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# A national, prospective observational study of first recurrence after primary treatment for gynecological cancer in Norway

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**Key words**
Gynecological cancer, ovarian cancer, endometrial cancer, cervical cancer, recurrence, follow up

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**Conflict of interest**
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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## Abstract

*Introduction.* Gynecological cancer patients are routinely followed up for five years after primary treatment. However, the value of such follow up has been debated, as retrospective studies indicate that first recurrence is often symptomatic and occurs within two to three years of primary treatment. We prospectively investigated time to first recurrence, symptoms at recurrence, diagnostic procedures, and recurrence treatment in gynecological cancer patients after primary curative treatment. *Material and methods.* Clinicians from 21 hospitals in Norway interviewed 680 patients with first recurrence of gynecological cancer (409 ovarian, 213 uterine, and 58 cervical cancer patients) between 2012 and 2016. A standardized questionnaire was used to collect information on self-reported and clinical variables. *Results.* Within two years of primary treatment, 72% of ovarian, 64% of uterine, and 66% of cervical cancer patients were diagnosed with first recurrence, and 54, 67, and 72%, respectively, had symptomatic recurrence. Of symptomatic patients, 25–50% failed to make an appointment before their next scheduled follow-up visit. Computer tomography was the most common diagnostic procedure (89% of ovarian, 76% of uterine, and 62% of cervical cancer patients), and recurrence treatment in terms of chemotherapy was most frequently planned (86% of ovarian, 46% of uterine, and 62% of cervical cancer patients). *Conclusions.* A majority of patients experienced symptomatic recurrence, but many patients failed to make an appointment earlier than scheduled. Most first recurrences occurred within two years of primary treatment; the mean annual incidence rate for years 3–5 after primary treatment was <7%. New models for follow up of gynecological cancer patients could be considered.

**Abbreviations:** CA125, cancer antigen 125.


 

## Introduction

Women who have completed treatment for gynecological cancer are normally followed up in hospital outpatient clinics for at least five years, to detect and manage cancer recurrence, and to monitor physical and psychosocial late effects of treatment. Current practice is not evidence-based, and the value of the surveillance has been debated due to related costs and lack of demonstrable survival benefits (1–5). Furthermore, recurrences are often detected due to symptoms that manifest between scheduled follow-up visits (6) within two to three years of primary treatment (1,7,8). Symptomatic recurrence has been reported to vary: 18–49, 41–83, and 46–96% for ovarian cancer, uterine cancer, and cervical cancer, respectively (1,2,9–18). Most studies do not report specific symptoms, but in those that have, pain and vaginal bleeding were most common (5,10,12,19). It is unclear whether symptomatic patients delay seeking help until their next scheduled follow-up visit, as previous studies have been retrospective, based on medical records (6,7,15).

Most follow-up guidelines are based on medical tradition, not evidence-based knowledge, which has led to a call for randomized studies (7,8,20). Different research models have been proposed, but the large sample size needed, fear of delayed diagnosis, and possible negative effects on survival have kept researchers from conducting, and health authorities from supporting, studies with time to recurrence and/or survival as primary outcomes. As former studies published on follow up of gynecological cancer patients are retrospective and based on reviewed medical records, exact knowledge on recurrences is lacking. Though the retrospective studies indicate that most recurrences give symptoms and are detected by the women themselves between follow-up visits, only prospective registration of the recurrences can confirm these findings. To optimize the planning of a future intervention study on follow up of gynecological cancer, a first step should therefore be a prospective registration of recurrences. Thus, we aimed to investigate prospectively the time to first recurrence, symptomatic recurrence, diagnostic procedures, and treatment at recurrence in gynecological cancer patients after primary curative treatment.

## Material and methods

According to the Cancer Registry of Norway, the average annual number of new cases of gynecological cancer in Norway in 2010–2014 was 1636 (21), and the five-year relative survival is 45.1% for ovarian cancer, 83.5% for uterine cancer and 80.6% for cervical cancer. The majority of the patients receive primary treatment at the gynecological department of one of the four regional university hospitals, with the exception of low-risk International Federation of Gynecology and Obstetrics (FIGO) stage IA endometrial cancer. According to national guidelines, patients can receive follow-up after primary treatment either at the same regional university hospitals or at the gynecological departments of one of 27 local hospitals in collaboration with the regional university hospitals (22). In addition, some patients are followed up by gynecologists in private practice. Standard follow up for all gynecological cancers consists of clinical examination with vaginal ultrasound three to four times annually the first two years, twice a year over the next three years, and annually thereafter depending on the recommendations of her clinician. In addition, ovarian cancer patients are tested for cancer antigen 125 (CA125) at the clinician's discretion, and it is recommended that cervical cancer patients undergo yearly chest X-ray, and vault cytology after surgery (22). When recurrence is suspected or diagnosed, the regional university hospital is consulted, and treatment, if any, is decided in multidisciplinary tumor boards. Recurrences are not routinely reported to the Cancer Registry of Norway.

In 2011, we invited the 31 gynecological departments of the regional and local hospitals mentioned above to take part in a national investigation of first recurrence of gynecological cancer. Information about the study was given through e-mails and telephone conversations with chief consultants and was disseminated in national and regional meetings for gynecologists and in the Norwegian journal, *Gynekologen* (23). Ten local hospitals chose not to participate due to lack of resources. To be included, patients had to have a primary diagnosis of ovarian, uterine, cervical or vulvar cancer and to have received primary treatment with a curative intent. Upon diagnosis of recurrence, patients were interviewed by their clinician, after informed consent was given. A standardized questionnaire was used to collect information on self-reported information (type and duration of symptoms, whether recurrence was suspected by the patient, whether symptoms led to earlier contact with health services), as well as clinical variables taken from medical records (primary histology, primary treatment, duration of primary

### Key Message

The majority of recurrences among gynecological cancer patients were symptomatic and pain was the most common symptom. In all, 42% of the patients delayed seeking help despite symptoms. Two-thirds of the recurrences occurred within two years of primary treatment.

treatment, number of follow-up visits after primary treatment, place of visits, method of recurrence detection, location of recurrence, and planned recurrence treatment). Recurrences in the vault of the vagina and in the pelvis were classified as local and all other sites as distant.

Between March 2012 and April 2016, the 21 participating gynecological departments recruited 743 eligible patients. We excluded four with primary borderline ovarian cancer, and removed 27 cases of duplicate registration. Moreover, as curative vs. palliative intent was not specified in all cases, unless disease-free post-treatment status was documented, recurrences diagnosed less than three months after primary treatment were classified as disease progression or an incomplete response to primary treatment, and were excluded ($n$ = 18). Finally, due to small numbers, we excluded all 14 vulvar cancer patients (Figure 1).

### *Statistical analyses*

Due to the exploratory nature of this study, no power analyses were performed beforehand. Crude differences between pairs of categorical variables were assessed with chi-square tests. A $p$-value <0.05 was considered statistically significant and all tests were two-sided. Statistical package for the social sciences for Windows version 21.0 was used for all statistical analyses (SPSS Inc., Chicago, IL, USA).

### *Ethical approval*

The study was considered quality assurance by the Regional Committee for Ethics in Medical Research, Region South (2011/1732 B) and did not require approval. The Norwegian data inspectorate (2012/29194) approved the study. The data protection authorities at all participating hospitals also approved the study.

## Results

Of the 680 included patients, 409 had ovarian cancer, 213 had uterine cancer, and 58 had cervical cancer (Table 1). Within two years of primary treatment, 72%, 64%, and 66% of the ovarian, uterine and cervical cancer patients, respectively, were diagnosed with first recurrence (Figure 2). The corresponding numbers three years after primary treatment were 84%, 75%, and 85%. Annual incidence rates of first recurrence during the next three years after primary treatment were 5.2%, 7.0%, and 6.7% for the three cancer groups, respectively (Figure 2). The majority of patients had symptomatic recurrence

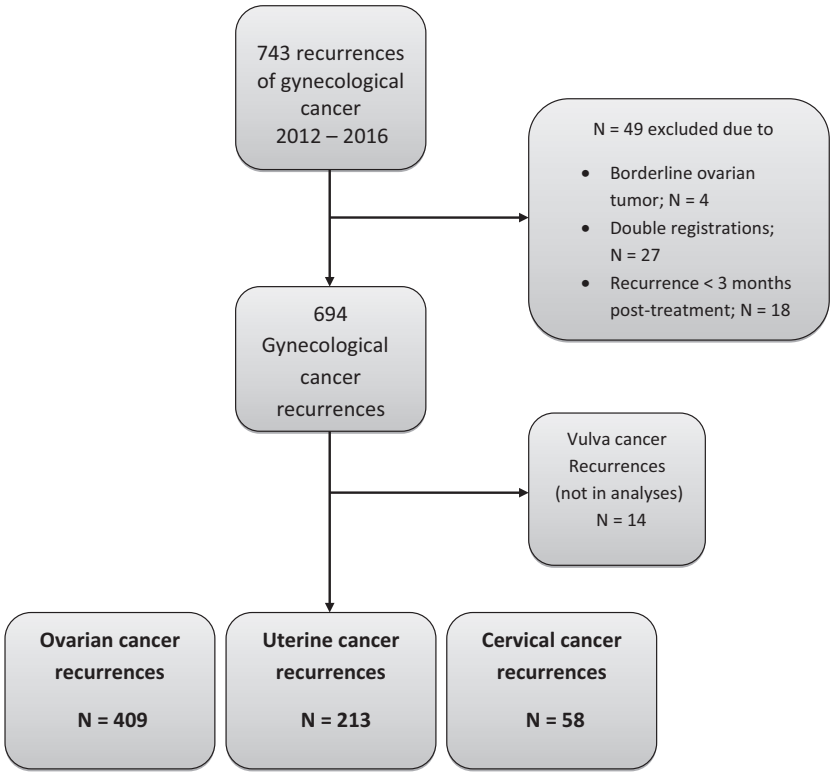


**Figure 1.** Flow chart of included patients in the Norwegian gynecological cancer recurrence study.

  

**Table 1.** Patient characteristics.

| | Ovarian cancer ($n$ = 409) | Uterine cancer ($n$ = 213) | Cervical cancer ($n$ = 58) |
|---|---|---|---|
| Median age at end of treatment, year | 63 | 69 | 49 |
| Median age at recurrence, year | 66 | 71 | 51 |
| Stage of disease | | | |
| I | 41 (10.0) | 129 (60.6) | 26 (44.8) |
| II | 30 (7.3) | 14 (6.6) | 20 (34.5) |
| III | 280 (68.5) | 58 (27.2) | 5 (8.6) |
| IV | 58 (14.2) | 11 (5.2) | 7 (12.1) |
| Unknown | – | 1 (0.5) | – |
| Histopathological type | | | |
| Endometroid | 26 (6.4) | 134 (62.4) | |
| Serous carcinoma | 325 (79.5) | 32 (15.0) | |
| Adenocarcinoma | 25 (6.1) | 12 (5.6) | 17 (29.4) |
| Clear cell | 15 (3.7) | 8 (3.8) | |
| Mucinous | 2 (0.5) | 3 (1.4) | |
| Sarcoma | 4 (1.0) | 21 (9.8) | |
| Squamous cell | | | 39 (67.2) |
| Other | 12 (2.8) | 4 (2.0) | 2 (3.4) |
| Primary treatment | | | |
| Surgery | 31 (7.5) | 117 (54.9) | 17 (29.3) |
| Radiotherapy | – | 2 (0.9) | 10 (17.2) |
| Chemotherapy | 27 (6.6) | 2 (0.9) | 4 (6.9) |
| Surgery + chemotherapy | 351 (85.8) | 81 (38.0) | 3 (5.2) |
| RT + chemotherapy | | | 18 (31.0) |
| Surgery + RT | | 9 (4.2) | 3 (5.2) |
| Surgery + chemotherapy + RT | | 2 (0.9) | 3 (5.2) |

RT, radiotherapy.

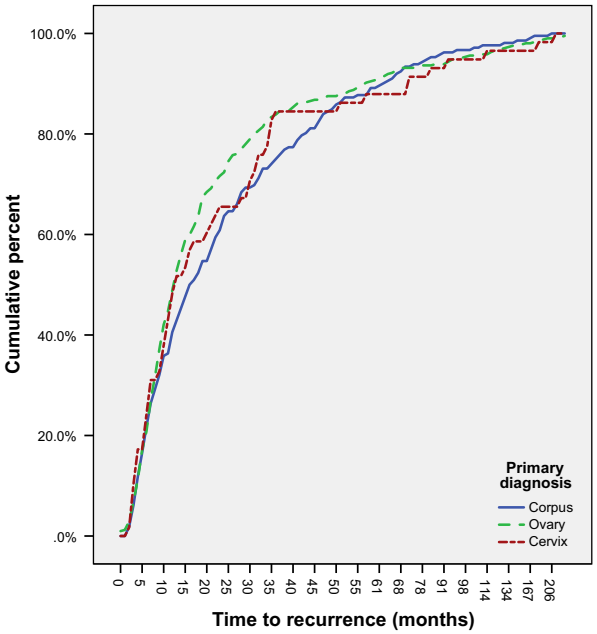


**Figure 2.** Time to recurrence for ovarian, uterine, and cervical cancer. [Color figure can be viewed at wileyonlinelibrary.com].

(Table 2). Approximately 50% had symptoms less than one month before their recurrence was confirmed; however, symptoms lasting six months or longer were reported in 18 ovarian cancer patients, 12 uterine cancer patients, and five cervical cancer patients. Pain was the most frequently reported symptom, either alone or in combination with other symptoms (Table 2). The probability of presenting with symptoms at recurrence in the total patient group (69.5%) did not differ between those who had recurrence within two years of primary treatment and those with a later recurrence ($p$ = 0.53). Furthermore, there was no correlation between stage and symptoms in any of the cancer groups. Asymptomatic recurrences in endometrial cancer patients were primarily detected by biopsy (68%) and in ovarian cancer patients by increased CA125. Of the 16 asymptomatic cervical cancer patients, eight recurrences were detected by histology, four by cytology, four by computed tomography alone, and none by chest X-ray.

In contrast to uterine cancer patients, the majority of ovarian and cervical cancer patients had distant metastases at recurrence (Table 2). Local recurrence was significantly associated with a primary diagnosis of stage I disease among uterine cancer patients ($p < 0.001$), but there was no such association in the other cancer groups. Computer tomography was the most common diagnostic procedure in all cancer groups, often in combination with histology or cytology.

## Discussion

This is the first prospective, nationwide study to record information systematically on gynecological cancer recurrences. Most Norwegian gynecological departments, including those at the four regional university hospitals, participated. The majority of patients had symptomatic recurrence. Despite this, 25–50% did not expedite their next scheduled visit. Most recurrences occurred within two years of primary treatment.

Only 54% of the ovarian cancer patients had symptomatic recurrence, despite a primary diagnosis of advanced disease. This is in line with the findings of Geurts et al. (15), where 49% of the 127 included ovarian cancer patients had symptomatic recurrence. However, our number is higher than the range of 18–44% reported by other authors (17,18,24). Those studies had small sample sizes and were based on data retrieved from medical records. In the present study, 116 symptomatic ovarian cancer patients had their recurrence confirmed at a routine follow-up visit. Thus, routine follow up may have led to delayed diagnosis and treatment in this group.

**Table 2.** First recurrence of ovarian, uterine, and cervical cancer in Norway in 2012–2016 ($n$ = 680).

| | Ovarian cancer | | Uterine cancer | | Cervical cancer | |
|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % |
| Median time to recurrence (months) | 13 | | 16 | | 15 | |
| Symptoms at recurrence | | | | | | |
| Yes | 221 | 54.0 | 142 | 66.6 | 42 | 72.4 |
| No | 188 | 46.0 | 71 | 33.3 | 16 | 27.6 |
| Status in symptomatic patients ($n$ = 405) | | | | | | |
| Symptoms ≤1 month | 122 | 55.2 | 78 | 54.9 | 20 | 47.6 |
| Symptoms >1 month | 99 | 44.8 | 64 | 45.1 | 22 | 52.4 |
| Prescheduled visits | | | | | | |
| Yes | 105 | 47.5 | 103 | 72.5 | 26 | 61.9 |
| No | 116 | 52.5 | 39 | 27.5 | 16 | 38.1 |
| Type of symptoms[a] | | | | | | |
| Pain | 131 | 59.3 | 63 | 44.4 | 27 | 64.3 |
| Vaginal bleeding | 5 | 2.3 | 46 | 32.4 | 10 | 23.8 |
| Ascites | 47 | 21.3 | 5 | 3.5 | 1 | 2.4 |
| Fatigue | 38 | 17.2 | 13 | 9.2 | 9 | 21.4 |
| Intestinal problems[b] | 56 | 25.3 | 14 | 9.9 | 2 | 4.8 |
| Site of recurrence | | | | | | |
| Local | 72 | 17.6 | 115 | 54.0 | 24 | 41.4 |
| Distant | 337 | 82.4 | 98 | 46.0 | 34 | 58.6 |
| Investigations[c] | | | | | | |
| Histology | 121 | 29.6 | 159 | 74.6 | 39 | 67.2 |
| Cytology | 71 | 17.4 | 34 | 16.0 | 9 | 15.5 |
| Computer tomography | 366 | 89.5 | 162 | 76.1 | 36 | 62.1 |
| MRI | 16 | 3.9 | 34 | 16.0 | 20 | 34.5 |
| Ultrasound[d] | 87 | 21.3 | 53 | 24.9 | 2 | 3.4 |
| Planned recurrence treatment | | | | | | |
| Chemotherapy | 351 | 85.8 | 96 | 45.6 | 36 | 62.1 |
| Radiotherapy | 5 | 1.2 | 74 | 34.7 | 10 | 17.2 |
| Surgery | 12 | 2.9 | 5 | 2.3 | 4 | 6.9 |
| Combination[e] | 30 | 7.3 | 23 | 10.8 | 5 | 8.6 |
| Hormones | 2 | 0.5 | 8 | 3.8 | – | – |
| No treatment | 9 | 2.2 | 6 | 2.8 | 3 | 5.2 |

MRI, magnetic resonance imaging.

[a]Most frequent symptoms reported. Several symptoms could co-occur.

[b]Ileus, constipation, blood in stools.

[c]Several methods could be combined.

[d]Transvaginal or abdominal ultrasound.

[e]Combination of surgery and/or chemotherapy and/or radiotherapy.

Asymptomatic recurrences in ovarian cancer patients were primarily detected by increased CA125. This is challenging because early initiation of recurrence treatment based on elevated CA125 has shown no survival benefit when compared with treatment at clinical evidence of recurrence (25). By the same token, the majority of the patients had distant disease at recurrence and only 7.3% were treated with cytoreductive surgery, often in combination with chemotherapy.

In Norway, 80% of uterine cancers are diagnosed as localized disease, which explains the high number of stage I uterine cancer recurrences (21). Two-thirds of the recurrences in our study were symptomatic, which is in line with a pooled analysis of 12 retrospective studies conducted by Fung-Kee-Fung et al. (26), in which 70% of uterine cancer recurrences were symptomatic. Though pain was the leading symptom in uterine cancer patients, one-third of those presenting with symptoms had vaginal bleeding. In retrospective series involving 27–214 cases of uterine cancer patients, the reported frequency of vaginal bleeding varied from 7 to 24% and abdominal and pelvic pain from 31 to 47% in symptomatic patients (9,12,19,27). In our study, vaginal bleeding was more frequent (33%) than in the aforementioned studies. This may be related to brachytherapy, which is rarely used in the primary treatment of uterine cancer in Norway, but may be more common in other countries. In our study, 47.8% of recurrences were treated with radiotherapy, surgery or a combination of both, which may successfully cure isolated vaginal vault recurrences. We did not specifically ask where in the pelvis the recurrence was located, and unless the recurrence is located in the vaginal vault or in the minor pelvis, the prognosis is poor (9,11,12).

We have no information on why computed tomography was carried out in asymptomatic cervical cancer patients, but we assume that biopsies from asymptomatic patients were taken from suspect lesions. As in other studies, most cervical cancer patients had symptomatic recurrence, with pain being the most frequently reported. Symptoms led to prescheduled visits for 62% of the cervical cancer patients, which is higher than the 39% reported by Brooks et al. (28). In the retrospective study by Ansink et al. (3), 29/112 (26%) of disease recurrences in patients with cervical cancer were detected at the time of routine follow-up visits. Although 45% of cervical cancer patients in the present study had stage I disease at primary diagnosis, two-thirds had distant metastasis at recurrence. This was reflected in planned recurrence treatment, which was with curative intent solely in the patients without distant metastasis.

The main strength of the present study is the nationwide prospective study design. The other major asset is that all participating gynecological departments used the same questionnaire to collect patient-reported and clinical variables extracted from medical records at the time of recurrence. Indeed, reliable information on time to recurrence and planned recurrence treatment can be extracted from medical records, but information on symptoms (length, type) and timing of doctor visits are prone to recall bias and are thus more reliable when prospectively registered. Another strength is that all participating departments were public, free-of-charge hospitals using

the same national guidelines for follow up. Furthermore, this is the most comprehensive study to date, including nearly 700 patients with first recurrence of gynecological cancer. Randomized controlled trials comparing conventional follow up of gynecological cancer patients with alternative methods of care are the optimal way to derive evidence-based guidelines. However, our findings add information of a higher level of evidence compared with studies based on retrospective data from medical records.

The main limitation of the present study is that we have no information on the total number of patients with first recurrence during the study period, and no national registry of recurrences exists. Furthermore, gynecologists in private practice did not recruit patients in the study. However, in this study we did not intend to make a complete recurrence analysis, but rather to describe patterns of recurrence. Due to the high number of included patients from both local hospitals and the regional university hospitals, we assume that our study sample is representative of recurrent ovarian and uterine cancers, but not necessarily cervical cancers, as these comprised only 58 patients. Also, there were very few vulvar cancer patients, which prevented us from performing analyses in this group. Furthermore, we did not ask for information on the extent of primary surgery, which may influence the recurrence rate, especially for ovarian cancer.

Our findings indicate that hospital-based routine follow up beyond two years after primary treatment has a low cost-benefit, as a great number of consultations must be carried out for each detected recurrence. We have not evaluated recurrence by stage and we have no survivor data yet, preventing us from proposing changes to the present follow-up program. However, because most recurrences are detected by the patients themselves within two years after primary treatment, studies comparing short follow up (< two years) with long follow up (> two to five years) should be safe also for patients with advanced disease.

Follow up of cancer patients is performed not only to detect recurrence but also to provide help with side effects after treatment, psychosocial support, and counseling. Therefore, different models of care should be tested among gynecological cancer patients after treatment. The Norwegian Directorate of Health has developed guidelines for cancer follow-up, proposing greater involvement of the patient's general practitioner (29,30). In a study of general practitioners' attitudes toward follow up after cancer treatment in Norway, general practitioners agreed that they should be involved at an earlier stage in follow-up care, and the majority felt confident in their ability to provide the care needed (29). Other low-cost alternatives include self-referral in the event of symptoms or nurse-led follow up.

Depending on cancer type, 25–50% of the symptomatic patients in the present study did not seek help before their scheduled follow-up visit, which underlines the need for better information on symptoms to watch for, and when or whom to contact should symptoms occur. It may be time to shift the focus from a lengthy, hospital-based surveillance program to enabling patients to engage in self-management. A follow-up care plan may be a useful tool for cancer patients, and should be provided after primary treatment (29). It should include information on possible signs of recurrence and information on frequent late and long-term treatment-related symptoms and side effects. Furthermore, it should explicitly appoint the providers responsible for each aspect of ongoing care and provide information on sexual, psychosocial, and other practical issues that may arise as a result of cancer diagnosis.

The purpose of this prospective, nationwide study was to record systematically both self-reported and clinical information extracted from medical records on gynecological cancer recurrences. The results showed that the majority of patients experienced symptomatic recurrence, but a significant proportion of women awaited the routine scheduled follow-up visit to report the occurrence of symptoms. Most recurrences occurred within two years of primary treatment; after two years the yearly mean incidence rate for new recurrences was less than 7%. As hospitalized-based follow-up is resource-demanding, our results imply that shorter hospital follow up should be considered also among patients with advanced disease.

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