

## CASE REPORT

# Comments on the definition of ovarian cancer stage IC2, related to fertility-sparing treatment

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**Abstract**

Fertility preservation is a significant concern in young patients with ovarian cancer due to its impact on the quality of life. Fertility-sparing surgery (FSS) in patients with epithelial ovarian cancer (EOC) should be reserved for those with stage IA disease. This article presents a patient diagnosed with stage IC2 endometrioid adenocarcinoma of the ovary who underwent FSS, subsequently became pregnant, and delivered a healthy baby. The favorable disease progression suggests a less aggressive nature, raising questions about the clarity of the International Federation of Gynecology and Obstetrics (FIGO) definition for stage IC2, specifically regarding the distinction between the presence of a tumor and the presence of invasive tumor on the ovarian surface. The clinical significance of differentiating between the presence and absence of invasive tumor on the ovarian surface requires further investigation. If deemed important, recognizing the absence of invasive tumor on the ovarian surface may lead to the classification of more cases as stages lower than IC, consequently increasing the utilization of fertility-sparing procedures.

**Keywords**

Ovarian cancer; Fertility-sparing surgery; FIGO classification of ovarian cancer

## 1. Background

Ovarian cancer is the leading cause of death among the gynecological cancers, mainly due to the absence of effective screening methods and advanced disease at the diagnosis. While accounting for 4% of all new female cancer diagnoses, about 8–12% of ovarian cancers occur in women younger than 40 years of age [1, 2].

Approximately 19% of ovarian cancer patients are classified as localized disease (early epithelial ovarian cancer (EOC)), with five-year relative survival rates over 90% [3].

As the standard treatment for ovarian cancer implies removal of the internal genital organs with or without systemic treatment, these definitively affect reproductive function in younger women. While fertility-preservation management is a current issue in these patients, adequate diagnosis of the clinical stage of the disease is critical.

## 2. Case presentation

A 32-year-old patient presented at a fertility clinic due to infertility concerns. During a routine ultrasound, a complex cyst was detected on the right ovary. Further evaluation through pelvic Magnetic Resonance Imaging (MRI) revealed a predominantly solid structure with high vascularity, measuring 24/30/35 mm, suggesting a potential neoplastic lesion. No other abnormalities were observed in the imaging scans.

The patient's serum markers showed slight elevation (Risk of Ovarian Malignancy Algorithm (ROMA) score = 12.43% (Human Epididymis Protein 4 (HE4) = 63.1 pmol/L; Cancer Antigen 125 (CA-125) = 18.8 U/mL; Carcinoembryonic Antigen (CEA) = 2.03 ng/mL).

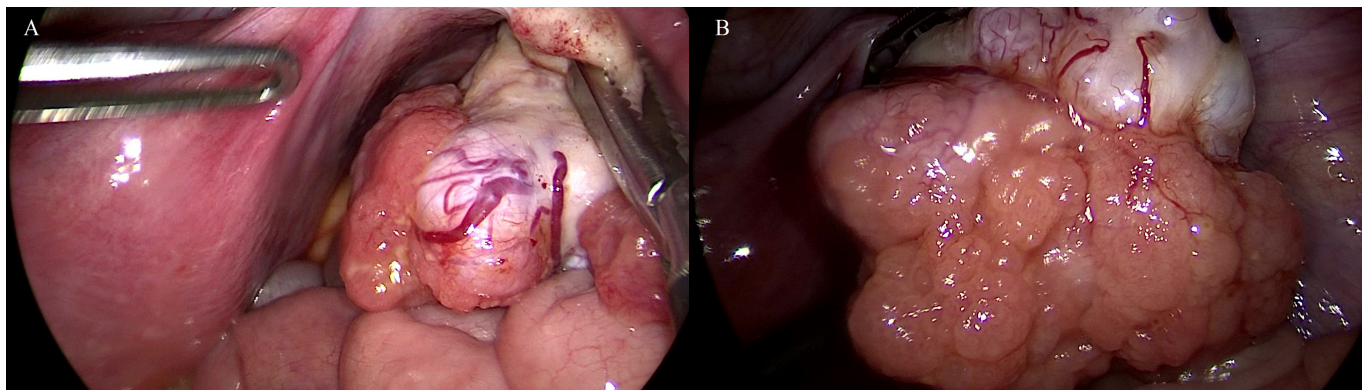
Subsequently, a laparoscopy was performed, revealing a tumoral right ovary with visible vegetations on the surface. The tumor was initially suspected to be a borderline tumor. The affected area of the right ovary was surgically removed without attempting to locate the cyst capsule (Fig. 1).

The frozen section analysis indicated a borderline mucinous cystadenoma with endometriotic foci. Peritoneal washing yielded negative results for tumoral cells.

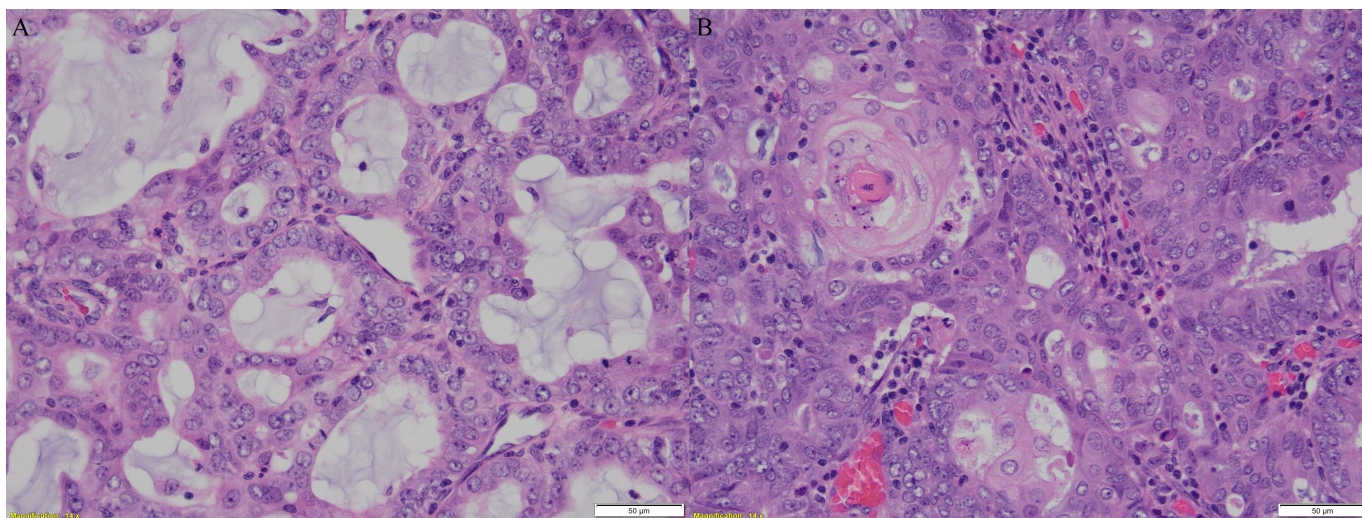
However, the final pathological report unexpectedly revealed an endometrioid adenocarcinoma G1, with an invasion depth of more than 5 mm, superimposed on an endometrioid borderline tumor (Figs. 2,3). No lymphovascular or perineural invasion was identified. Immunohistochemistry (IHC) performed at two different centers revealed Estrogen Receptor (ER)—60%, Progesterone Receptor (PR)—80%, p53—25%, Ki67—30%, *MutS homolog 6 (MSH6)* positive, *MutL homolog 1 (MLH1)* positive, *MutS homolog 2 (MSH2)* positive, and *Post-meiotic segregation increased 2 (PMS2)* positive, indicating the absence of microsatellite instability.

The patient was staged as pT1c2 pNx pMx. The oncological board recommended completion of the surgery followed by systemic treatment. However, the patient sought a second

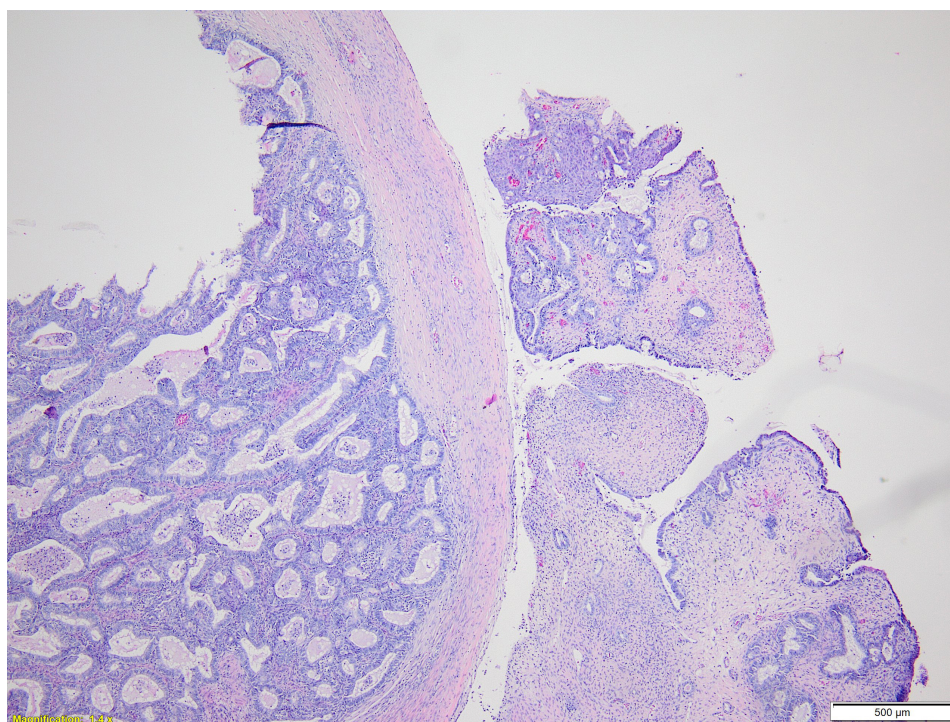




**FIGURE 1. Intraoperative images of the right ovary.** (A) Image of the tumoral right ovary with obvious vegetations on the surface. (B) Close-up of the tumoral right ovary. Frozen section: borderline mucinous cystadenoma, with endometriotic foci.



**FIGURE 2. Pathology images of the ovarian tumor.** (A,B) Endometrioid adenocarcinoma G1 with foci of squamous differentiation, with invasion >5 mm, no lymphovascular or perineural invasion.



**FIGURE 3. Endometrioid adenocarcinoma G1, with vegetations on surface displaying endometrioid borderline tumor.**



opinion from a different tumor board, which was delayed due to the Covid-19 pandemic.

During this time, the patient unexpectedly became pregnant. Despite seeking opinions from various tumor boards, no consensus was reached among the oncological board regarding the appropriate course of treatment for the pregnant patient, specifically regarding the use of chemotherapy. Consequently, the patient expressed her desire to abstain from any treatment during her pregnancy. The pregnancy progressed without complications.

Under the conditions where there is no specific protocol for monitoring pregnancies achieved after ovarian cancer treatment, a simultaneous monitoring scheme for both pregnancy and ovarian disease has been proposed. Obstetrical monitoring was conducted according to usual protocols. Since visualizing the ovaries through transvaginal ultrasound is not possible during pregnancy due to the ascending uterine fundus, and the availability of MRI for pregnant patients is limited, ultrasound evaluation of the presence of fluid in the Douglas pouch was proposed as a marker for ovarian tumor recurrence, along with monitoring of serum markers (CA-125 and HE-4). No fluid presence was visualized in any evaluation of the Douglas pouch (Fig. 4), and the serum markers were consistently normal.

In addition, for this patient a pelvic MRI was available at 17 weeks of gestation, showing no abnormal findings.

At 39 weeks of gestation, the patient successfully delivered a healthy baby boy weighing 3380 grams through vaginal delivery. Five days postpartum, the patient underwent a laparoscopy, which included a comprehensive exploration of the peritoneal cavity, peritoneal washing, right adnexectomy, biopsy of the left ovary, infracolic omentectomy, bilateral pelvic lymphadenectomy, and resection of the peritoneum in the Douglas pouch area (Fig. 5). The pathology report revealed no evidence of disease.

During the follow-up period, the medical team recommended performing a hysterectomy and left adnexectomy as a completion of the surgical treatment. However, the patient chose not to go through with these procedures. Two years after the initial diagnosis and eleven months after giving birth, the patient remains disease-free, as confirmed by negative imaging results and tumor markers.

Table 1 shows a clear timeline of the patient's evolution.

### 3. Discussions

The preservation of fertility in young ovarian cancer patients is a complex issue that has not yet been fully resolved, as it lacks extensive prospective randomized trials and cohort studies. However, retrospective data from individual institutions are available [4–6].

Fertility-sparing surgery (FSS) for ovarian cancer involves preserving the uterus and at least one ovary during the surgical procedure, followed by any appropriate chemotherapy regimen, without the need for adjuvant pelvic radiation therapy [7]. The primary concern associated with FSS is the risk of recurrence and overall survival. It has been suggested that FSS in patients with epithelial ovarian cancer should be limited to stages IA–IC [8].

In a study conducted by Morice *et al.* [9], involving 34 patients with stage IA–IIA epithelial ovarian cancer who underwent fertility-sparing treatment along with platinum-based chemotherapy for stages  $\geq$ IC, 10 recurrences were reported. All recurrences, except one, occurred in patients with stage IAG1 disease or higher, and all patients with stages  $\geq$ IC experienced invasive recurrences. This led the authors to conclude that FSS should be restricted to young patients with stage IA disease. Notably, all patients with stages  $\geq$ IC developed invasive recurrences in this study.

Similarly, Gaughran *et al.* [10] conducted a study involving 36 patients and found a significant correlation between fertility-sparing surgery (FSS) and higher mortality rates for disease stage  $>1A$  ( $p = 0.02$ ) and tumor grade  $>1$  ( $p = 0.02$ ). Disease recurrence was associated with disease stage  $>1A$  ( $p = 0.07$ ) and the use of *in vitro* fertilization (IVF) ( $p = 0.03$ ).

Out of the 17 patients (47%) who attempted to conceive after FSS, 10 (59%) successfully had at least one live birth. Interestingly, none of the patients who conceived died, but one experienced disease recurrence. This observation likely reflects the less aggressive nature of the tumor.

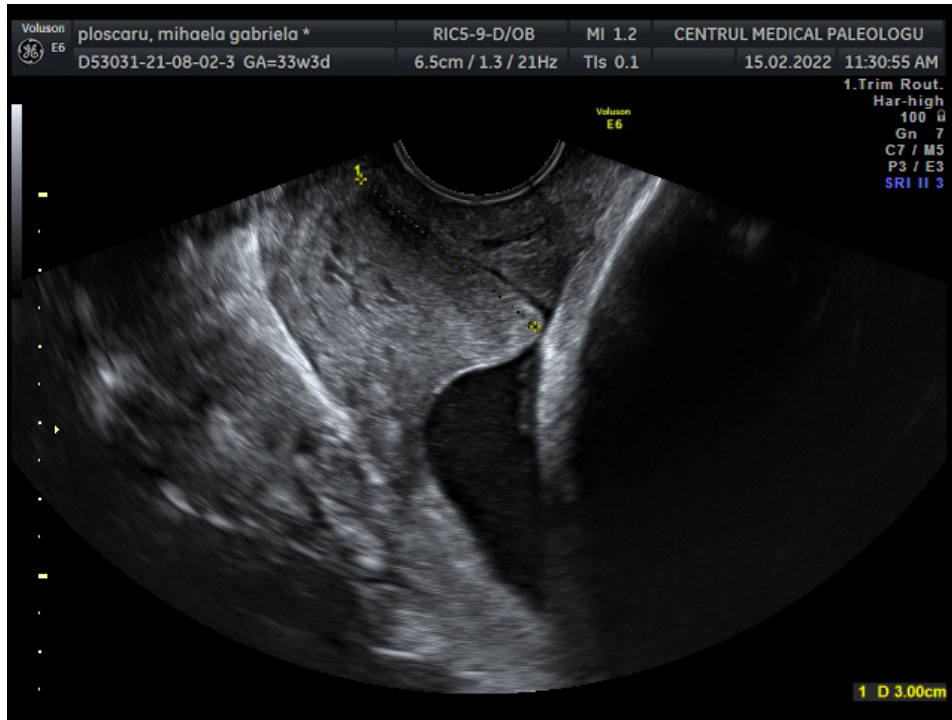
Accurate classification of stage I requires comprehensive surgical staging. Although the International Federation of Gynecology and Obstetrics (FIGO) staging criteria determine the allocation of different stages, distinguishing between FIGO stage IA and FIGO stage IC can sometimes be challenging.

While the literature suggests that stage IA ovarian cancer is likely the only stage suitable for FSS, assigning a case to this stage can be difficult at times. In the aforementioned case, it was classified as stage IC2 due to the evident presence of tumor on the ovarian surface (Fig. 1). However, pathological examination did not demonstrate invasive cancer on the ovarian surface. The case's progression, including a spontaneous pregnancy followed by a vaginal delivery at term, and the absence of residual disease during laparoscopic staging surgery performed 10 months after the primary surgery, indicates a less aggressive disease, possibly reflecting an earlier stage.

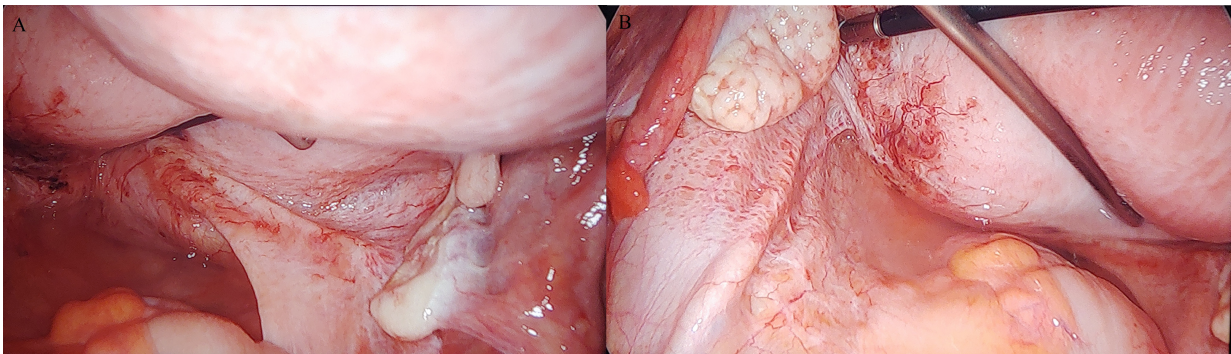
The explanatory notes of the "Protocol for the Examination of Specimens from Patients with Primary Tumors of the Ovary, Fallopian Tube, or Peritoneum" [11], issued by the College of American Pathologists, state that involvement of the ovarian surface is a significant element for staging and treatment decisions. It is acknowledged that even very small areas of involvement on the ovarian surface have the potential to be lethal. However, it is not explicitly stated whether involvement of the ovarian surface should be associated with invasive or borderline tumor. For instance, regarding sampling considerations for borderline serous/mucinous tumors with micropapillary foci or microinvasion, the notes emphasize the need for adequate documentation of the extent of invasion and its relationship with the surface.

The neighboring stages of IC2 ovarian cancer assume the interaction between malignant cells from the invasive region and the external environment of the ovary, either through surgical spillage (stage IC1) or the detection of malignant cells in ascites or peritoneal washings (stage IC3). Consequently, it is reasonable to expect a similar interaction for stage IC2, where the tumor is present on the ovarian surface and invasive.

In light of this, one may question whether the presented case



**FIGURE 4.** Absence of the fluid in Douglas pouch on vaginal ultrasound evaluation of the cervical length.



**FIGURE 5. Intraoperative images of second-look laparoscopy.** (A,B) In the fifth postpartum day, laparoscopy was performed. The remaining right ovary looked macroscopically normal; however, right adnexectomy and resection of the peritoneum of Douglas pouch were performed, demonstrating the absence of the disease.

should be downgraded to stage IA grade. The visible tumor on the surface of the right ovary is actually an endometrioid borderline tumor without invasiveness (see Fig. 3). There is no contact between malignant cells from the invasive area and the ovarian surface. It is already known that for borderline ovarian tumors, invasive implants behave like carcinomas and are likely metastatic (associated with a 66% survival rate), while non-invasive implants exhibit a benign behavior (associated with a 95% survival rate) [12]. In the presented case, the presence of a non-invasive borderline tumor on the ovarian surface can be likened to a non-invasive implant, while the invasive tumor remains confined within the interior of the ovary.

#### 4. Conclusions

Based on the findings, fertility-sparing surgery appears to be a viable option for patients with epithelial ovarian cancer who

are limited to stages IA–IC.

For stage IC2, it may be beneficial to have a clear distinction in the FIGO classification that specifically mentions the presence of invasive tumor on the ovarian surface, rather than simply the presence of a tumor.

Currently, there is a lack of detailed definitions to differentiate between invasive carcinoma, non-invasive carcinoma, and borderline tumor in ovarian cancer staging. This case serves as a starting point for discussing and establishing a precise definition for staging invasive carcinoma and borderline tumors, particularly in relation to fertility-sparing surgery.

The clinical significance of distinguishing between the presence and absence of invasive tumor on the surface of the ovary needs further investigation. If deemed important, the absence of invasive tumor on the ovary surface could lead to more cases being classified as stages lower than IC, thereby increasing the number of fertility-sparing procedures.



**TABLE 1. Follow-up of the case.**

Name of the event	Date	Months since pathology diagnosis	Results
Transvaginal ultrasound	12 April 2021	−2.5	Complex cyst of right ovary
Risk of Ovarian Malignancy Algorithm (ROMA) score	12 April 2021	−2.5	Elevated
Pelvic Magnetic Resonance Imaging (MRI)	29 April 2021	−2.0	Suspicious
Upper abdominal MRI	21 May 2021	−1.0	Normal
Thoracic x-ray			
Laparoscopy	08 June 2021	−0.5	Complex cyst of right ovary removal Frozen-section pathology report: Borderline mucinous cystadenoma, with endometriotic foci Peritoneal washing: Negative Endometrioid ovarian adenocarcinoma G1 Estrogen Receptor (ER) +; Pax8+; p53 = 25%; <i>Wilms Tumor (WT1)</i> negative; Ki67 = 30% ER = 60%; Progesterone Receptor (PR) = 80%; <i>MutS homolog 6 (MSH6)</i> +; <i>MutL homolog 1 (MLH1)</i> +; MSH 2+; <i>Post-meiotic segregation increased 2 (PMS2)</i> +; microsatellite stable profile pMMr
Definitive pathology report	23 June 2021	0	
Last menstrual period	26 June 2021		
Serum markers	13 July 2021	1.0	Normal
Tumor board	21 July 2021	1.0	Recommendation to complete surgery
Tumor board (second-opinion)	26 July 2021	1.0	Recommendation to observe
Pregnancy	02 August 2021 30 March 2022	1.5 9.0	5 W + 2 (Last Menstrual Period (LMP) = 26 June 2021) 39 W + 4 D
Pelvic, abdominal MRI	16 October 2021	4.0	16 W + 0 D; MRI—normal
Serum markers			Normal
Birth	30 March 2022	9.0	39 W + 4 D
Laparoscopy	05 April 2022	9.5	Ovarian tumor staging surgery—no residual tumor
Follow-up	13 May 2022	11.0–20.5	ROMA score—normal MRI—normal

**AVAILABILITY OF DATA AND MATERIALS**

The data are contained within this article.

**AUTHOR CONTRIBUTIONS**

NŞ and DC—designed the research study and performed the research. SAC and RMC—analyzed the data. NŞ—wrote the manuscript. All authors read and approved the final manuscript.

**ETHICS APPROVAL AND CONSENT TO PARTICIPATE**

This case report obtained the approval from the Local Ethics Committee of “Dr. Ion Cantacuzino” Clinical Hospital (approval #15/31.03.2023). Informed consent was obtained from the patient for the elaboration and publication of this article.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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