

## ORIGINAL RESEARCH

# The role of intraoperative consultation in the management of ovarian masses and endometrial carcinomas: a 7-year experience

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**Abstract**

Intraoperative consultation (IC) is often used for surgical planning in gynecological oncology, primarily in ovarian and endometrial cancer surgery. However, there is limited research that compares IC diagnoses and results from definitive analyses. This retrospective study compares IC results and definitive analysis findings in terms of ovarian mass diagnoses and endometrial carcinoma patients consulted for myometrial invasion (MI) depth across 7 years (2012–2019). IC was performed in 282 cases to evaluate ovarian masses. The sensitivity of IC was 94% for benign ovarian masses and 90% for malignant ovarian masses. 92 cases were submitted to IC for endometrial carcinoma. Sensitivity was 80% for tumors with <50% MI and 74% for tumors with ≥50% MI. IC is an important method with high sensitivity and specificity for diagnosing ovarian masses and determining MI depth in endometrial carcinomas.

**Keywords**

Frozen section; Intraoperative consultation; Endometrial carcinoma; Ovarian masses

## 1. Introduction

Intraoperative consultation (IC) is often used for surgical planning in gynecologic oncology. However, researchers have not discussed the use of IC in gynecological surgery to the same extent as in other surgical fields. In gynecological surgery practice, IC is most frequently used in ovarian mass surgery and endometrial carcinoma staging, followed by cervical carcinoma operations. The aim is to appropriately manage the operation by making an accurate diagnosis and swiftly determining the extent of disease spread. In this process, the surgeon and the pathologist should consider the limitations of IC as well as its effectiveness.

Determining the histological type of a tumor and deciding whether the mass is benign, malignant, or borderline are critical for treatment planning in patients with ovarian tumors. Preoperative imaging techniques and tumor marker levels in serum offer limited efficiency in differential diagnosis. For this reason, IC is widely used to determine a course of action during the operation in ovarian mass surgery [1]. IC allows to determine the histological nature of the mass to swiftly inform the surgeon whether the mass is benign, malignant, or borderline. Therefore, both the promptness and the accuracy of IC are critically important. In the literature, the sensitivity and specificity of IC have been reported in the ranges of 65–97% and 97–100% [2, 3]. Large masses and mucinous and borderline tumors are some of the factors that unfavorably affect the accuracy of IC diagnosis [2].

On the other hand, in endometrial cancers (EC), IC informs the surgeon about the tumor grade, histological type, tumor diameter, myometrial invasion (MI) depth and whether there is a cervical invasion. The histological type and the grade of the tumor are usually reported through the examination of preoperative diagnostic curettage specimen. However, tumor diameter, MI depth and whether there is a cervical invasion are examined during IC. Depending on the results, surgeons can decide whether to perform lymph node dissection additional to total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH + BSO). In many current guidelines on ECs, IC is replaced by algorithms based on sentinel lymph node procedure. Still, IC remains a viable option for patients with no hemi-pelvic mapping, as lymph node dissection may be omitted in these patients according to the result of intraoperative pathological evaluation, as stated in the latest NCCN guideline on uterine neoplasms [4]. The accuracy of IC in EC is reported as 68–95% for tumor grade and 72–95% for MI depth [2].

Given that IC is critical in determining the course of action during surgery for both ovarian masses and EC, the accuracy and positive/negative predictive value of IC gains great significance. Here, we discussed the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of IC in comparison with frozen section and paraffin section reports for patients who underwent IC in our institution due to ovarian masses and EC across 7 years.

## 2. Material and methods

We retrospectively analyzed the IC reports and frozen section and paraffin section examinations of specimens studied in a pathology laboratory for ovarian masses and EC from 2012 to 2019. We used the hospital information system to retrieve the patients' demographic and clinical data and pathology reports.

### 2.1 Ovarian masses

The oophorectomy or/and hysterectomy materials of the patients operated on for ovarian masses were freshly sent to the laboratory. The measurements of samples that were sent macroscopically were recorded and capsule integrity was evaluated. Surgical margins were stained and opened properly. Changes in the cross-sectional surface of the mass (solid, cystic, hemorrhagic, necrotic, *etc.*) were recorded and 1–3 samples were taken from different areas and frozen in a cryostat. 4–5-micrometer sections were taken, and routine *hematoxylin-eosin* (H&E) staining was performed. The operation team was informed by telephone after all sections were examined by the responsible pathologist under a light microscope. Frozen section diagnosis was reported as “benign”, “malignant”, “at least borderline”, “at most borderline” or “deferred until paraffin section examination”. During statistical calculation, cases reported as “at least borderline” were included in the malign category, while those reported as “at most borderline” were included in the benign category. The specimens were frozen in 10% formaldehyde overnight and then the next day, at least 1 sample was taken per centimeter of mass. These were examined under a light microscope to make a definitive report after routine tissue follow-up and H&E staining. We considered the diagnoses in definitive reports as gold standard and compared them to frozen section diagnoses as the gold standard.

We categorized the frozen section examination results of 282 cases into three groups: benign, malignant or deferred until paraffin section diagnosis. The sensitivity, specificity, PPV, NPV and accuracy of IC were calculated separately in each group. In this calculation, the definitive report after paraffin section examination was considered the gold standard.

### 2.2 Endometrial carcinomas

Hysterectomy of patients diagnosed with endometrial hyperplasia or EC was freshly sent to the laboratory for frozen section examination. The uterus was cut from both lateral walls and divided into two wings after measuring the specimen macroscopically and staining the surgical margins. The total measurements of the anterior and/or posterior mass were recorded in a carpet-like fashion; in the presence of a mass in the endometrial cavity, the largest dimension of the tumor was noted as tumor diameter. After opening the cavity, transverse parallel incisions were performed at 2–3 mm intervals from the anterior and posterior fundus to the beginning of the endocervical canal. Each slice was examined; 1–2 samples were taken from the area where the tumor was thought to show the deepest MI, and these were frozen in a cryostat. 4–5 micron sections taken from frozen samples were evaluated under a light microscope by the responsible pathologist after

rapid H&E staining. In most cases, the aim was to inform the operation team about tumor diameter and grade, cervical invasion status and MI depth intraoperatively. However, since tumor diameter and MI depth were fully available in all cases (other parameter data was missing), we only analyzed these data.

We investigated the MI status of 97 patients who underwent IC and were operated on for benign conditions, hyperplasia or an EC diagnosis. We excluded 5 cases that required frozen section examinations for benign causes. The remaining 92 cases were divided into four groups: MI <50%, MI ≥50%, no tumor observed, and deferred until paraffin section diagnosis. Cases where MI depth could not be precisely determined through frozen examinations were deferred until paraffin section examinations. The sensitivity, specificity, PPV, NPV and accuracy of IC were calculated separately for each group.

The frozen sections were examined separately by 8 pathologists, only 2 of whom specialized in gynecology.

### 2.3 Statistical analysis

The sensitivity, specificity, PPV, NPV and accuracy of ovarian data were studied separately under three groups: benign, malignant and deferred until paraffin section examination. We used definitive diagnoses (results of paraffin section examinations) as gold standard and created 2 × 2 contingency tables. For benign tumors, true positive data consisted of tumors that were diagnosed as benign in frozen section examinations; false negative data included those that were diagnosed as malign and/or were deferred until paraffin section examination. For malign tumors, true positive data contained those that were diagnosed as malign in frozen section examinations; false negative data consisted of those that were diagnosed as benign and/or were deferred until paraffin section examination. Tumors that were deferred until paraffin section diagnosis after frozen section examinations are shown separately in the table ahead, along with their definitive diagnoses (after paraffin examinations).

The sensitivity, specificity, PPV, NPV and accuracy of endometrium data were studied separately under four groups: MI <50%, MI ≥50%, no gross tumor, and deferred until paraffin section examination. Again, we used definitive diagnoses as gold standard and created 2 × 2 contingency tables. For MI results, true positive data included tumors with matching MI findings in frozen section examinations (either MI <50% or MI ≥50%) and the others were considered false negative. Likewise, gross tumor findings were deemed true positive only for cases with matching frozen section results; the rest were deemed false negative. Again, tumors that were deferred until paraffin diagnosis after frozen analyses are given separately, along with definitive diagnoses.

We present the data in frequencies and percentages. We used dummy coding to demonstrate the presence/absence of disease in ovarian and endometrium data (0 means absence of disease for frozen and definitive diagnoses; 1 refers to presence of disease). The 2 × 2 contingency tables were created using SPSS (V28, IBM Corp, Armonk, NY, USA).

### 3. Results

#### 3.1 Ovarian masses

IC was performed in 282 cases to evaluate ovarian masses. The mean age of the cases was  $49.4 \pm 15.36$  years. Bilateral ovarian masses were present in 28 (9.9%) cases.

The result of IC was a benign tumor in 210 cases. Paraffin section reports diagnosed 221 cases as benign. In IC, 59 cases were diagnosed as malignant. The definitive diagnoses of these cases were deferred until paraffin section examinations, which revealed a malignant diagnosis in 4 and a benign tumor in 9 (Table 1).

Table 2 below shows the definitive diagnoses of cases that were deferred until paraffin examinations after frozen section analyses.

Table 3 shows the sensitivity, specificity, PPV, NPV and accuracy of IC for the benign and malignant categories.

**TABLE 1. Correlation between IC results and paraffin section diagnoses in ovarian masses.**

| IC        | Paraffin Section Diagnoses |            |           |
|-----------|----------------------------|------------|-----------|
|           | Benign (n)                 | Malign (n) | Total (n) |
| Benign    | 208                        | 2          | 210       |
| Malign    | 4                          | 55         | 59        |
| Deferred  | 9                          | 4          | 13        |
| Total (n) | 221                        | 61         | 282       |

IC: Intraoperative consultation.

**TABLE 2. Cases that were deferred until paraffin examinations and possible causes of error.**

| Paraffin Diagnosis                    | n       | Cause  |
|---------------------------------------|---------|--|
|                                       |         | Nonrepresentative sample                                 |
| Teratoma (mature/immature)            | 4 (3/1) | Foci of immature areas not sampled during frozen section |
|                                       |         | Nonrepresentative due tumor size                         |
| Mucinous neoplasia (benign-malignant) | 3 (2/1) | Tumor size: 200–300 mm                                   |
| Serous neoplasia (benign-borderline)  | 6 (4/2) | Nonrepresentative due tumor size and torsion             |
| Total                                 | 13      |  |

**TABLE 3. Sensitivity, specificity, PPV, NPV and accuracy of IC for ovarian masses.**

|             | Benign | Malign |
|-------------|--------|--------|
| Sensitivity | 94.0%  | 90.0%  |
| Specificity | 97.0%  | 98.0%  |
| PPV         | 99.0%  | 93.0%  |
| NPV         | 82.0%  | 97.0%  |
| Accuracy    | 95.0%  | 96.0%  |

#### 3.2 Endometrial carcinomas

92 cases were submitted to IC. The mean age of the cases was  $60.27 \pm 9.85$  years. 86 cases underwent total abdominal hysterectomy plus bilaterally salpingo-oophorectomy.

According to the IC results, 51 cases had  $<50\%$  MI depth, 21 cases had  $\geq 50\%$  MI depth, and 13 cases displayed no macroscopic tumors (Table 4).

Of 13 cases that did not exhibit tumors on frozen examination, 6 were diagnosed with atypical hyperplasia. These cases were sent for IC and no tumors were found on paraffin sections. Six cases demonstrated endometrial carcinoma on preoperative curettage materials, no gross mass on frozen section investigations, and microscopic ( $<1$  cm) carcinoma foci on definitive analyses. The remaining case required frozen section examinations to investigate for tumors in the endometrial cavity due to ovarian granulosa cell tumor, however, no macroscopic or microscopic carcinoma was observed.

Table 5 shows the sensitivity, specificity, PPV, NPV and accuracy of IC for MI depth.

**TABLE 4. Comparison between IC results and paraffin section diagnoses in EC cases.**

|                      | IC (n) | Paraffin section (n) |
|----------------------|--------|----------------------|
| MI depth $<50\%$     | 51     | 56                   |
| MI depth $\geq 50\%$ | 21     | 27                   |
| No tumor observed    | 13     | 9                    |
| Total                | 85*    | 92                   |

\*7 cases were deferred until paraffin section examinations.

IC: Intraoperative consultation; MI: myometrial invasion.

**TABLE 5. Sensitivity, specificity, PPV, NPV and accuracy of IC in determining myometrial invasion depth in endometrial carcinoma.**

|             | MI depth $<50\%$ | MI depth $\geq 50\%$ | No tumor observed |
|-------------|------------------|----------------------|-------------------|
| Sensitivity | 80.0%            | 74.0%                | 78.0%             |
| Specificity | 83.0%            | 98.0%                | 93.0%             |
| PPV         | 88.0%            | 95.0%                | 54.0%             |
| NPV         | 73.0%            | 90.0%                | 97.0%             |
| Accuracy    | 81.0%            | 91.0%                | 91.0%             |

MI: myometrial invasion; PPV: positive predictive value; NPV: negative predictive value.

### 4. Discussion

#### 4.1 Ovarian masses

IC is mostly used in ovarian mass operations in gynecological oncology. Besides preoperative imaging methods, intraoperative determination of the characteristics of an ovarian mass, whether benign, borderline or malignant, is critical for the surgeon to perform optimal surgery on the patient.

Determination of the histologic type and malignancy po-

tential of the mass is important for accurate and adequate surgical intervention, for which preoperative biochemical and radiological methods are not always sufficient. Therefore, IC is very important in directing the operation in such cases. However, overdiagnosis or underdiagnosis that can be in IC could cause patients to be exposed to excessive surgery or lead to tumor spread due to insufficient surgery [5, 6].

Diagnosis of benign and malignant tumors by frozen section analysis is largely compatible with paraffin section examinations [6–12]. This is mainly because the malignancy criteria (such as nuclear atypia, pleomorphism, stromal invasion, *etc.*) can be easily distinguished on frozen sections [6]. In the present study, we found that IC had a sensitivity of 94% for benign tumors and 90% for malignant tumors, and a PPV of 99% for benign tumors and 93% for malignant tumors. Gol *et al.* [7] investigated 22 cases and reported a sensitivity of 95.2% for benign tumors and 96.5% for malignant tumors (Table 6). IC can contribute significantly to determining the malignant or benign nature of ovarian tumors.

**TABLE 6. Sensitivity of IC in ovarian tumors in the literature.**

| Author                              | Year | Benign (%) | Malign (%) |
|-------------------------------------|------|------------|------------|
| Gol <i>et al.</i> [7]               | 2003 | 98.0       | 88.7       |
| Yarandi <i>et al.</i> [9]           | 2008 | 97.4       | 91.6       |
| Sukumaran <i>et al.</i> [10]        | 2014 | 99.2       | 82.9       |
| Acikalin <i>et al.</i> [20]         | 2014 | 97.5       | 95.6       |
| Morton <i>et al.</i> [21]           | 2017 | 100.0      | 75.9       |
| Aidos <i>et al.</i> [2]             | 2018 | 100.0      | 96.9       |
| Kung <i>et al.</i> [11]             | 2019 | 100.0      | 81.3       |
| Palakkan <i>et al.</i> [8]          | 2020 | 93.0       | 85.0       |
| Sahin <i>et al.</i> (current study) |      | 94.0       | 90.0       |

The most important causes of diagnostic problems in frozen sections besides borderline tumors are mucinous morphology and large tumor diameter [13, 14]. Houck *et al.* [15] report that there may be more misdiagnosis in cases confined to the ovary with non-serous histology and a tumor greater than 20 cm in size. Song *et al.* [16] emphasize the factors that may cause errors in frozen examinations of borderline tumors of the ovary (BOT) as mucinous histology, unilaterality and tumor size larger than 15 cm. Studies show that large tumor size negatively influences the accuracy of frozen section diagnosis [17]. In the present research, 3 of the cases that were deferred until paraffin examination demonstrated mucinous tumors over 20 cm in diameter. Cases where the tumor diameter is greater than 10 cm can entail false negative or false positive results due to the limited number of samples that can be taken during frozen sampling [18]. Intratumoral heterogeneity of tumors in mucinous morphology makes diagnosis very difficult when combined with frozen cross-sectional artefacts [13, 18]. Similarly, heterogeneity of tumors in teratomas and the limited number of samples taken during frozen sampling lead to an inability to detect immature components. Besides, 1 of the 6 serous neoplasia cases that were deferred until paraffin ex-

aminations demonstrated diagnostic difficulties due to torsion. For the remaining 5 cases, the diameter of the tumor made the sample less likely to represent the diagnostic region. Still, there is no clear data in the literature regarding an optimal number of samples for correct diagnosis on frozen examination. Tempfer *et al.* [19] recommend taking multiple sections for tumors larger than 5 cm in diameter, while highlighting that frozen examination may not always be the right option in large tumors.

## 4.2 Endometrial carcinoma

Surgical staging of EC is important in determining the prognosis and the need for postoperative adjuvant chemotherapy [22]. For surgical staging and planning the correct treatment procedure, tumor diameter, tumor grade, histological type, cervical invasion status, and MI depth should be known (also known as the Mayo Clinic criteria). Of these parameters, preoperative imaging methods provide information about tumor size and partly about the status of cervical and myometrial invasion [22, 23]. Similarly, information about the histological type and grade of the tumor can be obtained by examining preoperative diagnostic curettage specimen. In our hospital, preoperative diagnostic curettage is performed on patients with suspected EC. The histological type and International Federation of Obstetrics and Gynecology (FIGO) grade of the tumor are determined by examining curettage material and included in the pathology report. Therefore, we could not include the histologic tumor grades of the cases in this research.

MI depth may be the most important parameter in EC staging, because it is considered predictive for lymph node metastases [24, 25]. In many current guidelines on ECs, IC is replaced by algorithms based on sentinel lymph node procedure. However, IC remains a viable option for patients with no mapping on a hemi-pelvis, as lymph node dissection may be omitted in these patients according to the result of IC, as stated in the latest The National Comprehensive Cancer Network (NCCN) guideline on uterine neoplasms [4]. MI depth allows to identify high-risk EC patients [24, 25].

Kumar *et al.* [27] reported a 98.9% concordance between frozen section and paraffin examinations in determining MI depth, while Aidos *et al.* [2] reported an accuracy of 94.8%. The sensitivity and specificity values reported by different researchers for determining MI depth *via* IC have been highly variable, ranging from 65% to 98.7% [22, 26–28]. Acikalin *et al.* [22] reported a sensitivity of 86%, specificity of 98%, PPV of 92% and NPV of 96%. In the present research, the sensitivity and specificity of IC were calculated separately for cases with MI <50% and MI ≥50%. Accordingly, we found a sensitivity of 80% in tumors with MI <50% and 74% in tumors with MI ≥50%.

Of 13 cases that showed no macroscopic tumors in the endometrial cavity, 6 revealed microscopic tumor foci. Although, the 6 cases that required frozen examination due to atypical hyperplasia did not demonstrate gross or microscopic tumors in the endometrial cavity. Based on this information, the absence of a gross tumor mass in the endometrial cavity and the tumor heterogeneity in atypical hyperplasia with carcinoma foci may cause misleading findings on frozen analyses [29].



Other potential causes of error include serous intraepithelial carcinomas and the serous morphology of the tumor, which occurred in two of our cases with a reported absence of tumor and endometrial polyp on frozen examination. However, one of these cases showed areas of serous intraepithelial carcinoma on polyp surface in paraffin sections. This case was overlooked due to misinterpretation, despite the presence of atypia in the areas of serous intraepithelial carcinoma. Another case similarly contained invasion in an area adjacent to the intraepithelial serous areas, though it was overlooked due to misinterpretation and limited sample in frozen sections. Besides, research reports that areas of adenomyosis can be mistakenly interpreted as MI, although we did not encounter such a problem [22].

A wide range of accuracy rates for IC (65 to 98.7%) have made it controversial to perform a frozen examination in surgical operations to determine low-risk and high-risk EC cases [23, 30]. Minimizing technical artefacts (such as freezing artefacts, thick sections, *etc.*) during IC, establishing a good communication network between the surgeon and the pathologist for sampling from the appropriate area, and ensuring definitive evaluation by an experienced pathologist or even a gynecopathology specialist, if possible, will increase the compatibility between frozen section results and definitive diagnosis [31].

## 5. Conclusions

In gynecologic oncology surgery, intraoperative consultation is often used to avoid overtreatment and undertreatment. We report that intraoperative consultation offers high sensitivity and specificity in determining the benign or malignant potential in ovarian masses. We conclude that ovarian tumors over 20 cm in diameter (mucinous or serous) cause a greater likelihood of sampling errors and a lesser possibility of sampling from the correct area, thus being the most important factor for erroneous diagnoses. Regardless of tumor size, sampling errors constitute another reason for misdiagnosis. Nevertheless, a frozen section examination before the operation would be appropriate for ovarian masses with unknown malignant potential.

Similarly, when myometrial invasion depth cannot be fully evaluated through preoperative imaging methods, frozen section examinations can help avoid unnecessary treatment in endometrial carcinomas. Still, it should be noted that both evaluation methods have their limitations (*e.g.*, mucinous ovarian masses and endometrial tumors with intraepithelial serous morphology).

## AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

## AUTHOR CONTRIBUTIONS

NS, ZG and DSA—designed the research study. NS and BCT—performed the research. NS, GC and OT—analyzed the

data. NS and GK—wrote the manuscript. All authors read and approved the final manuscript.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by our Institutional Review Board, with reference 54022451-050.05.04.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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