

# Frozen Section Examination for Ovarian Cancer Diagnostic in Sanglah General Hospital: A Diagnostic Test

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**Abstract:** *From all gynecological cancers reported in Sanglah General Hospital, 35% of them are ovarian cancer cases. In 5 years, life expectancy rate is only 15%. Frozen section during surgery procedure is one of the common techniques to diagnose a malignancy. This study focused on diagnostic test with histopathological examination as the gold standard. The study was done in Obstetrics and Gynecology Polyclinic and in Pathology Anatomy Laboratory of Sanglah General Hospital, Denpasar. Consented subjects took part in this study for 1 year, from May 1<sup>st</sup> 2019 until May 31<sup>st</sup> 2020. Frozen section accuracy for ovarian cancer diagnosis was 90.8%. Its sensitivity was reported 91.4%, while the specificity was 86.7%.*

**Keywords:** Ovarian cancer, frozen section, diagnostic test, sensitivity, specificity

## 1. Introduction

According to American Cancer Society, 12 - 15% of all cancers found in women are gynecological tumor. One of its top contributors is ovarian cancer with the prevalence of 40%. Ninety percent of the cases are epithelial type and commonly found in menopause women.<sup>1</sup> In Sanglah General Hospital, 35% percent of gynecological cancer cases are ovarian cancer. In 5 years, life expectancy rate is only 15%.<sup>2</sup> Women in productive age is more prone to suffer ovarian cancer, with two thirds of ovarian cancer cases found in women older than 55 years old. Around 70 - 75% of ovarian cancer cases are often diagnosed in later stage because it doesn't show specific signs and symptoms in earlier stage. This can be economical and psychological burden for patient because the treatment become more aggressive.<sup>3</sup> Thus, early diagnosis while the tumor size is still small and restricted to ovary are the most important prognosis factor.<sup>4</sup>

Intraoperative frozen section is a diagnostic procedure that is beneficial to evaluate histological type of a mass. This procedure was done by freezing part of the tissue inside cryostat machine and then stained.<sup>5</sup> Aside for diagnostic tool, frozen section is widely used to detect enlargement of tumor as well as classification of tumor as benign, borderline, and malignant so clinicians could determine the level of surgical treatment especially in patients who want to retain their fertility.<sup>3, 6</sup> It is safe to assume that frozen section plays big part in the treatment of gynecology patient and is vital for malignancy diagnostic.<sup>7</sup>

The accuracy of frozen section examination has been reported. The newest study found that its sensitivity ranged from 25% to 92% while its specificity was 60% to 99%.<sup>8</sup> Overall, the accuracy of frozen section ranged from 73% to 98% in determining malignancy. This number has been consistently increased in the last decade, reflecting improvements in this procedure. But there are factors than

can influence the accuracy of frozen section such as patient characteristics, tumor size, histological type, and the pathology specialists experience.<sup>3, 5</sup> Frozen section accuracy has never been reported in Bali, especially in Sanglah General Hospital. Thus, it is considered important to evaluate the accuracy of frozen section as a diagnostic tool of ovarian cancer.

## 2. Methods / Approach

### 2.1 Study Design

This study focused on diagnostic test with histopathological examination as the gold standard.

### 2.2 Location and Period

This research was done in Obstetrics and Gynecology Polyclinic and in Pathology Anatomy Laboratory of Sanglah General Hospital, Denpasar. Consented subjects/parents/guardians took part as samples from May 1<sup>st</sup> 2019 to May 31<sup>st</sup> 2020. Before the samples were collected, subjects went through interview, physical examination, supportive examination, received information regarding to study, and signed the informed consent form after explanation.

### 2.3 Population and Sample

All women above 18 years old with ovarian tumor who went to Obstetrics and Gynecology Polyclinic of Sanglah General Hospital, Denpasar during the period of study were taken as the population study. Intended samples were the one who fulfilled the inclusion criteriasuch as:

- 1) Women above 18 years old with ovarian tumor diagnosis
- 2) No history of prior ovarian cancer treatment
- 3) Ovarian tumor case that underwent intraoperative frozen section examination

- 4) Subjects/parents/guardian who consented to participate

The exclusion criteria were women with ovarian tumor in conjunction of primary tumor on another organ.

#### 2.4 Sample Size

The formula to obtain the sample size is explained as follows:<sup>9</sup>

$$n = \frac{z\alpha^2(1 - spec)}{d^2}$$

Note:

n = amount of subjects

spec = specificity that aimed to be achieved = 95% (0, 95)

1 - spec = 0, 05

d = error of specificity prediction within accepted limit = 5% (0, 05)

In this study,  $\alpha$  was 5%. The value of  $\alpha = 5\%$  was set to type 1 error (false positive and occurs when a researcher incorrectly rejects a true null hypothesis).  $Z\alpha = 1, 96$ . According to the formula, number of minimal samples were 73. To avoid dropout, 20% of sample were added. Thus, the minimal samples of this study became 88 samples.

#### 2.5 Materials and Equipment

Materials used for this research were intraoperative frozen section tumor samples, collected from dense area or suspicious area. Number of samples varied from one to three (average samples were two). The equipment needed for this study are listed:

- 1) Data and information of samples contained in questionnaire
- 2) Patient medical history
- 3) Cryostat
- 4) Slide glass
- 5) 5 cc syringe to collect blood plasma sample
- 6) Blood plasma storage tube

#### 2.6 Procedure

- 1) The study started with socialization in Obstetrics and Gynecology Polyclinic of Sanglah General Hospital. The purpose of the study, risks, benefits, as well as the procedure were informed. Selected subjects who fulfilled inclusions and exclusion criteria then signed informed consent form.
- 2) All samples were handled according to diagnostic and therapy guideline of Obstetrics and Gynecology Department of Sanglah General Hospital. Samples were obtained using consecutive sampling method.
- 3) Research steps:
  - a) After signed the informed consent, samples filled a comprehensive personal information form. An interview was conducted to collect information regarding sample's name, age, address, education, parity, and past history of disease.
  - b) General physical examination to determine patient's health status
  - c) Gynecology examination

#### 2.7 Sample Collection

Blood serum collected using 5 cc syringe on median cubital vein to examine CA - 125 level. The personnel from Laboratory of Sanglah General Hospital performed this procedure. Sample volume was taken and then stored inside serum storage tube. Blood was taken before administration of drugs. Sample storage tube labeled with patient's name and register number.

#### 2.8 Intraoperative Frozen Section Examination

Before incised, gross tumor examination was performed. Then frozen section sample harvested from dense or suspicious part. Pathology specialist provided the consultation. Fresh specimen was being froze with cryostat, cut into 5  $\mu$ m, put on slide glass and stained with hematoxylin and eosin.

#### 2.9 Histopathology Examination

Main parameter from histopathological form involved patient's age, largest tumor diameter, report of dense part that was found, papillary growth, necrotic area, bilateral tumors, and frozen section diagnosis. The writer referred to World Health Organization (WHO) definition in determining the diagnosis of benign, borderline, and malignant epithelial ovarian tumor.

#### 2.10 Histopathology Classifications

World Health Organization defined the histopathological classifications of ovarian tumor from the structure and the cell's nucleus:

- 1) Benign epithelial ovarian tumor has benign histological features with cell differentiation similar to fallopian tube epithelium for serous type, endocervical or gastrointestinal epithelium for mucinous type, endometrium epithelium for endometrial type, epithelium that consists of hobnail cells for transparent cell type, and mature urothelium for transitional/Brenner type.<sup>1</sup>
- 2) Borderline epithelial ovarian tumor has more defined proliferative features and atypical nucleus than benign tumor, but not accompanied with stromal invasion.<sup>1</sup>
- 3) Malignant epithelial ovarian tumor has more defined proliferative features and atypical nucleus than borderline tumor, accompanied with stromal invasion. Expansile pattern can also be used to determine proliferative pattern to glandular/cystic structure, in the form of confluence growth, interconnecting gland, cribriform, and solid.<sup>1</sup>

#### 2.11 Histopathology Examination Interpretation

All frozen section diagnoses were made by a team of pathology experts. Then the results of frozen section and histopathology were compared.

## 2.12 Data Analysis

Data analysis was done using SPSS program for Windows, version 22.0. The results from this analysis were analyzed as follows:

- 1) Sample characteristics were descriptive using charts and tables.
- 2) Data normality test using Kolmogorov - Smirnov test. Data homogeneity test using Levene's T test.
- 3) A 2x2 table was used to determine sensitivity, specificity, positive predictive value, negative predictive value, and frozen section accuracy.

## 2.13 Ethical Clearance

Subjects consented and filled informed consent form. This research was approved by Ethical Commission, Research and Development of Faculty of Medicine Udayana University/Sanglah General Hospital. The writer funded his own research. Patients and their family had rights to object or withdraw without further consequence. The patient's identity remained secret.

## 3. Results and Discussion

### 3.1 Sample Characteristics

Eighty - eight women with ovarian tumor participated in this study. All samples were patient that went to Obstetrics and Gynecology Polyclinic of Sanglah General Hospital. Average age and proportion of the women post - menopause were not significantly different between two groups. Parity rates in benign ovarian tumor cases were significantly more common. This result was similar to a study by Schorge, et al. in 2008 that stated higher parity rates correspond with lower risk of ovarian tumor.<sup>10</sup> A child would reduce the risk of ovarian cancer with risk reduction of 0.3 - 0.4. Ovarian cycle that continues throughout reproductive period would continuously stimulates ovarian epithelium thus increasing the risk of malignancy.<sup>11</sup>

**Table 3.1:** Age, Parity, Menopause Status, Histological Type, and Stadium Characteristics

Variables	Ovarian Tumor		P
	Malignant	Benign	
Age (in years) average $\pm$ SD	43, 2 $\pm$ 13, 4	42, 1 $\pm$ 10, 2	0, 672
Parity Median (IQR)	1, 0 (2, 0)	2, 0 (1, 0)	0, 028
Menopause Status N (%)			
Yes	24 (41, 4%)	7 (23, 3%)	0, 093
No	34 (58, 6%)	23 (76, 7%)	
Total	58 (100%)	30 (100%)	
Histological Type N (%)			
Epithelial	42 (72, 4%)	9 (30%)	
Non epithelial	9 (15, 5%)	3 (10%)	
Borderline	7 (12, 1%)	2 (6, 7%)	
Others	0 (0%)	16 (5, 3%)	
Total	58 (100%)	30 (100%)	
Stadium N (%)			
I	16 (27, 6%)		
II	9 (15, 5%)		
III	27 (46, 6%)		
IV	6 (10, 3%)		
Total	58 (100%)		

## 3.2 Frozen Section Accuracy in Diagnosing Ovarian Cancer

Frozen section accuracy in diagnosing ovarian cancer was analyzed as below:

**Table 3.2:** Frozen Section Accuracy in Diagnosing Ovarian Cancer

		Histopathology		
		Malignant	Benign	Total
FZ	Malignant	53	4	57
	Benign	5	26	31
	Total	58	30	88

Sensitivity: 91.4%

Specificity: 86.7%

Positive predictive value: 92.9%

Negative predictive value: 83.8%

Accuracy: 90.8%

Out of 88 subjects, 9 of them were diagnosed differently when underwent frozen section examination. Five cases were under diagnosed (false negative) while 4 cases were over diagnosed (false positive). Thus, the histopathological accuracy of frozen section in diagnosing ovarian cancer in Pathology Anatomy Department of Sanglah General Hospital from May until November 2019 was 90.8%.

The sensitivity in this study was 91.4%, which meant from all the malignancy diagnosis of pathology anatomy results, 91.4% of frozen section results were indeed malignant. Specificity of 86.7% stated from all the benign diagnosis made from pathology anatomy results, 86.7% were indeed benign when frozen section examination was conducted. Positive predictive value of 92.9% declared that 92.9% from all the results of frozen section examination were indeed malignant pathology - anatomically while the negative predictive value of 83.8% stated that 83.8% of all the frozen section results were indeed benign. This concludes that frozen section examination as diagnostic means of ovarian cancer in Sanglah General Hospital is already done well thus the results can be trusted.

### 3.3 Analysis of Frozen Section Accuracy in Diagnosing Epithelial Type Ovarian Cancer

Frozen section accuracy as diagnostic tool of epithelial type ovarian cancer is shown as below:

**Table 3.3:** Accuracy of Frozen Section in Diagnosing Epithelial Type Ovarian Cancer

		Histopathology		
		Malignant	Benign	Total
FZ	Malignant	40	2	42
	Benign	2	7	9
	Total	47	9	51

Sensitivity: 95.2%

Specificity: 77.7%

Positive predictive value: 95.2%

Negative predictive value: 77.7%

Accuracy: 92.1%

From this study, sensitivity value of 95.2% meant from all malignant pathology anatomy results, 95.2% of frozen section examination were indeed malignant. Specificity of 77.7% concluded that from all benign pathology anatomy results, 77.7% of frozen section were indeed benign. Positive predictive value of 95.2% declared that 95.2% of all malignant frozen section examination results were indeed malignant. Negative predictive value of 77.7% stated from all the benign frozen section results, 77.7% were indeed benign pathology - anatomically.

### 3.4. Analysis of Frozen Section Accuracy in Diagnosing Non - Epithelial Type Ovarian Cancer

Accuracy analysis of frozen section as means of non - epithelial ovarian cancer diagnostic tool is shown as below:

**Table 3.4:** Accuracy of Frozen Section in Diagnosing Non - Epithelial Type Ovarian Cancer

		Histopathology		
		Malignant	Benign	Total
FZ	Malignant	7	1	8
	Benign	2	2	4
	Total	9	3	11

Sensitivity: 77.7%

Specificity: 66.7%

Positive predictive value: 87.5%

Negative predictive value: 50%

Accuracy: 75%

Table 3.4. shown the comparison between frozen section histopathology results with routine histopathology examination according to potency of non - epithelial ovarian tumor malignancy. Correctly diagnosed ovarian tumor cases during frozen section examination were 9 cases. There were 3 cases of different diagnoses during examination with a case was overdiagnosed while 2 others were under - diagnosed. From the results it is safe to assume that the accuracy of frozen section in diagnosing non - epithelial ovarian tumor was 75%. Sensitivity of frozen section in determining non - epithelial ovarian tumor wasn't too superior, which valued 77.7%. This meant from all malignant diagnoses made during pathology anatomy examination, 77.7% of frozen section results were indeed malignant. Specificity of 66.7% stated that all benign diagnoses made from pathology anatomy examination, 66.7% of frozen section were indeed benign. Positive predictive value of 87.5% dictated that of malignant frozen section results, 87.5% were pathology - anatomically malignant. On the other side negative predictive value of 50% concluded that of all benign frozen section diagnoses, 50% were indeed benign when pathology anatomy examination was conducted. This stems from non - epithelial ovarian tumor that has wide spectrum. Therefore, potentially hinders frozen section examination process. Conservative surgery has role in non - epithelial type ovarian tumor because of lower progressivity, even when frozen section result stated otherwise.

### 3.5 Analysis of Frozen Section Accuracy in Diagnosing Borderline Type Ovarian Cancer

Accuracy analysis of frozen section as means of borderline type ovarian cancer diagnostic tool is shown as table below:

**Table 3.5:** Accuracy of Frozen Section in Diagnosing Borderline Type Ovarian Cancer

		Histopathology		
		Malignant	Benign	Total
FZ	Malignant	6	1	7
	Benign	1	1	2
	Total	7	2	9

Sensitivity: 85.7%

Specificity: 50.9%

Positive predictive value: 85.7%

Negative predictive value: 50%

Accuracy: 77.7%

According to Table 3.5. frozen section accuracy as diagnostic tool in determining borderline type ovarian cancer was 77.7%. There were 7 cases of borderline type ovarian cancer that had malignant histopathology features. Both an under - diagnosed and over diagnosed cases occurred on frozen section examination. Therefore, frozen section as a diagnostic test on this type of ovarian tumor had sensitivity rate of 85.7% which meant from all malignant diagnoses made during pathology anatomy examination, 85.7% of frozen section were indeed malignant. Specificity of 50.9% stated from all benign pathology anatomy, 50.9% of frozen section were indeed benign. Positive predictive value of 85.7% concluded that of all malignant diagnoses made during frozen section examination, 85.7% of pathology anatomy has similar results. Zero percent result of negative predictive value happened because there was only 1 under diagnosed case and few borderline cases.

## 4. Conclusions

Taken from the research's results therefore it can be concluded that:

- 1) Frozen section accuracy as means of ovarian cancer case diagnosis in Sanglah General Hospital Denpasar was 90.8%.
- 2) Frozen section sensitivity as means of ovarian cancer case diagnosis in Sanglah General Hospital Denpasar was 91.4%.
- 3) Frozen section specificity as means of ovarian cancer case diagnosis in Sanglah General Hospital Denpasar was 86.7%.
- 4) Positive predictive value of frozen section as means of ovarian cancer case diagnosis in Sanglah General Hospital Denpasar was 92.9%.
- 5) Negative predictive value of frozen section as means of ovarian cancer case diagnosis in Sanglah General Hospital Denpasar was 83.8%.

## 5. Future Scope

Frozen section currently cannot be utilized as a single modality in diagnosing ovarian cancer. Further study is advised to verify the accuracy of frozen section in

conjunction with other tumor markers. Therefore, multivariate model can be achieved in ovarian cancer diagnosis.

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