

Research Article

Cytological Examination versus Traditional Biopsy in Detection of Right Diaphragmatic Copula Affection in Advanced Ovarian Cancer

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Abstract

Introduction: With involvement of the upper abdomen, metastasis to diaphragm, especially to the right hemi-diaphragm, are very common and up 40% of patients advanced-stage ovarian cancer have bulky metastatic diaphragmatic disease which leads to suboptimal cytoreduction and therefore to a lower rate of survival. The best technique for obtaining cytological specimens necessary for evaluation of diaphragmatic spread among women undergoing surgical staging for ovarian cancer has yet to be determined. Although diaphragmatic wash specimens provide better-quality smears than scrape specimens, both techniques are equally diagnostic of diaphragmatic involvement in women undergoing surgical staging for ovarian cancer.

Aim: To evaluate the accuracy of cytological scraping of the diaphragm in relation to the standard traditional biopsy in detection of right diaphragmatic copula affection in cases of advanced ovarian cancer.

Methods: Type of the study was prospective cohort study and Was conducted in El Shatby University Maternity Hospital on 40 patients with advanced ovarian malignancy stage III, IV and No history of radiation neither chemo therapy. They underwent surgical staging for ovarian cancer, the surgical approach is by laparotomy. In each patient, Two samples will be obtained, The first sample (sample 1) Rt. Diaphragmatic copula scrap specimen was obtained using a sterile Ayers spatula then the undersurface of the diaphragm was inspected and palpated. The specimen was fixed by 95% alcohol on a sterile microscopic glass slide and was sent to be examined by the pathologist using papanicolaou stain for the presence or absence of malignant cells. The second sample (sample 2) the right copula of diaphragm was surgically biopsied using a conventional knife, then specimen was fixed immediately on a glass slide using formalin then stained by H&E stain to be examined for presence or absence of malignant cells.

Results: Comparison between the two groups showed that the mean of RMI in biopsy negative patients was 462.62±400.43u/l lower than the mean in biopsy positive patients 4593.43±4830u/l which showed a statistical significance (p-value=0.000). Comparison between the two groups showed that the mean of RMI in Scratch negative patients was 1528.81±3238 u/l lower than the mean in Scratch positive patients 3426±4044u/l which showed non statistical significance (p-value=0.166)

Conclusions: In the ovarian cancer diaphragm is the third most affected organ of occult diseases just after the peritoneum and the colon. Cytological diaphragmatic smears were suggested to be done as a supplemental tool; however, they not routinely taken and their usefulness is still unclear. Cytological diaphragmatic smears by scratch can provide a great additional benefit in the detection of the peritoneal disease within these patients. There was fair agreement between biopsy outcomes with statically significantly related to scratch outcomes with 42.95 % sensitivity; 92.33 % specificity and 75% accuracy within these patients with ovarian cancer patients. Scraping is less sensitive than biopsy in case of right compilation peritoneum dissection

Keywords: Ovarian Cancer; Scraping; Biopsy; Diaphragm

Introduction

Epithelial ovarian cancer is the second most common genital

malignancy in women and it is the most lethal gynecological malignancy, with an estimated five-year survival rate of 39% [1].

Despite efforts to develop an effective ovarian cancer screening method, 60% of patients still, present with advanced (Stages III-IV) disease. CA-125 serum levels, transvaginal ultrasound, and pelvic examination have long been thought to be potentially effective screening tools. However, none of them have proved effective in decreasing mortality from ovarian cancer [2]. An epithelial ovarian tumor arises from the serosal lining of the ovary, which communicates with the serosal lining of the abdomino-pelvic cavity known as the peritoneum. As a consequence of tumor growth, malignant cells exfoliate and shed, becoming free floating in the peritoneal fluid [3].

They typically implant in the pelvis and sub-diaphragmatic recesses owing to gravity and the recumbent position. This spread of the tumor within the peritoneum is termed peritoneal carcinomatosis, and it is a typical feature of cancer spread in patients with primary advanced or recurrent epithelial ovarian cancers [4]. Intraoperatively, it is characterized by the presence of macroscopic tumor nodules of variable sizes and consistencies that can coalesce to form plaques or masses within the abdominopelvic cavity [5]. Tumor dissemination from the peritoneal cavity into the pleural cavity might also occur through the lymphatic lacunae within the diaphragmatic peritoneum. This results in severe pleural effusion, which compromises lung and cardiac function. It typically presents with vague gastrointestinal symptoms, such as abdominal bloating, distension, weight loss, and fatigue. Due to the heterogeneity and lack of specificity of these early clinical symptoms, diagnosis is often delayed [6].

With involvement of the upper abdomen, metastasis to diaphragm, especially to the right hemi-diaphragm, are very common and up 40% of patients advanced-stage ovarian cancer have bulky metastatic diaphragmatic disease which leads to suboptimal cytoreduction and therefore to a lower rate of survival [6]. The best technique for obtaining cytological specimens necessary for evaluation of diaphragmatic spread among women undergoing surgical staging for ovarian cancer has yet to be determined [10]. Although diaphragmatic wash specimens provide better-quality smears than scrape specimens, both techniques are equally diagnostic of diaphragmatic involvement in women undergoing surgical staging for ovarian cancer [7].

The AIM OF THE WORK was to evaluate the accuracy of cytological scraping of the diaphragm in relation to the standard traditional biopsy in detection of right diaphragmatic copula affection in cases of advanced ovarian cancer.

Methods

Type of the study was prospective cohort study and Was conducted in El Shatby University Maternity Hospital on 40 patients with advanced ovarian malignancy stage III, IV and No history of radiation neither chemo therapy. They underwent surgical staging for ovarian cancer, the surgical approach is by laparotomy. In each patient ,Two samples will be obtained, The first sample (sample 1) Rt. Diaphragmatic copula scrap specimen was obtained using a sterile Ayers spatula then the undersurface of the diaphragm was inspected and palpated . The specimen was fixed by 95% alcohol on a sterile microscopic glass slide and was sent to be examined by the pathologist using papanicolaou stain for the presence or absence of malignant cells. The second sample (sample 2) the right copula of diaphragm

Table 1: Comparison between patients biopsy results as regards RMI.

RMI	Biopsy						T-Test	
	Negative (n = 26)			Positive (n= 14)			t	P-value
Range	39	-	1323	165	-	12951	4.38	0.000**
Mean±SD	462.62	±	400.43	4593.43	±	4830		

*p-value < 0.05 statistically significant.

This table shows that Comparison between the two groups showed that the mean of RMI in biopsy negative patients was 462.62±400.43u/l lower than the mean in biopsy positive patients 4593.43±4830u/l which showed a statistical significance (p-value=0.000).

was surgically biopsied using a conventional knife, then specimen was fixed immediately on a glass slide using formalin then stained by H&E stain to be examined for presence or absence of malignant cells. After performance of pathological examination of two specimens, sample (1) i.e. cytology, was compared to sample (2) i.e. conventional biopsy which was regarded as the gold standard.

Results

The patients mean of age was 48.75±12.766 years and of the BMI was 29.05±4.624 kg/m². the patients` mean of CA125 was 388.7±756.9466u/l and of the RMI was 1908±3444.363u/l. 6 (15%) patients had DM, 2 (5%) had DM & HTN, 2 (5) had DM & HTN and were cardiac, 2 (5%) with hyperthyroid, 2 (5%) with hypothyroid, 2 (5%) with ischemic heart disease and 20 (50%) were free. The patients were distributed according to their menopausal state into perimenopausal 8 (20%), 20 (50%) postmenopausal and 12 (30%) premenopausal. Patients were distributed according to their Gravidity Parity where the G0P0 included 8 (20%) patients, and G2P2, G3P3, G4P3+1 each included 4 (10%) and G1P1, G5P4+1, G6P4+2, G6P5+1, G7P6+1, G8P6+2, G8P8 each included 2 (5%) and finally G4P4 included 6 (15%) patients. Patients that had HCV were 4 (10%), HBV were 2 (5%), HBV & HCV were 2 (5%) and 32 (80%) patients were HBV &HCV negative. patients were distributed according to Radiology stage into 36 (90%) in stage three and 4 (10%) in stage four. patients were distributed according to biopsy outcomes into 26 (65%) negative and 14 (35%) positive. Patients were distributed according to scratch outcomes into 32 (80%) negative and 8 (20%) positive. Comparison between the two groups showed that mean of CA125 in biopsy negative patients was 67.68±45.32u/l lower than the mean in biopsy positive patients 842±1138u/l which showed a statistical significance (p-value=0.001). Comparison between the two groups showed that the mean of CA125 in Scratch negative patients was 186.8±354.31u/l lower than the mean in Scratch positive patients 946.25±1452.32u/l which showed a statistical significance (p-value=0.009) (Table 1,2).

Discussion

Although women with this advanced ovarian cancer have a history being treated with the primary debulking surgery followed by the platinum and taxane based chemotherapy, this standard management of this advanced stage cancer ovary remains as a subject of debate [8]. A recent studies demonstrated that the amount of residual tumor after surgery is the most important prognostic factor for the survival in such patients. The study also revealed that each ten percent increase in this proportion of patients undergoes a cytoreduction without any macroscopic residual disease is associated with a significant and

Table 2: Comparison between patients scratch results as regards RMI.

RMI	Scratch						T-Test	
	Negative (n = 26)			Positive (n= 14)			t	P-value
Range	39	-	12951	285	-	9894	1.412	0.166
Mean ±SD	1528.81	±	3238	3426	±	4044		

*p-value < 0.05 statistically significant.

This table shows that Comparison between the two groups showed that the mean of RMI in Scratch negative patients was 1528.81±3238 u/l lower than the mean in Scratch positive patients 3426±4044u/l which showed non-statistical significance (p-value=0.166).

independent 2.3 month increasing of the survival [8].

Therefore, the primary aim in the ovarian cancer treatment is to achieve the most optimal cytoreductive surgery. However, in advanced ovarian cancer patients often present with an upper abdominal metastases. In these patients, diaphragmatic metastasis always observed in approximately 40% of the cases and in fact precludes an optimal cytoreductive surgery in up to 76% of cases. Nevertheless, little attention is paid to the mechanisms of the diaphragmatic metastasis in ovarian cancer or to this pathological factors that predict the metastasis [8].

The diaphragm is a one of the widest organs; it is separating the thoracic and the abdominal cavities, forming a dome-like structure with a steep slope in the back. The diaphragm’s main role is thought to involve any breathing movement. However, the diaphragm plays also another important role by absorbing the substances from abdominal cavity using the lymphatic drainage system. The diaphragm situated in the abdomen adjacent to liver, esophagogastric junction, inferior vena cava, abdominal aorta, thoracic duct, spleen, adrenal gland, kidney, and pancreas. In combination with a ventilatory movement, these anatomical features often make the diaphragmatic inspection and its operations difficult and a time-consuming. Accordingly, some investigators hypothesize that diaphragmatic metastasis could be underestimated during the ovarian cancer surgery [8].

The identification of these predictive factors for the diaphragmatic metastasis enables the stratification of patients regarding to the decision of whether to dedicate efforts to these diaphragmatic investigation during surgery. However, no adequate data are available for demonstrating pathological predictors of the diaphragmatic metastasis [9]. Thus, as an initial step toward investigating such factors, this study was conducted to characterize the accuracy of cytological scraping of diaphragm in relation to standard traditional biopsy in detection of right diaphragmatic copula affection in cases with advanced ovarian cancer.

This prospective cohort study was done in El Shatby University Maternity Hospital on 40 patients with advanced malignant ovary stage III, stage IV. In each patient two samples will be obtained then compared; the first sample: the right diaphragmatic copula scrap specimen (i.e. cytology) and the second sample: the right diaphragmatic copula biopsy specimen.

The current study showed that patients’ mean of their age was 48.75 years with standard deviation of ±12.766 years and of the Body Mass Index (BMI) was 29.05 with standard ±4.624 kg/m². These results were in agreement with the results of Leitzmann et al., 2016 [9] who studied body mass index and the risk of ovarian cancer and

suspected that obesity is associated with risk of enhanced ovarian cancer through a hormonal mechanism.

The current study showed that the patients’ the mean of cancer antigen 125 (CA125) was 388.7 with standard deviation ±756.9466 U/L and of Risk of Malignancy Index (RMI) was 1908 with standard deviation ±3444.363 U/L. Similar results were discussed by Al-Musalhi et al., 2015 [10] who studied the validity of this cancer antigen-125 (CA-125) and the Risk of Malignancy Index (RMI) in the diagnosis of ovarian cancer and it was found that both CA-125 and RMI have a good validity in the diagnosis of tumors of ovary. CA-125 has a higher sensitivity; however, RMI has a higher specificity. In combination, CA-125 should be more valid for the diagnosis of the malignant ovarian cancer while RMI is more valid for exclusion of the diagnosis of these tumors.

The present study showed that 6 patients (15%) had DM; 2 patients (5%) had DM & HTN; 2 patients (5%) had DM & HTN and were cardiac; 2 (5%) with hyperthyroid; 2 patients (5%) with hypothyroid; 2 patients (5%) with ischemic heart disease and 20 patients (50%) were free of diseases. Another study of Akhavan et al., 2018(11) who studied the impact of diabetes mellitus on Epithelial Ovarian Cancer (EOC) survival and found that 20% of the studied group had DM, 7% had DM & HTN, 7% had DM & HTN and were cardiac. He reported that the relation between ovarian cancer and diabetes is complex. So, the association between diabetes mellitus and epithelial ovarian cancer should be considered with cautions due to the small number of participants, misclassification bias based on a diagnostic method of DM and the residual confounding regarding these unmeasured variables such as the life style habits, participants physical activity and their medical condition.

Minlikeeva et al., 2017 [12] who studied the thyroid disease history and survival of the ovarian cancer patients: resulting from the Ovarian Cancer Association Consortium; and reported that this large study of women with an ovarian cancer with a recent history of hyperthyroidism and overall history of hypothyroidism were associated with worse five year survival. Shinn et al., 2013 [13] who studied impact of cardiovascular comorbidity on mortality of the ovarian cancer and it was found that 8.5% of ovarian cancer patients had a clear history of ischemic heart disease and when careful management of the cardiovascular comorbidities may extend survival in patients with the ovarian cancer.

The current study showed that patients were distributed according to their menopausal state into eight (20%) patients with perimenopausal; twenty patients (50%) with postmenopausal and a twelve patients (30%) with premenopausal. These results were in accordance with these of Trabert et al., 2016 [14] who studied the circulating estrogens and postmenopausal ovarian cancer risk and found that 17% patients with perimenopausal; 60% with postmenopausal and 33% with premenopausal were at risk of ovarian cancer.

This present study showed that the patients that had HCV were 4 (10%), HBV were 2 (5%), HBV & HCV were 2 (5%) and 32 (80%) patients were HBV &HCV negative. These results were agreed with that of Liu et al., 2017 [15] who studied cancer risk in patients with hepatitis B, C virus infection: a population-based study in Sweden,

and found that presence of HCV+HBV increase the risk of mortality more than if presence one of them alone.

The current study showed that the patients were distributed according to Radiology stage into 36 (90%) in stage three and 4 (10%) in stage four. Similar results reported by Mathieu et al., 2018 [16] who was Screening for this ovarian cancer: imaging challenges and opportunities for improvement and found that most patients were screened during 3rd stage with 20% mortality reduction was achieved.

In ovarian cancer the diaphragm is known as the third most affected organ of occult disease after the peritoneum and the colon. Peritoneal Biopsies (PB) and Washing (PW) are known as routine measures in the abdominal staging of the gynecological malignancies and they are used particularly for a further assessment of any occult microscopic tumor spread to the peritoneal surface included the diaphragm. Peritoneal Biopsies (PB) and washing (PW) (including omental biopsies) done routinely employed to assess the microscopic tumor spread to the peritoneal surface including the diaphragm [17].

The current study showed that the cancer ovary patients were distributed according to their biopsy outcomes into 26 patients (65%) were negative and 14 patients (35%) were positive. Another study of Mari et al., 2019 [18] who studied the Liquid Biopsies for Ovarian Carcinoma and discussed that the clinical researches related to biopsies which is liquid and OvC have been increased since 2010. The ability of these biopsies to be repeated at a several time points and with some recent technological advances allowing the early detection of OvC-related abnormalities that will likely lead to their use in the clinical practice in the next two years, notably for treatment monitoring, detection of any minimal residual of the disease, and early diagnosis of relapses. Extension to another settings, as screening and early diagnosis, also requires more exploration. Nevertheless, the clinical validity and utility must be proven, first simplified and all costs should be reduced before they may be widely recommended and routinely available. Results of the prospective cohort studies and these randomized trials by using the liquid biopsies for the agnostic purposes are thus warranted.

Cytological Diaphragmatic Smears (DS) have been also suggested as a supplemental tool; however, they are not routinely taken and their usefulness is still not clear. Then, Peritoneal Smears (PS) and in particular diaphragmatic smears are not commonly recommended and also routinely taken. However, a cytology via scraping or diaphragmatic washing, or even with blind biopsies even with the absence of an obvious macroscopic diaphragmatic disease also suggested, and the National Comprehensive Cancer Network (NCCN) Guidelines for the surgical treatment of ovarian cancer recommend blind diaphragmatic biopsies or, alternatively, scraping [19].

The present study confirmed that the ovarian cancer patients were distributed according to their scratch outcomes into 32 patients (80%) were negative and 8 patients (20%) were positive. These results were in agreement with that of Montavon et al., 2018 [19] who studied diaphragmatic smears in the detection of peritoneal spread in gynecological cancers and found that DS is not of any additional (to PB and PW) benefit in diagnosing peritoneal spread in gynecological cancers. Positive DS results did not reveal peritoneal diseases left

undetected by PB and PW, meaning that these two measures together detected all positive cases of peritoneal disease and that hence additional DS were not of additional diagnostic value.

This is largely consistent with an earlier study of Jacques and Selvaggi, 2002 [20] that evaluated the utility of DS as a diagnostic measure and considered that it was limited: DS were occasionally of insufficient quality and of low specimen yield, and identified only few as positive cases.

When compare between patients biopsy results as regards CA125 & RMI; the present study showed that the mean of CA125 in biopsy negative patients was 67.68 ± 45.32 u/l lower than the mean in biopsy positive patients 842 ± 1138 u/l which was statistically significant (p -value=0.001); the mean of RMI in biopsy negative patients was 462.62 ± 400.43 u/l lower than the mean in biopsy positive patients 4593.43 ± 4830 u/l which was statistically significant (p -value=0.000).

These results were in accordance that of Karimi-Zarchi et al., 2016 [21] who Evaluated serum CA 125 & MRI level and its relation to surgical, histopathologic and ultra sonographic findings in patients with ovarian mass and also found statistically significant (p -value=0.001).

When compare between patients scratch results as regards CA125 & RMI; the present study showed that the mean of CA125 in biopsy negative patients was 186.8 ± 354.31 u/l lower than the mean in biopsy positive patients 946.25 ± 1452.32 u/l which was statistically significant (p -value=0.009); the mean of RMI in biopsy negative patients was 1528.81 ± 3238 u/l lower than the mean in biopsy positive patients 3426 ± 4044 u/l which was not statistically significant (p -value=0.166). These results resemble that of Montavon et al., 2018 [22] as he noticed that the cytoreductive surgery have great value with CA125 over RMI because of the former most significant postoperative factor for prognosis this residual tumor.

The current study showed that the biopsy outcomes were statically significantly related to scratch outcomes with 42.95 % sensitivity; 92.33 % specificity and 75% accuracy by Chi Square test. Also by another method with fair agreement as kappa co-efficient = 0.39; (p -value=0.008). However, Montavon et al., 2018 [23] found that when assessing the relationship between the cytological/histopathological results and the FIGO stage; found that utility of cytology in tumor staging in ovarian cancer reporting 85% sensitivity and 95% specificity for a detection of malignant cells found in the peritoneal cavity in FIGO stage I and stage II ovarian cancer; were FIGO III/IV they showed about 53% sensitivity and 89% specify.

Conclusion

In the ovarian cancer diaphragm is the third most affected organ of occult diseases just after the peritoneum and the colon. Cytological diaphragmatic smears were suggested to be done as a supplemental tool; however, they not routinely taken and their usefulness is still unclear. Cytological diaphragmatic smears by scratch can provide a great additional benefit in the detection of the peritoneal disease within these patients. There was fair agreement between biopsy outcomes with statically significantly related to scratch outcomes with 42.95% sensitivity; 92.33% specificity and 75% accuracy within these patients with ovarian cancer patients.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from the patient included in the study.

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