

## Feasibility, accuracy and advantages of frozen section examination of ovarian masses with normal tumor markers. A tertiary referral center experience

Wykonalność, dokładność i zalety badania śródoperacyjnego guzów jajnika u pacjentek z prawidłowymi markerami nowotworowymi.  
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### Abstract

**Introduction:** Proper design of the operative plan for patients with ovarian masses is a must to avoid unnecessary surgical steps, the need for another surgery or empirical chemotherapy. We investigated the role of frozen section examination in this design. **Methods:** This was a prospective study in which 64 complex adnexal masses with normal tumor markers underwent frozen section examination. The patients were divided into two parallel groups: group A in which the decision whether to proceed for complete staging or not was built on the result of the examination, and group B in which the patients underwent panhysterectomy at baseline regardless of their frozen section examination result. Postoperative stay, estimated blood loss and the incidence of complications were compared. **Results:** When comparing the two groups, including patients with tumors that turned out to be benign, there were no significant differences in postoperative complications, but there were for the operative time (60 vs. 120 minutes,  $p = 0.004$ ) and blood loss, which were significantly lower in group A (50 vs. 100 mL,  $p = 0.001$ ), and hospital stay, which was statistically insignificantly shorter than in group B (1 day vs. 2 days,  $p = 0.062$ ). The sensitivity of frozen section examination for benign, borderline, and malignant ovarian masses was 91.9%, 76.9%, 53.3%, respectively, while the specificity was 85.2%, 87.5%, 95.9% and the overall diagnostic accuracy was 89.6%, 85.2%, 85.9%, respectively. **Conclusion:** The use of frozen section examination in the assessment of complex ovarian masses in patients with normal tumor markers offers an acceptable accuracy with a significant decrease of the operative time, blood loss as well as hospital stay.

**Keywords:** frozen sections, ovarian neoplasms, surgical blood loss

### Streszczenie

**Wstęp:** W celu uniknięcia zbędnych etapów leczenia operacyjnego, konieczności powtarzania zabiegu lub wdrożenia chemioterapii empirycznej u pacjentek z guzami jajnika niezbędne jest właściwe opracowanie planu leczenia chirurgicznego. W pracy oceniono rolę badania śródoperacyjnego w planowaniu takiego leczenia. **Metoda:** W prospektywnym badaniu przeprowadzono analizę badań śródoperacyjnych pochodzących z 64 złożonych guzów przydatków wykrytych u pacjentek z prawidłowymi markerami nowotworowymi. Pacjentki podzielono na dwie grupy: grupę A, w której decyzję o ewentualnym przejściu do pełnej oceny stopnia zaawansowania choroby oparto na wyniku badania, oraz grupę B, w której pacjentki poddano zabiegowi radykalnego usunięcia macicy niezależnie od wyniku badania śródoperacyjnego. Porównano długość hospitalizacji pooperacyjnej, szacowaną utratę krwi i częstość występowania powikłań. **Wyniki:** Porównanie obu grup, w tym pacjentek ze zmianami, które okazały się łagodne, nie ujawniło istotnych różnic w zakresie występowania powikłań pooperacyjnych, natomiast takie różnice stwierdzono w odniesieniu do czasu trwania operacji (60 vs 120 minut,  $p = 0,004$ ) i utraty krwi (istotnie niższej w grupie A – 50 vs 100 ml,  $p = 0,001$ ) oraz hospitalizacji (statystycznie nieistotnie krótszej niż w grupie B – 1 dzień vs 2 dni,  $p = 0,062$ ). Czulość badania śródoperacyjnego zmian łagodnych, guzów o granicznej złośliwości i guzów złośliwych jajnika wyniosła odpowiednio 91,9%, 76,9% i 53,3%, swoistość – 85,2%, 87,5% i 95,9%, a ogólna dokładność diagnostyczna – 89,6%, 85,2% i 85,9%. **Wnioski:** Badanie śródoperacyjne w ramach oceny guzów złożonych

jajników u pacjentek z prawidłowymi markerami nowotworowymi zapewnią dopuszczalną dokładność przy znacznym skróceniu czasu operacji i hospitalizacji oraz zmniejszeniu utraty krwi.

**Słowa kluczowe:** badanie śródoperacyjne, nowotwory jajnika, śródoperacyjna utrata krwi

## INTRODUCTION

Ovarian cancer is a challenging health problem with an estimated count of 313,959 new cases annually (1.6% of total cancer incidence) and 207,252 annual cancer-related deaths (2.1% of all cancer-related mortality)<sup>(1)</sup>. It constitutes about 25% of all gynecological cancers and accounts for up to 50% of gynecological cancer-related mortality<sup>(2)</sup>. Ovarian cancer rarely occurs before the age of 40 years and its incidence increases in older age groups, especially in perimenopausal and postmenopausal women. The most important risk factors include positive family history, advanced age, and nulliparity<sup>(3)</sup>.

Surgical staging for early ovarian cancer includes bilateral salpingo-oophorectomy, hysterectomy, omentectomy, peritoneal biopsy, iliac and paraaortic lymphadenectomy<sup>(4)</sup>, which can carry more morbidity than oophorectomy.

In the case of for malignant ovarian tumors, this staging is important to provide adequate data for the postoperative treatment plan and to help evaluate the prognostic status as well<sup>(5)</sup>.

Frozen section procedure, a useful intraoperative tool with a rapid result, can help design proper operative plan for patients with ovarian masses to avoid any unnecessary surgical steps or the need for another surgery or empirical chemotherapy. Frozen section analysis can differentiate between benign, borderline, and malignant ovarian masses with acceptable accuracy. It hence provides a practical solution to answer the question about the nature of complex ovarian masses with normal tumor markers, which can constitute up to 50% of early ovarian cancers, as well as helps avoid overtreatment in benign ovarian masses with mild reactionary ascites<sup>(6-10)</sup>.

In this study, we evaluated the accuracy of frozen section examination in the diagnosis of ovarian masses with normal tumor markers and its effects on operative time, blood loss, and hospital stay.

## METHODS

### Study design

This prospective study was conducted in 64 patients in our center between April 2019 and October 2020. All patients were females presenting with complex adnexal masses with normal tumor markers. Patients with pathologically confirmed ovarian cancer or patients who were unfit for general anesthesia were excluded from the study.

## Ethical approval

The study protocol was approved by the institutional review board at the faculty of medicine with the code number MS.19.08.751.

## Methodology

For every new patient, the following was performed: full history including age, body mass index, ASA (American Society of Anesthesiologists) score, medical and surgical history, clinical evaluation including general, abdominal, and gynecologic examination, CA-125 level assessment, imaging either by computed tomography (CT) or magnetic resonance imaging (MRI) for the abdomen and pelvis, and chest CT or x-ray as a metastatic workup when clinically indicated.

All patients underwent frozen section examination of the ovarian masses. Then, the patients were divided into two parallel groups: group A in which the decision to proceed for complete staging or not was built on the result of the frozen section examination of the ovarian masses, and group B in which the patients underwent baseline panhysterectomy. In group A, using general or spinal anesthesia and Trendelenburg position, exploration of the abdomen was done usually through a lower midline incision or laparoscopically. An assessment of the peritoneal surfaces, omentum, liver, stomach, and colon was performed first, followed by salpingo-oophorectomy for the ovarian mass. The specimen was sent immediately to the pathology laboratory. Frozen section was done using Leica CM1900 cryostat device, slicing tumor into five micro thick sheets, then dyed using hematoxylin-eosin stain. The slides were assessed at least by two pathology experts. The whole process lasted on average 30 to 60 minutes. Then, according to results of frozen section examination, either the procedure was ended in benign cases or proceeded to complete staging in borderline or malignant cases. In group B, panhysterectomy was performed at baseline regardless of the frozen section result. Postoperative stay, estimated blood loss and the incidence of complications were compared.

## Statistical analysis and data interpretation

The data of the enrolled patients were analyzed, and statistical values were obtained using SPSS version 22 (Inc, Chicago, IL). Continuous variables are presented as means when symmetrical or median and range when asymmetrical. Categorical variables are presented as proportions.

Total number – 64	
<b>Age – years:</b> • mean ± SD (range)	47.98 ± 14.20 (15–73)
<b>BMI (kg/m<sup>2</sup>):</b> • mean ± SD (range)	34.17 ± 8.89 (9.5–57)
<b>Comorbidities:</b>	n (%)
• hypertension	11 (17.2%)
• diabetes	10 (15.6%)
• cardiac	2 (3.1%)
<b>Number of offspring:</b> • median (range)	3.0 (0.0–6.0)
<b>CA-125:</b> • median (range)	19.30 (2.5–112)
<b>Radiology size (surface area – cm):</b> • median (range)	130 (13.5–750)
<b>Radiology:</b>	n (%)
• CT	23 (35.9%)
• MRI	40 (62.5%)
• US	1 (1.6%)
<b>Site:</b>	
• bilateral	2 (3.1%)
• left	25 (39.1%)
• right	37 (57.8%)
<b>Radiology types:</b>	
• complex	51 (79.7%)
• cystic	13 (20.3%)
<b>Radiology conclusion:</b>	
• benign	6 (9.4%)
• malignant	31 (48.4%)
• suspicious	27 (42.2%)
<b>Surgical method:</b>	
• laparoscopy	11 (17.2%)
• laparotomy	53 (82.8%)
<b>Operation type:</b>	
• total abdominal hysterectomy and bilateral salpingo-oophorectomy	13 (20.3)
• salpingo-oophorectomy	28 (43.8)
• complete staging	23 (35.9)

Tab. 1. The demographic, clinical and radiological data of the included patients

Univariate analysis was done using the Chi-square test, Fisher’s exact test (if cell count less than 5), Mann–Whitney test, Student *t*-test, and one-way ANOVA. A *p*-value <0.05 was considered significant.

## RESULTS

From April 2018 to October 2020, a total of 64 patients with complex ovarian masses with normal tumor markers were included in the study. The demographic, clinical and radiological data of the included patients are presented in Tab. 1.

Including benign masses only	Protocol		Test of significance
	A n = 21 (%)	B n = 16 (%)	
<b>Presence of complications:</b> • –ve • +ve	20 (95.2%) 1 (4.8%)	14 (87.5%) 2 (12.5%)	FET <i>p</i> = 0.568
<b>Type of complications:</b> • discovered to have AF • leucocytosis and distension • vesicovaginal fistula	0 1 (4.8%) 0	1 (6.2%) 0 1 (6.2%)	<i>p</i> = 1.0 <i>p</i> = 0.428 <i>p</i> = 1.0
<b>Operative duration – minutes:</b> • median (range)	60 (45–210)	120 (75–210)	<i>Z</i> = 0.285 <i>p</i> = 0.004*
<b>Estimated blood loss – mL:</b> • median (range)	50 (0–1,000)	100 (50–300)	<i>Z</i> = 3.39 <i>p</i> = 0.001*
<b>Postoperative stay – days:</b> • median (range)	1.0 (1.0–7.0)	2.0 (1.0–4.0)	<i>Z</i> = 1.86 <i>p</i> = 0.062
<b>Pan hysterectomy Salpingo-oophorectomy Complete staging</b>	0 21 (100%) 0	11 (68.8%) 0 (0.0%) 5 (31.2%)	MC <i>p</i> < 0.001*

Tab. 2. Comparison between the two treatment groups among the patients whose tumors turned out to be benign

The median operative time for the enrolled patients was 120 minutes (45–300) while the estimated blood loss was 70 mL (0–1,000). The average postoperative hospital stay was 2 days (1–7). Fifty-nine patients had an uneventful postoperative course. Only 5 patients developed postoperative complications. These were atrial fibrillation, ileus, pulmonary embolism, vesicovaginal fistula, and wound dehiscence. The patient who developed a vesicovaginal fistula was in the hysterectomy group.

Intraoperative frozen section examination of the excised ovaries was benign, borderline, and malignant in 38, 16 and 10 patients, respectively, while the final pathology after paraffin section examination was benign, borderline, and malignant in 37, 12 and 15 patients, respectively.

Frozen section examination revealed benign pathology in only one patient, and the paraffin section turned out to be benign. The frozen section examination described mucinous cystadenoma, which turned out to be a borderline mucinous tumor in the paraffin section.

When comparing the two treatment groups including only patients with tumors that turned out to be benign (meaning that oophorectomy only was sufficient), there were no significant differences as regards the postoperative

Frozen	Pathology			Sensitivity	Specificity	PPV	NPV	Accuracy	Kappa agreement
	Benign	Borderline	Malignant						
Benign	34 (91.9%)	1 (8.3%)	3 (20.0%)	91.9%	85.2%	89.5%	88.5%	89.6%	0.673
Borderline	2 (5.4%)	10 (83.3%)	4 (26.7%)	76.9%	87.5%	62.5%	93.3%	85.2%	
Malignant	1 (2.7%)	1 (8.3%)	8 (53.3%)	53.3%	95.9%	80.0%	87.0%	85.9%	

PPV – positive predictive value; NPV – negative predictive value.

Tab. 3. Analysis of intraoperative frozen sections in the diagnosis of ovarian tumors

complications, but the operative time (60 vs. 120 minutes,  $p = 0.007$ ) and blood loss were significantly reduced in group A (50 vs. 100 mL,  $p = 0.001$ ), while the hospital stay was statistically insignificantly lower than in group B (1 day vs. 2 days,  $p = 0.062$ ) (Tab. 2).

The sensitivity and specificity of frozen section examination in the diagnosis of benign, borderline, and malignant ovarian masses were 91.9%, 76.9%, 53.3%, and 85.2%, 87.5%, 95.9%, respectively. The negative predictive value was 88.5%, 93.3%, 87%, while the positive predictive value was 89.5%, 62.5%, 80.0%. The overall accuracy of frozen section examination in the diagnosis of benign, borderline, and malignant ovarian masses was 89.6%, 85.2%, 85.9%, respectively (Tab. 3).

## DISCUSSION

Unlike in many other tumors, no preoperative pathological diagnosis should be performed in early ovarian cancer. Oncologists depend mainly on pathological examination of the excised ovarian tumor<sup>(11)</sup>. Performing a complete surgical staging for every patient with a complex ovarian mass is a double-edged weapon. On the one hand, it indeed saves the patients from undergoing another surgical procedure, but on the other hand, it exposes many of them, especially young females where fertility issues and hormonal disturbances are major considerations, to overtreatment. In addition, every additional surgical step can expose the patient to more complications, more blood loss, and longer hospital stay<sup>(6,7,12,13)</sup>. While trying to reach a balanced management plan, it must be kept in mind that the diagnostic accuracy of the available radiological tools has limits and that we need an adjunctive tool to help guide the surgical strategy<sup>(3)</sup>. Building the decision on frozen section examination results in benign cases leads to significant improvement in blood loss and operative time.

Therefore, frozen section examination, which offers about 90% accuracy, can help plan a proper surgical strategy for every patient. And even in malignant tumors, distinguishing primary from metastatic, epithelial from non-epithelial, and serous from mucinous tumors can contribute to surgical decision-making as well<sup>(3,6,7)</sup>. This can save some patients, especially those with benign tumors, from such unneeded comprehensive surgical staging with its potential side effects, morbidity, even mortality, and financial costs<sup>(3,9)</sup>. The accuracy of frozen section examination in the diagnosis of benign, borderline, and malignant ovarian masses was 89.6%, 85.2%, 85.9%, respectively, which is still acceptable despite being lower than that reported in literature.

Overtreatment is more likely to occur in non-neoplastic lesions that mimic malignant ones, including endometriosis, granulomatous ovarian cysts, tuberculosis and corpus luteal cysts. Benign tumors which need to be identified intraoperatively include mucinous cystadenoma, serous cystadenoma, fibrothecoma, cystadenofibroma, and mature

teratoma<sup>(9)</sup>. The diagnosis of borderline tumors can lead to a more conservative approach, especially in fertility-desiring groups<sup>(9)</sup>.

Certain limitations can overwhelm the accurate interpretation of frozen section examination, especially the differentiation between primary and metastatic tumors and the overlapping pathological features in the grey zone or the borderline category. Low-grade, large-sized and mucinous tumors may also be misinterpreted<sup>(7,11,14–16)</sup>. In borderline tumors, the term “at least borderline” may be sufficient to inform the surgeon that the tumor is not totally benign and that surgical staging can be, in the majority of cases, justified<sup>(17,18)</sup>. Mucinous tumors show diagnostic diversity, and small foci of intraepithelial carcinoma or anaplastic carcinoma may be missed during the processing of frozen section examination<sup>(19)</sup>. In our series, frozen section examination was less sensitive in the diagnosis of borderline ovarian neoplasms. In addition, low sensitivity was noted in the diagnosis of malignant ovarian masses. This may be attributed to the morphological overlap with some borderline and benign lesions, interpretation errors as well as the relatively low number of patients with malignant ovarian masses included in the study.

In addition, inaccurate results of frozen section examination are mainly related to sampling errors followed by interpretation errors which may be related to the pathologist's experience level – apart from the hospital type – the number and quality of sections. Limitation of sampling errors is advised to improve the diagnostic accuracy. Active interaction between the pathologist and the surgeon is needed as sharing the intraoperative observations and clinical history with the pathologist can help reach a proper diagnosis<sup>(2,3,10,12,20–22)</sup>. The cornerstone in diagnosing frozen sections includes not only the microscopic examination of the ovaries, but the clinical history and gross examination as well<sup>(21)</sup>.

Limitations of this study include the small number of patients, the use of alternation rather than randomization as well as the heterogeneity in the group of surgeons and pathologists who dealt with the patients included in the study.

## CONCLUSION

Frozen section examination in the assessment of complex ovarian masses with normal tumor markers offers an acceptable accuracy with a significant decrease of the operative time, blood loss as well as shorter hospital stay. It should be offered as a reasonable alternative to comprehensive surgical staging and panhysterectomy in this group of patients.

### Ethics approval and consent to participate

All procedures performed in the study involving human participants followed the ethical standards of the institutional research committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Approval was obtained from the institutional review board at the faculty of medicine, Mansoura University (MFM-IRB) under code number MS.19.08.751. Having a written consent from participants is a prerequisite for having IRB approval.

### Availability of data and material

All the clinical, radiological and pathological data used in this manuscript is available on Mansoura University medical system (Ibn Sina Hospital management system). <http://srv137.mans.edu.eg/mus/newSystem/>

### Conflict of interest

All authors declare they have no conflict of interest.

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