categories and the overall survival ($p=0.03$)(Figure 6). Therefore our results could not rule out that positive peritoneal cytology may be an independent predictor of survival after adjusting for other synergic effects. We also analyze the survival of patients with FIGO 2009 stage IA-II and negative peritoneal cytology in comparison to 1988 IIIA patients with positive cytology only. At 15 to 60 months FIGO 2009 stage IA-II patients with negative peritoneal cytology had superior survival compared to 1988 IIIA patients with positive cytology only (Figure 7), although this difference failed to reach statistical significance ($p=0.94$). Multivariate analysis using Cox proportional hazards model was conducted to evaluate the effect of grade, stage, and result of peritoneal cytology on the survival (Table 1). It showed that stage and peritoneal cytology were predictors of death. It is in accordance to two other studies (Garg et al., 2013, Ulla-Maija et al., 2014) in which positive cytology was found to be an independent predictor of survival after adjusting for other contributory factors. Contrariwise, Kato et al.(2012) found similar overall survivals for FIGO 1988 stage IIIA with positive peritoneal cytology only and for FIGO 2009 stage I. While optimal adjuvant therapy for patients with positive peritoneal cytology remains unclear, recurrence patterns suggest that systemic therapies are appropriate. Only randomized clinical trials testing the benefice and adverse effect of different treatment modalities among these patients. This study has a relatively low statistical power due to the limited number of patients included.

In conclusion, our data suggest that there is good correlation of peritoneal cytology with prognosis in patients with epithelial ovarian cancer and although, no longer a part of the current FIGO staging criteria, peritoneal cytology status should still be considered for accurate risk-stratification of patients with endometrial carcinoma. In addition this test is relatively cheap, easy-to-perform, and relatively complication-free. Because all studies, including ours, have important shortcomings, no definitive conclusion on the importance of positive peritoneal cytology can be drawn and therefore, additional research is warranted.

Acknowledgements

The authors are indebted to Shahid Sadoughi University of medical Sciences, Yazd-Iran for cooperation and financial support in this study.

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