The Surgical Staging of Apparent Early-staged Ovarian Mucinous Carcinoma.

Zhen Yuan
Peking Union Medical College Hospital
Ying Zhang
Peking Union Medical College Hospital
Dongyan Cao (caodongyan@pumch.cn)
Peking Union Medical College Hospital https://orcid.org/0000-0003-4253-832X
Keng Shen
Peking Union Medical College Hospital
Jiaxin Yang
Peking Union Medical College Hospital
Mei Yu
Peking Union Medical College Hospital
Huimei Zhou
Peking Union Medical College Hospital
Tao Wang
Peking Union Medical College Hospital

Research Article

Keywords: ovarian mucinous carcinoma, staging surgery, upstaging

Posted Date: November 8th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1048262/v1

Abstract

Objectives: The study aimed to explore the rate of upstaging after surgical staging in patients with apparent International Federation of Gynecology and Obstetrics (FIGO) stage I ovarian mucinous carcinoma.

Methods: Ovarian mucinous carcinoma patients with surgical treatment were, retrospectively, reviewed in Peking Union Medical College Hospital between October 2020 and January 1994.

Results: Totally, 163 patients were included in this study, Surgical re-staging was performed in 89 patients after incomplete surgical staging and one-step surgical staging was performed in 74 patients. For these incompletely staged patients, residual tumors were found in 16 patients (16/89, 17.9%), For 19 patients with apparent FIGO stage IA, no patient was found to have residual tumor after incomplete staging surgery confirmed by the final pathology result of re-staging surgery. Both multipara (hazard ration [HR]= 6.532, 95% confidence interval [CI] = 1.416-30.137, P=0.016) and ovarian cystectomy (HR=8.269, 95% CI= 1.772-38.595, P=0.007) were independent risk factors for residual tumor after incomplete staging surgery. For all 163 patients, up-staging was found in 15 patients (15/163, 9.2%). For 44 apparent FIGO stage IA patients, no patient was found to up-stage to FIGO II-IVB. Moreover, both the history of ovarian mucinous tumor (HR=4.745, 95% CI= 1.132-19.886, P=0.033) and bilateral ovaries involved (HR=9.739, 95% CI= 2.016-47.056, P=0.005) were independent risk factors for up-staging to FIGO stage II-IVB.

Conclusions: We found that for apparent FIGO stage I ovarian mucinous carcinoma patients, residual tumors were found in 17.9 % after incomplete staging surgery and up-staging to FIGO II-IV in 9.2% after complete staging surgery. For patients of apparent FIGO stage IA, the possibility of residual tumors and up-staging is relatively low. While for patients of cystectomy, bilateral mucinous carcinomas, or history of ovarian mucinous tumors, complete staging surgery maintains greater significance.

Precis

For patients of cystectomy, bilateral mucinous carcinomas, or history of ovarian mucinous tumors, complete staging surgery maintains greater significance.

Highlights

1. For patients of apparent FIGO stage IA, the possibility of residual tumors and up-staging is relatively low
2. For patients of cystectomy, bilateral mucinous carcinomas, or history of ovarian mucinous tumors, complete staging surgery maintains greater significance.
3. For apparent FIGO stage I ovarian mucinous carcinoma patients, up-staging to FIGO II-IV was found in 9.2% of patients after complete staging surgery.

Introduction

Patients are typically diagnosed with mucinous ovarian carcinoma after surgery. In terms of diagnostic discordance in intraoperative frozen section diagnosis of primary ovarian tumor, mucinous carcinoma compromised the majority of discordant cases(40.5%)[1]. For epithelial ovarian cancer, comprehensive surgical staging is recommended to be performed to rule out occult higher-stage disease, because data show that approximately 30% of patients undergoing complete staging surgery are upstaged[2]. However, different from high-grade serous ovarian cancers, 65-80% of mucinous ovarian cancers are early-stage at diagnosis, and appear to evolve in stepwise fashion from benign epithelium to a preinvasive lesion to carcinoma[3]. Moreover, in 2019, in the study of “the value of surgical staging in patients with apparent early-stage epithelial ovarian carcinoma”, histology and grade of histology were identified to be important factors for upstaging. Patients with serious, especially with high-grade serious were more frequently upstaged than other histological subtypes[4]. The percentage of up-staging in mucinous ovarian carcinoma was unclear. Therefore, the aim of our study is to explore the rate of upstaging after surgical staging in patients with apparent International Federation of Gynecology and Obstetrics (FIGO) stage I mucinous ovarian carcinoma.

Materials And Methods

This study was approved by Peking Union Medical College Hospital Ethics Review Board. Preoperatively, all patients provided written informed consent for data collection for research purposes, and the data set was de-identified to protect patient privacy.

Mucinous ovarian carcinoma patients with surgical treatment were, retrospectively, reviewed in Peking Union Medical College Hospital between October 2020 and January 1994. Inclusion criteria were as follows: surgical staging performed in our hospital; histological confirmation of mucinous ovarian carcinoma by at least two experienced gynecological pathologists; apparent stage I according to the International Federation of Gynecology and Obstetrics (FIGO) 2014 guidelines. Exclusion criteria were as follows: apparent FIGO stage II-IV stage, pathological type of borderline mucinous tumor, borderline tumor with intraepithelial carcinoma, microinvasive carcinoma, seromucous carcinoma or metastatic mucinous carcinoma of the ovary.

Apparent FIGO stage I mucinous ovarian carcinoma was defined as tumors apparently limited to ovaries by intraoperative evaluation and/or by imaging evaluation before surgical re-staging as follow (Figure 1). Up-grading was defined as apparently FIGO I stage was found to be FIGO II-IV by final pathologic stage.

Categorical variables are summarized in frequency tables, whereas continuous variables are presented as median (25%-75% percentiles), as appropriate for data distribution. Binary logistic regression was used to explore the possible influential factors on outcomes. Variates with $P < 0.1$ in the univariate analysis were entered into the multivariate analysis. The data were analyzed using SPSS (version 23, IBM, Armonk, NY). A P value < 0.05 was considered statistically significant (two-tailed hypothesis).

Results

Totally, 163 patients were included in this study, and the clinical characteristics of the patients were summarized in Table 1. Surgical re-staging was performed in 89 patients after incomplete surgical staging and one-step surgical staging was performed in 74 patients.

For all 163 patients, the detailed information with regard to staging surgery scope and staging surgery-associated complications (severe or medically significant, hospitalization or prolongation of hospitalization indicated) was presented in supplementary table 1. Overall, 23 (14.1%) adverse events occurred, with 9 adverse events (10.1%) associated with re-staging surgery and 14 (18.9%) with one-step staging surgery, respectively.

Among 89 patients incompletely staged, the initial incomplete staging surgery consisted of bilateral adnexectomy in 7 patients, unilateral adnexectomy in 55, ovarian cystectomy in 26, omentectomy in 4, appendectomy in 7 and hysterectomy in 6. Moreover, for these 89 patients incompletely staged, residual tumors were found in 16 patients (16/89, 17.9%) during the completion of re-staging surgery by final pathologic confirmation, in other words, residual tumors were present in 16 patients at the prior incomplete staging surgery.

FIGO stage IA was defined as tumor limited to unilateral ovary (capsule intact), without malignant cells in ascites or peritoneal washings. While FIGO stage non-IA was defined as FIGO stage IB, IC, or undetermined IA/IB/IC, in other words, whether the tumor capsule ruptured or not was unclear.

With regard to the potential risk factors related to residual tumor after the incomplete staging surgery, for 19 patients with apparent FIGO stage IA, no patient was found to have residual tumor confirmed by the final pathology result of re-staging surgery, for 70 patients with clinical FIGO stage non-IA, as was shown in table 2, in the univariate analysis, residual tumors were significantly associated with the multipara (P=0.014), bilateral ovaries involved (P=0.036) and ovarian cystectomy (P=0.004). In the multivariate analysis, both multipara (hazard ration [HR]= 6.532, 95% confidence interval [CI] = 1.416-30.137, P=0.016) and ovarian cystectomy (HR=8.269, 95% CI= 1.772-38.595, P=0.007) remained independent risk factors for residual tumor after incomplete staging surgery.

Up-staging was found in 15 patients (15/163, 9.2%) (Table 3), of those 15 patients, surgical re-staging was performed in 10 patients and one-step surgical staging in 5 patients. For 44 apparent FIGO stage IA patients, of both re-staging surgery and one-step staging surgery, no patient was found to up-stage to FIGO II-IVB according to the final surgical pathologic result.

For 119 patients of apparent FIGO stage non-IA, 15 patients (15/119, 12.6%) had the stage elevated to II-IVB based on pathologic finding. As is shown in table 4. in the univariate analysis, up-staging to FIGO stage II-IV was significantly associated with the history of ovarian mucinous tumor (P=0.033) and bilateral ovaries involved (P=0.005). In the multivariate analysis, both the history of ovarian mucinous

tumor (HR=4.745, 95% CI= 1.132-19.886, P=0.033) and bilateral ovaries involved (HR=9.739, 95% CI= 2.016-47.056, P=0.005) remained independent risk factors for up-staging to FIGO stage II-IVB.

Discussion

In this study, the percentage of patients clinically thought to have stage I disease had the stage elevated to II-IV based on surgical staging pathologic findings was 9.2%, for the patients with FIGO stage IA and non-IA, the percentage was 0.0% and 12.6%, respectively.

As is shown in supplementary table 2, in previous studies, the percentage ranged from 12.8–31.8% [2, 4–6]. The percentage in our study in relatively lower than that in previous studies, the reason may be that, in our study, all the patients included were mucinous ovarian carcinoma, while the patients included in previous studies were ovarian epithelial carcinoma, the majority of those were serous carcinoma. As is mentioned before, high-grade serious were more frequently upstaged than other histological subtypes[4].

Interestingly, in our study, we found that, for apparent FIGO stage IA patients, no patient, of initial incomplete staging surgery, was found to have residual tumor confirmed by final pathological results of re-staging surgery, moreover, no patient, of whether restaging or one-step surgical staging surgery, was found to up-stage to FIGO stage II-IVB based on the final pathologic result.

To some extent, consistent with previous study, Peiretti M, et al found that surgical restaging seems to upstage a considerable number of ovarian granulosa cell tumors, mainly in the initial stage IC group of patients[7].

As we all know, to explore the possible risk factors of residual tumor during the initial incomplete staging surgery is of significance to clinical decision-making.

Unlike clear-cell and endometrioid carcinomas, which are frequently associated with marked adhesion to the surrounding tissues, due to endometriosis, mucinous carcinoma may be a possible candidate for cystectomy[8]. However, in our study, after the multivariate analysis, we found that preservation of tumor-involved ovary, cystectomy, was related to the residual tumor. The reason why cystectomy was related to the residual tumor may be obvious, which could be explained by the hypothesis that preservation of tumor-involved ovary may have a risk of leaving residual tumor within the remaining ovarian tissue. This hypothesis was also been supported by a large retrospective study[9]. In the above-mentioned study, the patients with cystectomy more frequently showed ovarian relapse than the patients with oophorectomy [9]. Although oophorectomy is considered as an appropriate operation, cystectomy may be an unavoidable option when it is the only surgical procedure available to preserve fertility [8]. In this situation, special care such as rigorous follow-up should be practiced to those patients with ovarian cystectomy.

There were a few studies which had investigated the possible risk factors of up-staging for epithelial ovarian carcinoma[4]. And, as far as we know, this is the first study to explore the possible risk factors of

up-staging specially for ovarian mucinous carcinoma, which may have greater significance. Interestingly, in our study, we found that the present of bilateral mucinous carcinomas was independent risk factors of up-staging to FIGO stage II-IVB.

Moreover, as we all know, to distinguish primary or metastatic mucinous carcinoma, continues a diagnostically challenging[10, 11]. It is thought that bilateral mucinous carcinomas may be an indicator for metastatic tumors[10] [12]. In the study of Seidman JD et al, among bilateral ovarian mucinous tumors, 6% (2/31)were primary and 94% (29/31) were metastatic, whereas, among unilateral ovarian mucinous tumors, 55% (10/19) were primary and 45% (9/19) were metastatic[12]. Therefore, for the patients with bilateral mucinous carcinomas, complete staging surgery maintain greater significance which may alter treatment strategies.

Ovarian mucinous carcinomas are thought to grow from benign epithelium to borderline tumor to invasive carcinoma[11]. And previous studies found the risk factors of borderline mucinous ovarian tumors evolving to carcinoma included residual disease after the initial surgery[13]. Interestingly, in our study, we also found that the history of ovarian mucinous tumors was also an independent risk factor of up-staging to FIGO stage II-IVB. Therefore, the patients with ovarian mucinous benign or borderline tumor, no residual disease remaining maintains very important significance.

This study was limited by the inadequate large sample size and its retrospective nature, which could have possibly introduced some degree of bias. Despite these limitations, our study observed several important factors. The primary finding was regarding the percentage of up-staging to FIGO II-IVB for apparently FIGO stage I patients. The second important finding was regarding the potential risk factors for residual tumors and up-staging. The third finding was that for patients of apparent FIGO stage IA, the possibility of residual tumors or up-staging was low.

In conclusion, this study showed that the residual tumor was found in 17.9 % of patients during incomplete staging surgery and the up-staging to II-IV stage in 9.2% of patients. The cystectomy was one independent risk factors for residual tumor, and both bilateral mucinous carcinomas and history of ovarian mucinous tumors were two independent risk factors for up-staging. For patients of apparent FIGO stage IA, the possibility of residual tumors and up-staging is relatively low. While for the patients with cystectomy, bilateral mucinous carcinomas, or history of ovarian mucinous tumors, complete staging surgery maintains great significance.

Declarations

Acknowledgements

No

Disclosure statement

The authors declare that they have no conflicts of interest and nothing to disclose.

Author contribution

Conception and design: Zhen Yuan, Dongyan Cao, Ying Zhang, Tao Wang, Keng Shen

Acquisition of data: Zhen Yuan, Dongyan Cao, Ying Zhang,

Analysis and interpretation of data: Zhen Yuan, Dongyan Cao, Ying Zhang,

Manuscript writing: Zhen Yuan, Ying Zhang,

Critical review of the manuscript: Zhen Yuan, Ying Zhang, Dongyan Cao, Keng Shen

Final approval of manuscript: Zhen Yuan, Dongyan Cao, Mei Yu, Keng Shen

References

1. Yoshida H., Tanaka H., Tsukada T. et al. Diagnostic Discordance in Intraoperative Frozen Section Diagnosis of Ovarian Tumors: A Literature Review and Analysis of 871 Cases Treated at a Japanese Cancer Center. Int J Surg Pathol 2020;1066896920960518.
2. Stier E. A., Barakat R. R., Curtin J. P. et al. Laparotomy to complete staging of presumed early ovarian cancer. Obstet Gynecol 1996;87: 737-740.
3. Morice P., Gouy S., Leary A. Mucinous Ovarian Carcinoma. N Engl J Med 2019;380: 1256-1266.
4. Hengeveld EM, Zusterzeel PLM, Lajer H et al. The value of surgical staging in patients with apparent early stage epithelial ovarian carcinoma. Gynecologic oncology 2019;154: 308-313.
5. Young R. C., Decker D. G., Wharton J. T. et al. Staging laparotomy in early ovarian cancer. JAMA 1983;250: 3072-3076.
6. Buchsbaum H. J., Brady M. F., Delgado G. et al. Surgical staging of carcinoma of the ovaries. Surg Gynecol Obstet 1989;169: 226-232.
7. Peiretti M., Candotti G., Fais M. L. et al. Comparison between laparoscopy and laparotomy in the surgical re-staging of granulosa cell tumors of the ovary. Gynecol Oncol 2020;157: 85-88.
8. Kajiyama Hiroaki, Suzuki Shiro, Niimi Kaoru et al. Oncologic and reproductive outcomes of cystectomy as a fertility-sparing treatment for early-stage epithelial ovarian cancer. International Journal of Clinical Oncology 2019;24: 857-862.
9. Fruscio R., Corso S., Ceppi L. et al. Conservative management of early-stage epithelial ovarian cancer: results of a large retrospective series. Ann Oncol 2013;24: 138-144.
10. Yemelyanova Anna V., Vang Russell, Judson Kara et al. Distinction of Primary and Metastatic Mucinous Tumors Involving the Ovary: Analysis of Size and Laterality Data by Primary Site With Reevaluation of an Algorithm for Tumor Classification. The American Journal of Surgical Pathology 2008;32: 128-138.

11. Babaier A., Ghatage P. Mucinous Cancer of the Ovary: Overview and Current Status. Diagnostics (Basel) 2020;10.
12. Seidman J. D., Kurman R. J., Ronnett B. M. Primary and metastatic mucinous adenocarcinomas in the ovaries: incidence in routine practice with a new approach to improve intraoperative diagnosis. Am J Surg Pathol 2003;27: 985-993.
13. Morice P., Uzan C., Fauvet R. et al. Borderline ovarian tumour: pathological diagnostic dilemma and risk factors for invasive or lethal recurrence. Lancet Oncol 2012;13: e103-115.

Tables

Table 1. The clinical characteristics of the patients. FIGO, International Federation of Gynecology and Obstetrics; CEA, carcinoembryonic antigen; CA, carbohydrate antigen.

N=163	89 patients of re-staging surgery	74 patients of one-step staging surgery	Total 163 patients
Age (y), median (25%-75%percentiles)	27.00 (23.00-34.00)	42.00 (26.00-54.00)	31.00 (24.00-45.00)
Body mass index, median (25%-75%percentiles)	22.10 (20.31-24.08)	22.42 (19.92-25.45)	22.27 (20.25-24.16)
Multipara	36(40.4%)	43(58.1%)	79(48.5%)
During the pregnancy	5(5.6%)	2(2.7%)	7(4.3%)
The history of ovarian mucinous tumor	8(9.0%)	8(10.8%)	16(9.8%)
CEA elevated at time of diagnosis	3(3.4%)	8(10.8%)	11(6.7%)
CA199 elevated at time of diagnosis	12(13.5%)	29(39.2%)	41(25.2%)
CA125 Elevated at time of diagnosis	12(13.5%)	32(43.2%)	44(27.0%)
Maximum diameter of tumor (cm), median (25%-75%percentiles)	15.00 (12.00-20.00)	15.00 (13.15-25.00)	15.00 (12.00-20.00)
Ascites	9(10.1%)	21(28.4%)	30(18.4%)
Tumor involving bilateral ovaries	4(4.5%)	4(5.4%)	8(4.9%)
Apparent FIGO staging			
IA	19(21.3%)	25(33.8%)	44(27.0%)
IC1	51(57.3%)	24(32.4%)	75(46.0%)
IC2	13(14.6%)	22(29.7%)	35(21.5%)
IC3	1(1.1%)	0(0.0%)	1(0.6%)
IA/IB/IC-undetermined	5(5.6%)	3(4.2%)	8(4.9%)
Surgical re-staging		-	
Time interval between surgeries (d), median (25%-75%percentiles)	42.00 (27.25-55.00)	-	-
First step surgery by laparoscopy	30(33.7%)	-	-

Preservation of tumor-involved ovary at first-step surgery	25(28.1%)	-	-
Residual tumor found after re-staging surgery	16(18.0%)	-	-
Finally pathological up-staging	10(11.2%)	5(6.8%)	15(9.2%)
Tumor of mural nodules	2(2.2%)	1(1.4%)	3(1.8%)
Tumor of poor differentiation	1(1.1%)	5(6.8%)	6(3.7%)
Tumor of expansive subtype	14(15.7%)	6(8.1%)	20(12.3%)

Table 2. The potential risk factors of residual tumors. FIGO, International Federation of Gynecology and Obstetrics; CEA, carcinoembryonic antigen; CA, carbohydrate antigen.

The potential risk factors of residual tumors after incomplete surgical staging for patients with apparent FIGO stage non-IA.	Univariate analysis		Multivariate analysis	
	P-value	OR (95%CI)	P-value	OR (95%CI)
Age	0.288	1.036 (0.970-1.106)		
Body mass index	0.829	0.981 (0.820-1.172)		
Multipara	0.014	4.333 (1.339-14.022)	0.016	6.532 (1.416-30.137)
During the pregnancy	0.063	6.000 (0.907-39.700)	0.684	1.754 (0.117-26.272)
The history of ovarian mucinous tumor	0.199	2.885 (0.573-14.526)		
CEA elevated at time of diagnosis	0.122	8.000 (0.572-111.958)		
CA199 elevated at time of diagnosis	0.590	1.600 (0.289-8.859)		
CA125 Elevated at time of diagnosis	0.247	0.266 (0.028-2.501)		
Laparoscopy at first-step surgery	0.722	1.227 (0.396-3.800)		
Ascites	0.896	0.860 (0.090-8.197)		
Tumor size	0.847	1.008		

		(0.928-1.096)		
Bilateral ovaries involved	0.036	12.231 (1.175-127.359)	0.676	1.840 (0.105-32.237)
Ovarian cystectomy	0.004	6.129 (1.808-20.776)	0.007	8.269 (1.772-38.595)
With malignant mural nodules	0.382	3.533 (0.208-59.901)		
Expansile subtype tumor	0.420	1.750 (0.449-6.825)		
Poorly differentiated tumor	0.341	2.234 (0.428-11.671)		
Time interval between surgeries	0.598	1.002 (0.996-1.008)		

Table 3. The information of up-staging patients. FIGO, International Federation of Gynecology and Obstetrics.

		Final pathologic FIGO stage				
		IIA	IIB	IIIA	IIIB	IIIC
Apparent FIGO stage	IC1		1	3	1	2
	IC2	1		3	2	1
	IC3					1

Table 4. The potential risk factors of up-staging. FIGO, International Federation of Gynecology and Obstetrics; CEA, carcinoembryonic antigen; CA, carbohydrate antigen.

The potential risk factor of up-staging	Univariate analysis		Multivariate analysis	
	P-value	OR (95%CI)	P-value	OR (95%CI)
Age	0.973	1.001 (0.960-1.043)		
Body mass index	0.468	0.934 (0.778-1.123)		
Multipara	0.288	1.819 (0.604-5.480)		
During the pregnancy	0.209	3.046 (0.535-17.334)		
The history of ovarian mucinous tumor	0.033	4.364 (1.128-16.878)	0.033	4.745 (1.132-19.886)
CEA elevated at time of diagnosis	0.772	1.429 (0.129-15.875)		
CA199 elevated at time of diagnosis	0.419	1.884 (0.405-8.765)		
CA125 Elevated at time of diagnosis	0.343	1.979 (0.483-8.111)		
Laparoscopy at first-step surgery	0.791	1.200 (0.312-4.622)		
Ovarian cystectomy	0.350	1.750 (0.541-5.658)		
Ascites	0.326	1.921 (0.522-7.063)		
Tumor size	0.153	1.057 (0.979-1.142)		
Bilateral ovaries involved	0.005	8.909 (1.949-40.718)	0.005	9.739 (2.016-47.056)
One-step staging surgery	0.511	0.682 (0.218-2.136)		

Time interval between surgeries	0.186	1.004 (0.998-1.010)
With malignant mural nodules	0.308	3.607 (0.307-42.419)
Expansile subtype tumor	0.943	0.948 (0.220-4.096)
Poorly differentiated tumor	0.417	0.418 (0.051-3.439)

Figures

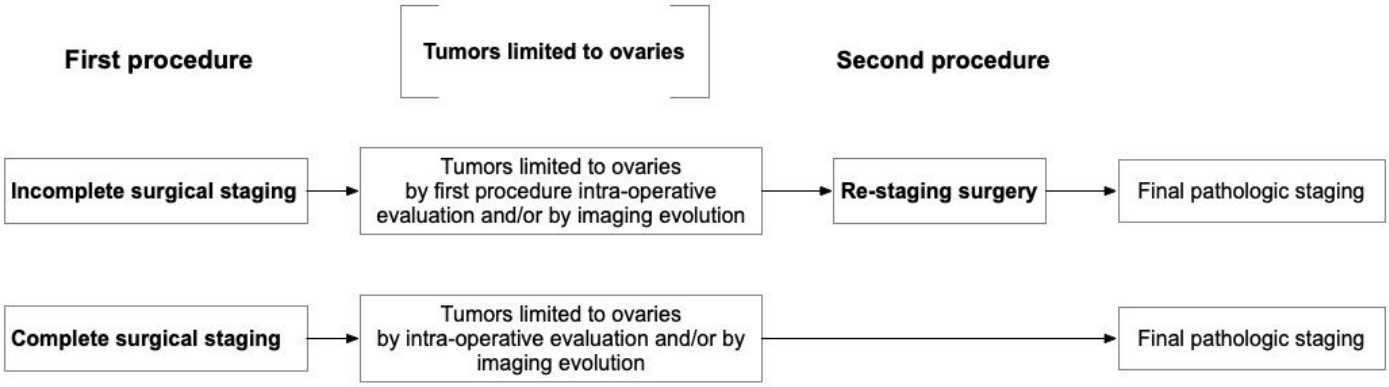

Figure 1

The study flowchart.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarytable1.Surgicaladverseeffects.docx
- Supplementarytable2.Previousstudies.docx