Symptom-triggered testing detects early stage and low volume resectable advanced stage ovarian cancer

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ABSTRACT

Objective Symptom-triggered testing for ovarian cancer was introduced to the UK whereby symptomatic women undergo an ultrasound scan and serum CA125, and are referred to hospital within 2 weeks if these are abnormal. The potential value of symptom-triggered testing in the detection of early-stage disease or low tumor burden remains unclear in women with high grade serous ovarian cancer. In this descriptive study, we report on the International Federation of Gynecology and Obstetrics (FIGO) stage, disease distribution, and complete cytoreduction rates in women presenting via the fast-track pathway and who were diagnosed with high grade serous ovarian cancer.

Methods We analyzed the dataset from Refining Ovarian Cancer Test accuracy Scores (ROCkeTS), a single-arm prospective diagnostic test accuracy study recruiting from 24 hospitals in the UK. The aim of ROCkeTS is to validate risk prediction models in symptomatic women. We undertook an opportunistic analysis for women recruited between June 2015 to July 2022 and who were diagnosed with high grade serous ovarian cancer via the fast-track pathway. Women presenting with symptoms suspicious for ovarian cancer receive a CA125 blood test and an ultrasound scan if the CA125 level is abnormal. If either of these is abnormal, women are referred to secondary care within 2 weeks. Histology details were available on all women who underwent surgery or biopsy within 3 months of recruitment. Women who did not undergo surgery or biopsy at 3 months were followed up for 12 months as per the national guidelines in the UK. In this descriptive study, we report on patient demographics (age and menopausal status), WHO performance status, FIGO stage at diagnosis, disease distribution (low/pelvic confined, moderate/extending to mid-abdomen, high/extending to upper abdomen) and complete cytoreduction rates in women who underwent surgery.

Results Of 1741 participants recruited via the fast-track pathway, 119 (6.8%) were diagnosed with high grade serous ovarian cancer. The median age was 63 years (range 32–89). Of these, 112 (94.1%) patients had a performance status of 0 and 1, 30 (25.2%) were diagnosed with stages I/II, and the disease distribution was low-to-moderate in 77 (64.7%). Complete and optimal cytoreduction were achieved in 73 (61.3%) and 18 (15.1%). The extent of disease was low in 43 of 119 (36.1%), moderate in 34 of 119 (28.6%), high in 32 of 119 (26.9%), and not available in 10 of 119 (8.4%). Nearly two thirds, that is 78 of 119 (65.5%) women with high grade serous ovarian cancer, underwent primary debulking surgery, 36 of 119 (30.3%) received neoadjuvant chemotherapy followed by interval debulking surgery, and 5 of 119 (4.2%) women did not undergo surgery.

Conclusion Our results demonstrate that one in four women identified with high grade serous ovarian cancer through the fast-track pathway following symptom-triggered testing was diagnosed with early-stage disease. Symptom-triggered testing may help identify women with a low disease burden, potentially contributing to high complete cytoreduction rates.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Major studies have not shown any survival benefit for screening in ovarian cancer. High grade serous ovarian cancer is the most lethal form of ovarian cancer and is usually diagnosed at advanced stages.

WHAT THIS STUDY ADDS

⇒ Symptom-triggered testing may contribute to the detection of high grade serous ovarian cancer at an early stage in women of good performance status and when the disease burden is low, thereby contributing to high complete cytoreduction rates.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Improving community awareness of symptoms of ovarian cancer and enhanced use of the symptom-triggered testing and fast-track pathway may contribute to improved oncological outcomes for women with high grade serous ovarian cancer.

INTRODUCTION

Ovarian cancer is the sixth most common cause of cancer-related deaths in the UK. The majority (93%) of women diagnosed with early stage ovarian cancer (International Federation of Gynecology and Obstetrics (FIGO) stage I) survive beyond 5 years compared with only 13% diagnosed in advanced stages (stage IV).[1] Although screening was associated with a stage shift in a major UK trial,[2] results from both

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the UK and US trials have not shown any mortality benefit with screening.[2 3] There is a growing body of evidence that symptoms precede a diagnosis by between 3 and 36 months.[4–8] However, the vague symptoms associated with ovarian cancer, as well as its low incidence, compound the challenges in its early detection.[9] Goff *et al* first described a symptom triad (pain, increased abdominal size and/or bloating, and early satiety) associated with ovarian cancer. This was subsequently modified to develop a symptom index which was incorporated into national guidelines to raise awareness among clinicians.[10] Symptom-triggered testing for ovarian cancer was endorsed by cancer organizations in the USA, namely the American Cancer Society, Foundation for Women's Cancer, and the Society of Gynecologic Oncology in 2007, and the UK followed suit in 2011. The National Institute for Health and Care Excellence (NICE) recommended that any symptomatic women should be prioritized for testing and referred to see a gynecologist within 2 weeks (fast-track pathway). The diagnostic pathway involves sequential testing of cancer antigen 125 (CA125) followed by a transvaginal ultrasound scan if the CA125 level is raised.[10]

Complete tumor resection after surgery is a favorable prognosticator in women with ovarian cancer.[11] The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) was a trial in which women were randomized to 'no screening' or 'multimodal screening' based on their CA125 results interpreted using the Risk of Ovarian Cancer Algorithm (ROCA). Although their results did not demonstrate any overall cancer-related mortality benefit in the average-risk general population, a recent exploratory analysis showed that screening is able to detect women with high grade serous ovarian cancer at stage 1 and 2 and leads to improved short-term outcomes.[12] Similarly, results from the Normal Risk Ovarian Screening Study (NROSS) demonstrated a marked stage shift whereby 70% of ROCA-detected cases of ovarian cancer and borderline tumors were stage 1 and 2.[13] Detection of early-stage disease potentially results in a higher proportion of women receiving treatments including surgery and adjuvant chemotherapy. The DOvE study,[14] a large pilot prospective study of facilitated prompt assessment of symptomatic women over 50 years, demonstrated that while this approach did not reduce the number of women diagnosed with high grade serous ovarian cancer at an advanced stage, a higher rate of complete cytoreduction was achieved in women with stage 3 and 4 ovarian cancer who accessed symptom-triggered testing (36%) compared with those presenting via other pathways (21%). DOvE authors concluded that symptom-triggered testing was associated with a lower tumor burden as evidenced by the lower CA125 level in study participants.

METHODS

In this descriptive study, we report on a subgroup of women recruited into ROCkeTS and who were diagnosed with high grade serous ovarian cancer via the fast-track referral pathway. In particular, we describe the demographics (age and menopausal status), WHO performance status, FIGO stage at diagnosis, disease distribution (low/pelvic confined, moderate/extending to mid-abdomen, high/extending to upper abdomen), and complete cytoreduction rates in these participants. This study conforms to the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) statement: guidelines for reporting observational studies.

Study Protocol

ROCkeTS is an observational prospective diagnostic test accuracy study to validate risk prediction models in pre-menopausal and post-menopausal women with suspected ovarian cancer.[15] Participants were recruited from 24 hospitals across the UK. Women were eligible if they had a raised CA125 at primary care level, any abnormal imaging results in the community, or both. These women were recruited after a referral to hospital through the fast-track pathway, routine outpatient referrals, or following emergency admissions. An information leaflet was given to all potential participants and their eligibility was checked by a doctor. Written consent was provided. Participants donated a blood sample for biomarker studies and underwent an ultrasound scan scored as per International Ovarian Tumor Analysis (IOTA) criteria by a doctor or sonographer who had completed face-to-face training in undertaking and in the interpretation of these scans.

Women completed a baseline questionnaire, and three further case report forms (participant, surgery, outcome) with details about their clinical presentation, baseline investigation results, obstetric, gynecological, and surgical histories; clinico-pathological outcomes such as the final histology result and treatment received were completed by the research nurse (Figure 1). The surgery case report form was completed for all women in whom a histological diagnosis was obtained at surgery or via a biopsy. The evaluation of the diagnostic accuracy of biochemical or imaging tests is underway.

Participants

Women between 16 and 90 years of age, who reported non-specific symptoms as per NICE guidelines and who had either an abnormal CA125 or ultrasound scan, or both, were recruited. Women with a current active non-ovarian malignancy, a previous history of ovarian cancer, or who were pregnant were excluded. Women were followed up until either a histological diagnosis (benign, borderline, ovarian cancer, non-ovarian cancer) was attained via a biopsy or surgery at 3 months, and those who did not undergo biopsy or surgery were followed up at 12 months. Patients could only be recruited prior to undergoing biopsy or surgery, that is, knowledge of the biopsy result was an exclusion criteria. Women were recruited between June 2015 and March 2023 to ROCkeTS or to ROCkeTS-GEN, a sub-study whereby postmenopausal women donate a plasma sample. In our analysis, we included women recruited until July 2022. Detailed histology information and details of surgery were collected through case report forms. The study design is presented in Figure 1.

Data Collection in the ROCkeTS study

Ovarian Cancer Staging

All cases were staged as per the FIGO Ovarian Cancer Staging System 2014.

Extent of Disease

Disease spread was classified as low (pelvic and retroperitoneal spread only), moderate (extending to the abdomen but not involving the upper abdomen), and high (upper abdominal spread to upper

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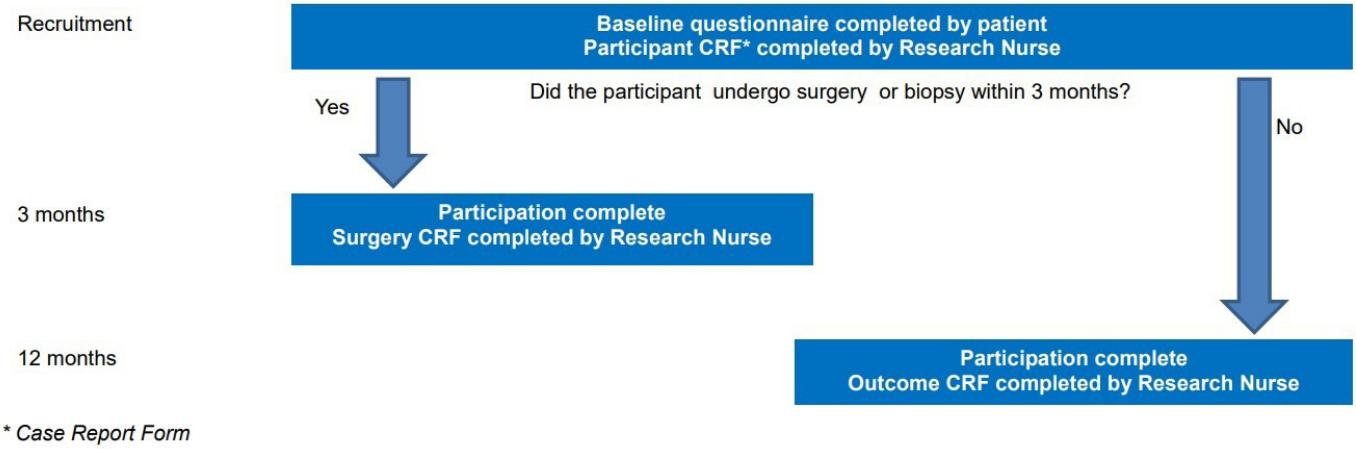

Figure 1 Study design.

abdominal viscera such as the diaphragm, spleen, liver, pancreas, or porta hepatis).

Cytoreduction

Standard definitions were used to define the residual tumor load, namely complete resection (no visible residual disease), residual disease ≤1 cm (1 cm or less of disease remaining), and residual disease >1 cm. Unresectable cancers whereby only an exploratory laparotomy was undertaken were classed as 'inoperable'.

Fast-Track Pathway

This is also known as a '2-week wait' pathway in the UK. It describes an expedited pathway with timelines by which patients should be seen by specialists and undergo further management following their referral from primary care physicians prior to the patient's appointment with a gynecologist in hospital.

Statistical Analysis

Categorical data were presented using numbers (frequencies) and proportions (percentage). The normality of distribution for continuous variables was ascertained using the Shapiro-Wilk Test and parametric variables were presented as mean and SD. All analyses were performed using Stata version 17. Women with high grade serous ovarian cancer of stage 1C and above were considered as a distinct subgroup, as current national guidance advocates chemotherapy in this population.[16]

RESULTS

Of the 2596 participants in ROCkeTS, 1741 (67.0%) were recruited via the fast-track pathway, 692 (26.7%) from outpatient clinics, and 163 (6.3%) following emergency presentations. Among women presenting via the fast-track pathway, 12.3% (215/1741) were diagnosed with primary ovarian cancer. The majority of these, that is 206 of 215 (95.8%), were epithelial tumors, six of 215 (2.8%) sex cord stromal tumors, and three of 215 (1.5%) germ cell tumors. Of the 206 women with primary epithelial ovarian cancer, 87 of 215 (40.5%) were non-high grade serous ovarian cancer. These included 27 (12.6%) mucinous, 22 (10.2%) endometrioid, 17 (7.9%) clear cell, 16 (7.4%) low grade serous, four (1.9%) unknown, and one (0.5%) undifferentiated subtypes (Table 1).

A total of 119 of 1741 (6.8%) women presenting via the fast-track pathway were diagnosed with high grade serous ovarian cancer. The median age was 63 years (range 32–89) and 107 of 119 (89.9%) of these women were post-menopausal. Most women, that is 112 of 119 (94.1%), were diagnosed with good performance status (0 and 1), while six of 119 (5.0%) had a performance status score of 2, and the performance status was unknown in one of 119 (0.9%). The extent of disease was low in 43 of 119 (36.1%), moderate in 34 of 119 (28.6%), high in 32 of 119 (26.9%), and not available in 10 of 119 (8.4%). Nearly two thirds, that is 78 of 119 (65.5%) women with high grade serous ovarian cancer, underwent primary debulking surgery, 36 of 119 (30.3%) received neoadjuvant chemotherapy followed by interval debulking surgery, and five of 119 (4.2%) women did not undergo surgery. Complete cytoreduction was achieved in 73 and 119 (61.3%), residual ≤1 cm in 18 of 119 (15.1%), residual >1 cm in two of 119 (1.7%), and surgical outcomes were not available in 17 of 119 (14.3%). The disease was deemed to be inoperable in nine of 119 (7.6%) women. Most (110 of 119 (92.4%)) participants with high grade serous ovarian cancer were stage 1C and above and 92 of 110 (83.7%) of these received chemotherapy (Table 2).

DISCUSSION

Summary of Main Results

Women were predominantly recruited to ROCkeTS via the fast-track pathway (67.0%). Our results demonstrate that one in four women with high grade serous ovarian cancer diagnosed through the fast-track pathway were diagnosed with early-stage disease (stage I or II). The majority (94.1%) of women diagnosed with high grade serous ovarian cancer via the symptom-triggered fast-track pathway were diagnosed with a good performance status (0 and 1), with low-to-moderate disease spread (64.7%), and complete cytoreduction or residual disease ≤1 cm was achieved in 76.5%.

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Table 1 Stage and histological subtype distribution

FIGO stage	Number of cases	High grade serous (% by stage), n (%)	Histological subtype	n (%)
1	78	12 (15.4)	Epithelial	
			Mucinous	25 (32.1)
			Endometrioid	16 (20.5)
			High grade serous	12 (15.4)
			Clear cell	12 (15.4)
			Low grade serous	6 (7.7)
			Unknown	1 (1.3)
			Non-epithelial	
			Germ cell tumor	1 (1.3)
			Sex cord stromal tumor	5 (6.3)
2	25	18	Epithelial	
			High grade serous	18 (72.0)
			Mucinous	2 (8.0)
			Endometrioid	1 (4.0)
			Low grade serous	2 (8.0)
			Undifferentiated	1 (4.0)
			Non-epithelial	
			Sex cord stromal tumor	1 (4.2)
3	94	75	Epithelial	
			High grade serous	75 (79.8)
			Low grade serous	7 (7.4)
			Endometrioid	5 5.3)
			Clear cell	5 (5.3)
			Unknown	1 (1.1)
			Non-epithelial	
			Germ cell tumor	1 (1.1)
4	13	11	Epithelial	
			High grade serous	11 (84.6)
			Low grade serous	1 (7.7)
			Non-epithelial	
			Germ cell tumor	1 (7.7)
NA	5	3 (100)	Epithelial	
			High grade serous	3 (60.0)
			Unknown	2 (40.0)
Total	215	114 (55.1)	Epithelial	
			High grade serous	119 (55.3)
			Mucinous	27 (12.6)
			Endometrioid	22 (10.2)
			Clear cell	17 (7.9)
			Low grade serous	16 (7.4)
			Unknown	4 (1.8)
			Undifferentiated	1 (0.5)
			Non-epithelial	
			Sex cord stromal tumor	6 (2.8)
			Germ cell tumor	3 (1.5)

FIGO, International Federation of Gynecology and Obstetrics; NA, not available.

Table 2 Demographic and clinical outcomes

	n=119
Age, mean (SD) years	65.0 (10.1)
Post-menopausal	n (%)
Yes	107 (89.9)
No	12 (10.1)
WHO performance status	n (%)
0	90 (75.6)
1	22 (18.5)
2	6 (5.0)
3	0 (0.0)
4	0 (0.0)
NA	1 (0.9)
Stage	n (%)
1	12 (10.1)
2	18 (15.1)
3	75 (63.1)
4	11 (9.2)
NA	3 (2.5)
Extent	n (%)
Low	43 (36.1)
Moderate	34 (28.6)
High	32 (26.9)
NA	10 (8.4)
Management decision	n (%)
Primary debulking surgery	78 (65.5)
Interval debulking surgery	36 (30.3)
No surgery	5 (4.2)
Cytoreduction rate	n (%)
Complete	73 (61.3)
Residual <1 cm	18 (15.1)
Residual ≥1 cm	2 (1.7)
Inoperable	9 (7.6)
NA	17 (14.3)
FIGO stage 1 C3 and above	n=110
Received chemotherapy	n (%)
No	16 (14.5)
Yes	92 (83.7)
NA	2 (1.8)

FIGO, International Federation of Gynecology and Obstetrics; NA, not available.

Five patients (4.2%) did not receive any treatment. Our figures demonstrate that in a real-world setting, symptom-based testing can potentially lead to diagnosis of high grade serous ovarian cancer with low disease spread and results in a high proportion of complete cytoreduction. Our results are consistent with findings from the DOvE research pilot[14] and demonstrate that high complete cytoreduction rates are achievable even for cases of advanced high grade serous ovarian cancer, provided that women presenting with symptoms are expedited for investigation and treatment.

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Results in Context of Published Literature

Early Stage Diagnosis and Performance Status

Some authors have questioned the benefit of symptom-based testing for ovarian cancer and hypothesized that once women experience symptoms, their disease should be presumed to be in its advanced stages and any effort to arrange earlier interventions including streamlining the route to diagnosis are therefore futile.[17] Instead, tumor biology was ascribed as the overarching prognosticator for survival of most cases of ovarian cancer.[17 18] Kurman *et al* suggested that ovarian cancer can be categorized as type 1 and type 2 tumors.[19] Type 1 includes well-differentiated tumors such as mucinous, low-grade serous, and endometrioid tumors. These subtypes of ovarian cancer are usually indolent and hence diagnosed in their early stages, and were initially believed to represent the majority of cases of primary ovarian cancer identified in screening trials.[20 21]

Our results demonstrated that three in 10 women diagnosed with early-stage ovarian cancer via the fast-track pathway were of the high grade serous subtype (type 2). This finding confirms that even high grade serous ovarian cancer, the most lethal subtype of ovarian cancer which usually accounts for 90% of ovarian cancer-related deaths, can be detected at an early stage in women diagnosed via the fast-track pathway following symptom-triggered testing. Results from the UKCTOCS randomized controlled trial demonstrated that multimodal screening results in a stage shift but without any survival benefit.[2] Recent analysis of the trial data demonstrated for the first time that multimodal screening was able to detect a larger proportion of early stage (I and II) high grade epithelial ovarian cancer (25%) compared with the 'no screening' (14%) arm.[22]

Our results demonstrate that similar outcomes are also attained via the symptom-based testing whereby 25.2% of cases of high grade serous ovarian cancer were diagnosed at an early stage. First, these findings challenge the assumption that the disease should always be considered to be in its advanced stages in women once they develop symptoms. More importantly, our findings emphasize the importance of increasing an awareness of ovarian cancer symptoms to facilitate earlier diagnosis via referral through the fast-track pathway to improve patient outcomes. A recent publication by Dilley *et al*[22] demonstrated that half of women experience symptoms before the signs of ovarian cancer manifest clinically. The authors further described how women with early-stage preclinical disease most commonly experienced gastrointestinal symptoms such as a change in bowel habits and dyspepsia, as well as systemic symptoms such as fatigue. Results of the Cancer Loyalty Card Study (CLOCS),[23] a retrospective case–control study of women with ovarian cancer, demonstrated that symptoms such as indigestion or pain usually emerge up to 8 months prior to the diagnosis, as evidenced by a higher purchase rate of medications for these symptoms.

Cytoreduction Rates

Recent studies have demonstrated that the majority of high grade serous ovarian cancer originates from its precursor serous tubal intra-epithelial carcinoma in the fimbrial ends of the fallopian tube. This has led clinicians to question whether early detection using CA125 or pelvic ultrasound scans may actually be of value.[9] In our study, nearly two thirds of women with high grade serous ovarian cancer were diagnosed when the disease distribution was low-to-moderate. Complete cytoreduction was achieved in 61.3% and in 15.1% of patients, ≤1 cm residual disease was achieved at surgery. We therefore conclude that symptom-based testing may play an essential role in facilitating the early detection of low-volume disease, and therefore high complete cytoreduction rates, as was previously proposed by the DOvE pilot study (Online Supplemental Table S1).

Strengths and Weaknesses

ROCkeTS is a prospective study and women were recruited from 24 sites across the UK. The study included over 2500 women among whom 1741 were recruited from the symptom-triggered fast-track pathway. ROCkeTS is the first large multicenter study that reports on the impact of symptom-triggered testing in women diagnosed with high grade serous ovarian cancer following the implementation of the fast-track pathway. Efforts were made during the data collection phase to obtain additional information for patients with missing data by contacting the patient's general practitioner or by accessing their medical records. Standard definitions were used for patient demographics, oncological outcomes, and the modes of presentation to ensure that the data collection process was robust and unambiguous.

We acknowledge that our study may be subject to selection bias and that this may have resulted in the stage distribution seen in our study. We had compared the performance status, disease stage, and cytoreduction rates by mode of presentation (Online Supplemental Table S2) and our results did not show any significant difference among these variables by route of presentation. However, it was not possible to draw a meaningful conclusion as the number of women recruited via the emergency pathway and from other outpatient referrals were modest. Dahlberg *et al*[24] demonstrated that critically unwell eligible patients are often omitted during study inclusion and identified barriers to recruitment such as practical, medical, or ethical issues from the patient or their next of kin. In our case, we presume that women with a good performance status (0 and 1) could have been preferentially approached by the research nurses. However, given that recruitment was research nurse-led and that knowledge of histology was an exclusion criterion for the study, we believe that our findings in relation to high grade serous ovarian cancer histology cannot be exclusively attributed to selection bias.

Implications for Practice and Future Research

Recent studies[25–27] have demonstrated a lack of understanding of the symptoms of ovarian cancer from women as well as primary care physicians across the UK. Improving community awareness of symptoms of ovarian cancer and enhanced use of the fast-track pathway are thus likely to contribute to improved oncological outcomes for women with high grade serous ovarian cancer.

CONCLUSION

Our results showed that one in four women with high grade serous ovarian cancer diagnosed through the fast-track pathway following symptom-triggered testing were diagnosed with early-stage disease. Symptom-triggered testing may help to identify women with low disease burden, potentially contributing to high complete

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cytoreduction rates and improving survival outcomes in these patients. As this is one of the largest prospective series in the UK, we consider that our data are generalizable and have implications for the UK but also other healthcare systems. These results support the current role of symptom-triggered testing to detect high grade serous ovarian cancer at good performance status and low disease load.

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Correction notice This article has been corrected since it was first published. The first sentence of the Introduction has been corrected to describe early stage as FIGO stage I and advanced stage as stage IV.

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