

# Ovarian cancer recurrence detection may not require in-person physical examination: an MSK team ovary study

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## HIGHLIGHTS

- Over 2 years, routine physical exam was not the initial method used to detect recurrence in any patients.
- In all patients, imaging, tumor marker, reported symptoms, or biopsy first led to detection of recurrence.
- It appears safe to continue tele-ovarian cancer surveillance with tumor marker and scans, without routine physical exam.

## ABSTRACT

**Objective** Given the inconvenience and financial burden of frequent ovarian cancer surveillance and the risks of in-person visits due to COVID-19, which have led to the acceleration of telehealth adaptation, we sought to assess the role of in-person physical examination for the detection of ovarian cancer recurrence among patients enrolled in a routine surveillance program.

**Methods** This was a retrospective study of patients initially seen from January 2015 to December 2017 who experienced ovarian cancer recurrence during first clinical remission. Descriptive statistics and bivariate analyses were performed to compare differences in detection methods and in patient and disease characteristics.

**Results** Among 147 patients who met our inclusion criteria, there were no recurrences detected by physical examination alone. Forty-six (31%) patients had recurrence first detected by tumor marker, 81 (55%) by radiographic scan, 17 (12%) by presentation of new symptoms, and 3 (2%) by biopsies taken during non-oncological surgery. One hundred and eleven patients (75%) had multiple positive findings at the time of recurrence. Of all 147 patients, 48 (33%) had symptoms, 21 (14%) had physical examination findings, 106 (72%) had increases in tumor markers, and 141 (96%) had changes on imaging.

**Conclusions** In-person physical examination was not a primary means of detection for ovarian cancer recurrence for any patient. Substituting in-person visits for virtual visits that include patient-reported symptoms, alongside a regular surveillance protocol that includes tumor marker testing and imaging, may be a suitable approach for the detection of ovarian cancer recurrence while also reducing patient inconvenience and risks to health.

## INTRODUCTION

In 2021, an estimated 21 410 women will be diagnosed with ovarian cancer in the USA.<sup>1</sup> Of these women, 70%–80% will experience clinical remission and subsequently enter a surveillance program.<sup>2</sup> While it is clear that surveillance is generally important for the detection of recurrence, the benefits of

specific surveillance programs in relation to cost are questionable.<sup>3 4</sup> While financial toxicity concerns have prompted research into the value of particular surveillance methods in the past, these concerns have become of immediate importance in the context of the COVID-19 pandemic, which practically overnight increased the risks of physical exams in terms of potential exposure to COVID-19, contributed to new international guidelines minimizing in-person contact, and helped drive a major shift toward virtual visits.<sup>5 6</sup>

The current standard of care for ovarian cancer surveillance in the USA is based on the guidelines of the National Comprehensive Cancer Network. The guidelines include physical examination with pelvic exam every 2–4 months for 2 years, every 3–6 months for 3 years, and annually thereafter.<sup>7</sup> CA-125 or other tumor marker surveillance is recommended in patients in whom these markers are initially raised, and scans are recommended as clinically indicated. These guidelines are based on consensus and guided by lower-level evidence. With the exception of the European Organization for Research and Treatment of Cancer 55955 trial, which found no added survival benefit to starting treatment for recurrence based on CA-125 changes in the absence of clinical symptoms, there are no other large, prospective trials examining the value of surveillance programs.<sup>8</sup> As such, there is significant variability among providers when it comes to ovarian cancer surveillance.<sup>9 10</sup>

Given the poor evidence supporting current surveillance programs and the challenges of maintaining frequent in-person surveillance visits for ovarian cancer, is it possible for patients who are undergoing routine symptom checks, tumor marker monitoring, and imaging to forgo in-person physical examinations for virtual visits? To address this question, we sought to identify the role of routine physical examination on recurrence detection in patients with ovarian cancer in first clinical remission.



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## Original research

### METHODS

Our institution's surveillance protocol for years 1 and 2 includes an in-person physical examination every 3 months, along with CA-125 laboratory tests and CT of the chest, abdomen, and pelvis with intravenous and oral contrast. For year 3, time between surveillance testing is extended to every 3–6 months. For years 4 and 5, it is extended to every 6 months. Beyond 5 years, physical examination and CA-125 testing are performed annually, and imaging is optional. Surveillance visits occur with either a medical oncologist with a subspecialty in gynecological cancer or a gynecological oncologist. Symptom assessment and review of systems is performed by a physician or advanced practice provider and recorded in free text for the History of Present Illness and then in a structured Review of Systems section of the Progress Note. Pelvic examination is performed by an attending physician and documented in a structured format in the electronic medical record (EMR). This protocol is followed for all patients treated at our institution because many patients treated are on clinical trials, which require this frequency of follow-up, lab testing, and imaging.

Using a prospectively collected institutional consecutive ovarian cancer database, we performed a retrospective review of all patients with a new diagnosis of ovarian cancer seen at our institution for initial visits between 1 January 2015 and 31 December 2017 in the institution's EMR. We included all patients with a documented recurrence within 2 years after completion of primary therapy for ovarian cancer. We used 2 years for our follow-up period based on the median progression-free survival of 16–22 months in patients treated with current standard treatments.<sup>11 12</sup> We excluded patients who never entered clinical remission (ie, platinum-refractory) and patients who had surveillance at outside hospitals and could not be tracked for recurrence. Recurrence is defined for each patient based on the diagnosis by individual providers that led to the recommendation and/or initiation of second-line treatment. We collected the number of visits, number of tumor marker laboratory tests, number of routine scans, and the method and location of ovarian cancer recurrence as documented in the EMR. We also collected patient characteristics, clinical and disease characteristics, and treatment methods. Additionally, we thoroughly reviewed the multiple visit notes from the time of recurrence to ensure full details of each patient were collected.

Recurrence location was further categorized for purposes of statistical analysis. All patients with recurrent disease outside of the abdominal cavity were categorized as 'extra-abdominal'. Patients with recurrence within the abdomen and pelvis, including peritoneal carcinomatosis, were categorized as 'multisite, peritoneal'. Patients with recurrences confined to the pelvis, excluding lymph-node only recurrences, were defined as 'pelvis/vaginal/inguinal'. Patients with recurrences confined to retroperitoneal lymph nodes were defined as 'retroperitoneal nodes'. Patients with disease only in the upper abdomen were defined as 'upper abdomen'. Patients without documented location of recurrence were defined as 'other'.

With regard to the methods of detection, first, we defined the methods of detection as patient-reported symptoms; physical examination findings; tumor marker; imaging; or opportunistic biopsy at time of non-oncological surgery. Second, for each patient, we recorded all methods of detection for which there was a positive finding before the start of recurrence therapy. Third, for each

patient, we identified which method of detection *first* identified the recurrence that led either to treatment (chemotherapy) or to a change from a routine surveillance protocol (shift to earlier check of tumor marker or imaging); that is, the definition of the *primary* method of detection. Fourth, when there were concurrent findings (in which two or more methods were positive on the same date), all methods of detection were recorded, and the primary method was identified based on the following two scenarios. In scenario one, patients with imaging and concurrent additional findings were recorded with "imaging" as the primary method according to the Rustin criteria because imaging is the most statistically specific finding compared with the other methods.<sup>13</sup> Of note, because imaging was obtained routinely for every patient in surveillance, the imaging recorded in this study as the primary method of detection is routine imaging. When imaging was obtained based on clinical presentation or other finding, imaging is noted as a method of detection (but not the *primary* one). In scenario two, for patients with symptoms and tumor marker findings recorded as concurrent, we classified 'symptoms' as the primary method to ensure methodological consistency.

Bivariate analysis was performed for each collected datapoint. For categorical data, the Fisher exact test was used. For continuous data, we used the Shapiro-Wilks test for normality to determine our use of either ANOVA or Kruskal-Wallis tests. Analysis was performed and figures created using R Studio Version 1.2 with packages `compareGroups` and `ggplot2`. This retrospective study was approved by our institutional review board.

### RESULTS

Seven hundred and nineteen patients with newly diagnosed ovarian cancer were initially seen and followed during the study period. There were 229 subsequent recurrences in this patient population between initial presentation and December 2019. Of these patients, 72 were excluded from the study because they did not achieve clinical remission (platinum-refractory or persistent disease). Ten other patients were excluded because they had follow-up at an outside hospital, with no information about recurrence detection. As such, 147 patients were included in the final analysis (Online supplemental figure 1).

Of these 147 patients, none had their recurrence detected on routine physical exam, including pelvic exam, as the primary method of detection. For 81 patients (55%), the *primary* method of recurrence detection (as defined in the Methods) was radiographic scan, for 46 (31%) it was tumor marker, for 17 (12%) it was presentation of new symptoms, and for 3 (2%) it was biopsy during a non-oncological surgery. Further, with regards to *all* methods of detection, by the time of treatment for recurrence (ie, from the time of first detection to time of initiation of second-line treatment), 111 patients (75%) had multiple positive findings. Forty-eight (33%) had symptoms, 21 (14%) had physical exam findings, 106 (72%) had increases in their tumor markers, and 141 (96%) had changes on their imaging.

Of the 147 patients, 131 (89%) had baseline increases in CA-125. Of the 16 patients without a baseline increase, 12 experienced a CA-125 increase during recurrence. Two of these 12 patients had their recurrence initially detected by CA-125. One of these patients

**Table 1** Patient characteristics by primary method of recurrence detection

	All patients n=147	Tumor marker n=46	Scan n=81	Surgery n=3	Symptoms n=17	P value
Age						0.911
<60 years	54 (37%)	18 (39%)	28 (35%)	1 (33%)	7 (41%)	
≥60 years	93 (63%)	28 (61%)	53 (65%)	2 (67%)	10 (59%)	
Race						0.989
White	107 (73%)	33 (72%)	57 (70%)	3 (100%)	14 (82%)	
Asian	13 (9%)	3 (6.5%)	8 (9.9%)	0 (0%)	2 (12%)	
Black	11 (7%)	4 (8.7%)	7 (8.6%)	0 (0%)	0 (0.00%)	
Not reported	13 (9%)	5 (11%)	7 (8.6%)	0 (0%)	1 (6%)	
Other	3 (2%)	1 (2.2%)	2 (2.5%)	0 (0%)	0 (0.00%)	
BMI						0.795
<30 kg/m <sup>2</sup>	113 (77%)	34 (74%)	63 (78%)	2 (67%)	14 (82%)	
≥30 kg/m <sup>2</sup>	34 (23%)	12 (26%)	18 (22%)	1 (33%)	3 (18%)	
At least two comorbidities						0.264
No	101 (69%)	30 (65%)	54 (67%)	2 (67%)	15 (88%)	
Yes	46 (31%)	16 (35%)	27 (33%)	1 (33%)	2 (12%)	
BRCA status						0.149
Negative	105 (71%)	35 (76%)	58 (72%)	2 (67%)	10 (59%)	
Positive	17 (12%)	8 (17%)	8 (9.9%)	0 (0%)	1 (6%)	
Unknown	22 (15%)	3 (6.5%)	12 (15%)	1 (33%)	6 (35%)	
VUS	3 (2%)	0 (0%)	3 (3.7%)	0 (0%)	0 (0.00%)	
Insurance type						0.871
Commercial	129 (88%)	39 (85%)	72 (89%)	3 (100%)	15 (88%)	
Public	17 (12%)	7 (15%)	8 (9.9%)	0 (0%)	2 (12%)	
Uninsured	1 (0.7%)	0 (0%)	1 (1.2%)	0 (0%)	0 (0%)	

BMI, body mass index; VUS, variants of uncertain significance.

had short-interval (4 week) CT changes showing recurrence and the other had CT changes after 5 months and was started on treatment.

There were no differences in age, race, comorbidities, insurance status, or *BRCA* status among patients by method of detection (Table 1). There were no differences in stage, histology, or chemotherapy type by method of detection (Table 2). There were no differences in length of clinical remission or recurrence location by method of detection (Table 3). Online supplemental figure 2 shows that even as length of time increased from onset of remission, no method of detection was favored.

We further examined the 17 patients who had recurrence first detected by symptoms (Table 4). Nine patients had abdominal pain or bloating and were found to have peritoneal or adnexal recurrences. One patient had a palpable mass in her groin and was found to have inguinal recurrence. Three patients had new onset neurological symptoms, which led to brain imaging and detection. Two patients had vaginal bleeding and were found to have pelvic recurrences. One patient had non-specific complaints, documented as uneasiness and fatigue, which led to a CT scan showing peritoneal recurrence. One patient had dyspnea and was found to have pulmonary nodules and pleural effusion.

We then further examined the 21 patients who had recurrence for which physical exam findings were positive after recurrence

had previously been detected (Table 5). Of these 21 patients, 19 had concurrent symptoms, and for six of these patients, symptoms were the primary method of detection. For the two patients without symptoms, recurrence was first detected in one patient by an increase in CA-125 on routine check, and subsequently was found to have nodularity on vaginal exam with vaginal cuff recurrence. In the other patient, recurrence was first detected by surveillance imaging, and the patient was then found to have abdominal distension with peritoneal recurrence.

## DISCUSSION

### Summary of Main Results

In this review of 147 patients with ovarian cancer recurrence, no recurrences were primarily detected by routine physical examination. Additionally, even when recurrence had already been identified by symptoms, tumor marker, imaging or biopsy, 86% of patients still had normal physical examinations. This finding suggests that virtual visits, which have quickly gained acceptance during the COVID-19 pandemic, combined with a surveillance protocol for tumor marker testing and imaging, may be sufficient to identify ovarian cancer recurrence.

**Table 2** Disease information by primary method of recurrence detection

	All patients n=147	Tumor marker n=46	Scan n=81	Surgery n=3	Symptoms n=17	P value
Stage						0.594
I	4 (2.7%)	0 (0%)	2 (2.5%)	0 (0%)	2 (12%)	
II	3 (2.0%)	1 (2.2%)	2 (2.5%)	0 (0%)	0 (0%)	
III	64 (44%)	20 (43%)	35 (43%)	1 (33%)	8 (47%)	
IV	76 (52%)	25 (54%)	42 (52%)	2 (67%)	7 (41%)	
Histology						0.304
Carcinosarcoma	5 (3.4%)	1 (2.2%)	3 (3.7%)	0 (0%)	1 (5.9%)	
Clear cell	10 (6.8%)	1 (2.2%)	8 (9.9%)	0 (0%)	1 (5.9%)	
High-grade serous	126 (86%)	41 (89%)	69 (85%)	3 (100%)	13 (76%)	
Low-grade serous	2 (1.4%)	1 (2.2%)	1 (1.2%)	0 (0%)	0 (0%)	
Mixed	2 (1.4%)	1 (2.2%)	0 (0%)	0 (0%)	1 (5.9%)	
Other	2 (1.4%)	1 (2.2%)	0 (0%)	0 (0%)	1 (5.9%)	
Chemotherapy type						1.000
Neoadjuvant and adjuvant	68 (46%)	21 (46%)	38 (47%)	1 (33%)	8 (47%)	
Postoperative	79 (54%)	25 (54%)	43 (53%)	2 (67%)	9 (53%)	

### Results in the Context of Published Literature

In previous studies of ovarian cancer surveillance techniques, physical examination has been noted to be of variable use, with findings noted in 5%–60% of recurrences, most commonly in patients with abdominal or pelvic recurrences.<sup>3 14–19</sup> In most of these studies, as with our study, physical exam findings of potential recurrences are combined with at least one additional method of surveillance. These other studies, however, did not examine whether physical examination alone (or first) identified recurrence in the absence of other findings. While there are often physical examination findings in patients with recurrent ovarian cancer, as there were in 14% of our recurrence population, it is not clear whether routine in-person physical examination adds benefit for patients otherwise receiving routine symptom, laboratory, and imaging evaluation for recurrence.

Surveillance protocols can be costly to patients, not only financially but emotionally as well, and can pose health risks for patients and providers because of potential COVID-19 exposure.<sup>20–22</sup> Moving to virtual visits that include patient-reported symptoms, along with a surveillance protocol for tumor marker testing and imaging, may help reduce burden to patients and has

previously been shown as feasible.<sup>23</sup> Regarding health, reducing in-person visits complies with the principle of social distancing by decreasing the density of patients in the office and number of interactions each patient is required to have. While we know CA-125 and CT scans cost several thousand dollars per recurrence and a protocol with more routine testing may lead to increased system wide costs,<sup>2</sup> it is harder to quantify the cost that patients directly bear by attending scheduled appointments for which they, and often a support person, have to take off from work and travel some distance to see a provider.

The emotional toll endured by patients in remission is also highly relevant. Patients consistently report high anxiety from the concern of recurrence,<sup>20–22</sup> and education has been highlighted as a key factor in reducing this anxiety. This education, as well as shared decision making, can be incorporated into virtual surveillance visits. Looking forward, the authors plan to assess patient-reported satisfaction with virtual visits in addressing survivorship issues like ongoing education and long-term side effects.

**Table 3** Surveillance information by primary method of recurrence detection

	All patients n=147	Tumor marker n=46	Scan n=81	Surgery n=3	Symptoms n=17	P value
Surveillance time, months		6.5 (5–10.8)	6 (4–10)	5 (3–6)	5.5 (3–8.25)	0.372
Recurrence location						0.078
Extra-abdominal	18 (12%)	5 (11%)	10 (12%)	0 (0%)	3 (18%)	
Multisite, peritoneal	89 (61%)	27 (59%)	51 (63%)	3 (100%)	8 (47%)	
Other	3 (2.0%)	3 (6.5%)	0 (0%)	0 (0%)	0 (0%)	
Pelvis/vaginal/inguinal	13 (8.8%)	4 (8.7%)	4 (4.9%)	0 (0%)	5 (29%)	
Retroperitoneal nodes	15 (10%)	6 (13%)	9 (11%)	0 (0%)	0 (0%)	
Upper abdomen	9 (6.1%)	1 (2.2%)	7 (8.6%)	0 (0%)	1 (5.9%)	

**Table 4** Patients primarily detected by symptoms and location of recurrence

Location of recurrence	Symptoms at time of recurrence
Pelvis	Heavy vaginal bleeding
Brain	Slurred speech
Brain	Aphasia, personality changes
Brain	Visual symptom
Peritoneal disease	Increased abdominal bloating and pain
Inguinal node	Bump in left groin
Retroperitoneal lymph nodes and left adenxa	New abdominal pain
Ascites, peritoneal disease, and pleural nodularity	Abdominal pain
Pelvic, retroperitoneal nodes	Vaginal bleeding
Peritoneal disease	Bloating and abdominal pain
Peritoneal disease	Uneasiness and fatigue
Left adnexa	Left-sided abdominal pain
Peritoneal disease	Abdominal pain and bloating
Hepatic	Abdominal bloating
Pulmonary nodule and pleural effusion	Dyspnea
Pulmonary nodules, hepatic, abdominopelvic nodes	Abdominal discomfort
Pelvis	Abdominal pain

### Strengths and Weaknesses

Our study benefited from its location at a high-volume cancer center in which we could review a larger volume of patients over a shorter period of time compared with previous studies. However, there are also importation limitations. The study is limited by its retrospective nature and resultant selection bias, but the findings can guide future prospective trials of ovarian cancer surveillance techniques. Furthermore, the protocol for patients studied included a robust surveillance program for all patients and included regular tumor marker testing and imaging, which may over-represent imaging as a primary detection method and demonstrate a lead-time bias for detection timing. As such, the findings may not be extrapolated to settings where these regular surveillance modalities are not available.

### Implications for Practice and Future Research

Due to the ongoing COVID-19 pandemic, recommendations for virtual surveillance programs have been published for patients with gynecological cancer.<sup>24</sup> Based on these recommendations and our findings, we plan to evaluate patient-reported outcomes in a pilot virtual intensive surveillance program. This program may benefit patients without recurrence in the first 2 years (490 patients who did not meet our inclusion criteria) and patients with recurrence.

**Table 5** Patients with physical exam findings and location of recurrence

Location of recurrence	Physical exam findings at time of recurrence
Vaginal cuff	Palpable mass on vaginal exam
Peritoneal disease	Abdominal distension
Peritoneal disease, supradiaphragmatic nodes	Abdominal distension and tenderness
Brain	Tandem gait imbalance
Pulmonary nodules, hepatic, peritoneal disease	Decreased breath sounds in right lung fields
Peritoneal disease, pulmonary nodules	Abdominal distension
Peritoneal disease, pulmonary nodules	Abdominal distension
Brain	Abnormal eye exam
Peritoneal disease, hepatic, supradiaphragmatic nodes	Abdominal distension
Inguinal node	Enlarged inguinal node
Peritoneal disease, supraclavicular nodes	Abdominal distension
Peritoneal disease	Abdominal distension
Peritoneal disease, pleural disease	Abdominal distension
Peritoneal disease, supraclavicular nodes	Abdominal distension and tenderness
Peritoneal disease, pleural disease	Abdominal tenderness
Pelvic, retroperitoneal nodes	Periurethral mass
Pelvic, peritoneal disease	Vaginal nodularity
Peritoneal disease	Abdominal distension and tenderness
Peritoneal disease	Abdominal tenderness
Peritoneal disease, hepatic, supradiaphragmatic nodes	Abdominal tenderness
Peritoneal disease, hepatic	Abdominal tenderness

### Conclusions

Our study indicates that for patients who are undergoing routine symptom checks, tumor marker monitoring, and imaging, virtual visits may be a suitable alternative to the frequent in-person visits with physical examination. Similar to other studies, our results call into question the value of frequent in-person examinations for ovarian cancer surveillance for patients also undergoing routine evaluation of tumor markers and imaging studies. We suggest it may be appropriate to re-evaluate the current surveillance guidelines and devise new monitoring strategies that are economical and effective in this new age of telemedicine.

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## Original research

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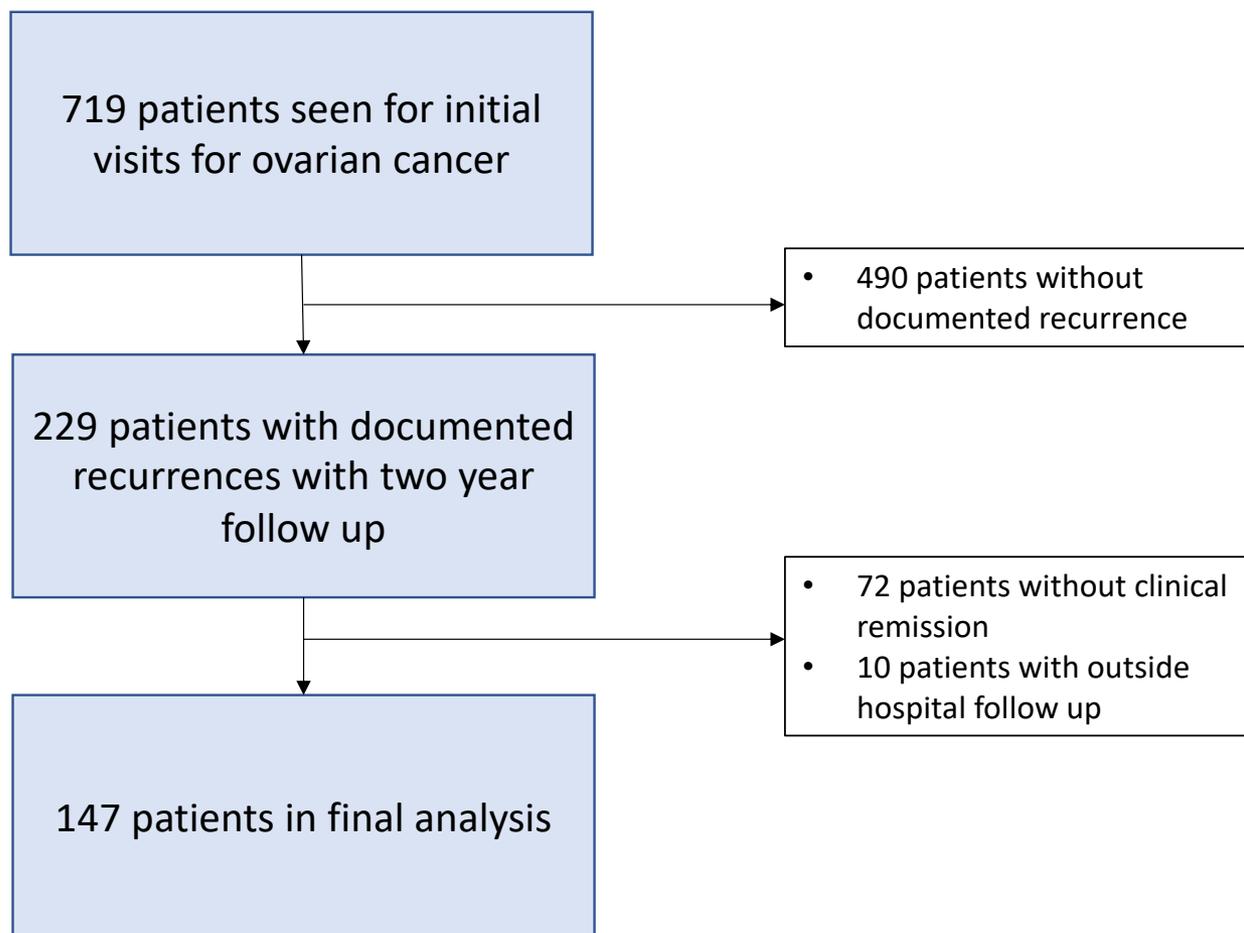
**Data availability statement** Data are available upon reasonable request. Data will be made available upon reasonable request according to institutional processes.

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## Supplemental Figure 1. Selection of study population with inclusion and exclusion criteria



## Supplemental Figure 2. Primary method of recurrence detection by number of months in surveillance

