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An update on post-treatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncology (SGO) recommendations

Ritu Salani [a,*], Namita Khanna [b], Marina Frimer [c], Robert E. Bristow [d], Lee-may Chen [e]

[a] Department of Obstetrics & Gynecology, The Ohio State University, Columbus, OH, United States
[b] Department of Gynecology & Obstetrics, Emory University, Atlanta, GA, United States
[c] Department of Obstetrics & Gynecology, Hofstra Northwell School of Medicine, New Hyde Park, NY, United States
[d] Department of Obstetrics & Gynecology, University of California Irvine, Los Angeles, CA, United States
[e] Department of Obstetrics & Gynecology, University of California San Francisco, San Francisco, CA, United States

HIGHLIGHTS

- Surveillance strategies for gynecologic cancer vary based on stage and recurrence risk.
- Review of symptoms, physical exam, and education are the most effective methods in surveillance.
- Data supports limiting/eliminating routine imaging and cytology in the surveillance period.

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ABSTRACT

Gynecologic cancers account for ~12% of all new cancer cases in women and ~15% of all female cancer survivors. Current and continued advances within the field have resulted in long-term outcomes and a high rate of survivors. Therefore determining the most cost-effective clinical surveillance for detection of recurrence is critical. Unfortunately, there has been a paucity of research regarding the most effective strategies for surveillance after patients have achieved a complete response. Currently, most recommendations are based on retrospective studies and expert opinion. Taking a thorough history, performing a thorough examination, and educating cancer survivors about concerning symptoms are the most effective methods for the detection of most gynecologic cancer recurrences. There is very little evidence that routine cytology or imaging improves the ability to detect gynecologic cancer recurrence that will impact cure or response rates to salvage therapy. This article provides an update on surveillance for gynecologic cancer recurrence in women who have had a complete response to primary cancer therapy.

1. Introduction

In 2017, gynecologic malignancies are expected to afflict approximately 107,470 women within the United States [1]. Improvements in cancer care have resulted in over 8 million female cancer survivors, and this number is expected to grow by over 25% in the next ten years [2]. As survivorship continues to grow, coordination of care between gynecologic oncologists, primary care providers, other healthcare providers (such as medical and radiation oncologists), and patients will allow for compliance with cancer follow-up care and routine health maintenance. The provision of a clear understanding of recommendations and responsibilities of appropriate surveillance will reduce unnecessary tests and, ultimately, result in cost savings. In regards to surveillance, the primary objective is to provide clinical and cost-effective practices that detect recurrence and impact survival outcomes. Acceptance of surveillance should be considered if there is utility of treatment for recurrence and decreased morbidity from both monitoring for disease recurrence and treatment. One should also consider the use of resources for conducting these tests and patients should be counseled on the benefits and pitfalls of disease monitoring, which should include the psychologic impact of surveillance programs.

* Corresponding author at: Division of Gynecologic Oncology, Department of Obstetrics & Gynecology, The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, 320 West 10th Avenue, M210 Starling-Loving Hall, Columbus, OH 43210, United States.
E-mail address: Ritu.Salani@osumc.edu (R. Salani).

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The Society of Gynecologic Oncology (SGO) published recommendations for post-treatment surveillance in 2011 with the goal of providing cost-effective strategies while maintaining oncologic outcomes [3]. These posttreatment guidelines recommended the surveillance intervals, indicated procedures/tests, and the transition back to the primary care team. Despite these data, supporting a less intensive surveillance regimen, several publications have demonstrated that more intensive surveillance continues to occur at high rates on survivors of gynecologic malignancies [4,5]. Furthermore, several additional studies have been published regarding the routine surveillance and we present an update to the original recommendations from 2011.

2. Endometrial cancer

Endometrial cancer is the most common gynecologic cancer and the fourth most common cancer in women. There will be approximately 61,380 new endometrial cancer cases and 10,920 deaths in the United States in 2017 [1]. At the time of initial diagnosis, patients commonly experience symptoms, such as abnormal or postmenopausal bleeding, which warrant further investigation with ultrasound imaging and/or endometrial sampling. The combination of symptoms and diagnostic testing results in 83% of patients being diagnosed in the early stages of the disease [6]. As a result of localized disease, 5-year survival rates exceed 95% for stage I and approach 83% overall. However, recurrence rates for patients with early-stage disease range from 2 to 15% and reach as high as 50% in advanced stages or in patients with aggressive histologic condition [6]. As many local recurrences from endometrial cancer are curable, determining the ideal time interval and diagnostic tools for surveillance of recurrent endometrial cancer that can impact survival outcomes is critical.

Typically, surveillance guidelines are more intensive the first few years after diagnosis as many studies have shown that most (70–100%) recurrences occur within 3 years after primary treatment [7–9].To date, there are no prospective studies that have evaluated the role of surveillance in endometrial cancer follow-up evaluation. Based on recommended guidelines and institutional practices, retrospective research and literature reviews comprise the best evidence that is available. The most consistently used method for surveillance is the physical examination. This alone accounts for a high rate of detection that ranges from 35 to 68% of cases [8–11].Even more striking is that the combination of physical examination alone or with review of symptoms has resulted in rates of detection that exceed 80% [11–13].Therefore, physical examination, which includes a thorough speculum, pelvic, and rectovaginal examination, should be conducted during each follow-up assessment.

The role of surveillance is based on the concept that detection of recurrences in the asymptomatic stage results in better therapeutic options and outcomes. Interestingly, even with intensive surveillance, many recurrences are detected based on the presence of symptoms, occurring in 41–83% of patients [8,9,11,14]. A common symptom, vaginal bleeding, may be indicative of a local recurrence that is often curable if it is an isolated site of disease [8,11]. Even in patients diagnosed with a distant recurrence, symptoms, such as coughing, pain, lethargy, weight loss, or headaches, are presents in ~70% of cases [8,14–16]. Survival outcomes have been evaluated on the basis of the presence or absence of symptoms at the time of recurrence. Sartori et al. reported that women who experienced a symptomatic recurrence had poorer outcomes compared to women diagnosed with asymptomatic diagnosis based on examination or imaging [9]. However, many other series have reported that the role of routine surveillance in patients with stage I endometrial cancer had no difference in survival based on the presence or absence of symptoms [8,14,16]. Of note, patients who had symptoms were undergoing the recommended follow-up evaluations, which provide an argument against the use of intensive routine surveillance. Therefore, patient education on the signs and symptoms is a critical component of posttreatment care and may lead to the early detection of recurrent disease. Although all of these studies were retrospective, they reiterate the importance of prospective trials to determine the true role and regimen for surveillance.

Because most recurrences occur at the vaginal cuff, the use of vaginal cytology has been advocated; however, many gynecologic oncologists have challenged this recommendation [9,10–15,21]. Although studies have reported that cytologic evaluation detected 25% of all recurrences; the use of cytology alone in these studies detected only 3 of the 44 (7%) recurrences [10–15]. Additionally, in a study of women with early stage disease with a low recurrence risk, Salani et al. detected all recurrences based on symptoms/clinical findings and noted that cytology did not add any clinical benefit [17]. Along these same lines, Novetsky and colleagues evaluated the role of post-operative Pap test in women who underwent hysterectomy for all stages of endometrial cancer. In their study, 51 of the 433 patients studied were diagnosed with an endometrial cancer recurrence and no recurrences were diagnosed by cytology [18]. Of note, 3% of all Pap tests were abnormal, with no diagnoses of malignancy and these abnormalities were more likely secondary to radiation changes [18]. Kiran et al. reported on 52 women with recurrent cancer and also noted the limited utility of cytology. They also noted that intensive surveillance did not improve outcomes compared to those with symptomatic recurrences [19]. Even in a study of type II endometrial cancers, in which there is a higher recurrence rate, almost half of the patients were diagnosed by examination or symptoms, and no patients were diagnosed by cytology [20]. The lack of utility is compounded by the fact that the use of vaginal cytology at each visit results in an estimated cost of $27,000 per case detected [8]. Because most recurrences at the vaginal cuff can be found on examination, routine vaginal cytology adds only significant healthcare costs without added benefit. In a recent review of SEER database looking into trends for endometrial cancer surveillance in early stage (I-II) patients, the use of vaginal cytology has declined but remains high with over 66% having cytology in 2011 [4]. Based on the aforementioned data, the SGO established guidelines for cost containment called Choosing Wisely and advocate for the elimination of the use of liquid-based cytology (Pap test) of the vaginal cuff to detect recurrent endometrial cancer [21].

Similarly to ovarian cancer, the use of cancer antigen 125 (CA-125) levels has been investigated as a marker for recurrence. Pre-treatment CA-125 levels were elevated in more than one-half of the patients with advanced stage and/or high-grade histologic endometrial cancer [3,22]. Frimer et al. reported that an elevated CA-125 level at diagnosis was significantly associated with disease recurrence and even increases by 10 U/mL in the normal range or values ≥15 U/mL were associated with disease recurrence in uterine serous carcinoma [22]. However, the role of CA-125 levels in low risk disease is negligible and one must be aware of elevated CA-125 levels secondary to other conditions, including prior radiotherapy [16]. At present, the use of CA-125 levels should not be used routinely in patients with endometrial cancer, but may be appropriate in select patients with advanced disease, serous histologic condition, or in patients who have an elevated CA-125 level before treatment.

The use of radiographic imaging has been suggested for the detection of recurrent disease. Because of low costs, chest radiographs have been advocated for the detection of asymptomatic recurrences, often on a semiannual or annual basis. The rate of detection that are found on chest radiographs ranges from 0 to 20%, and in one series, chest radiograph detected 7 asymptomatic pulmonary recurrences, accounting for 0.34% of all chest radiographs that were performed for surveillance [7–8]. Although reports of isolated pulmonary recurrences, albeit rare, may be amenable to therapies that allow for long-term survival outcomes, the routine use of chest radiographs is not recommended [15, 22]. In further evaluation of radiographic imaging for endometrial cancer surveillance, Fung Kee Fung et al. conducted a review of the literature and found that only 5–21% of asymptomatic recurrences were found by computed tomography (CT) scans [7]. Even in type II

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endometrial cancers, CT scans detected only 15% of recurrences [12]. Other studies have agreed that the role of CT scanning for asymptomatic patients is not warranted as survival of patients with disease that is detected on CT scan, compared with clinical examination, did not differ significantly [3,15]. Another modality studied to increase the detection of local recurrence, was the use of pelvic ultrasound scans. Although detection rates for local recurrence range from 4 to 31%, many of these recurrences were also detected on other diagnostic methods, which included physical examination [7,9,15–16]. Therefore, the use of routine pelvic ultrasound and CT scanning is not advocated; however, these modalities may play a role in the evaluation of patients with symptoms, because the rates of detection approach 50% in this setting [3]. In a study of positron emission test (PET)/CT scans for endometrial cancer recurrence, Park et al. reported excellent sensitivity and specificity for detection of suspected recurrence and even reported 100% diagnostic accuracy in asymptomatic patients [23]. However, its use for routine screening has not been well studied and the high cost of this test limit its use in this setting. Unfortunately, despite these data, the routine use of CT and PET/CT scanning has increased in the past several years and prospective studies are required to determine whether PET/CT will have a role in endometrial cancer surveillance [4].

In conclusion, most patients with endometrial cancer will be a low risk for recurrence, and more than one-half of all recurrences will be detected with examination and symptoms. With the exception of local disease, recurrent endometrial cancer is associated with a poor prognosis, regardless of the time of detection. On the basis of the data, we recommend a surveillance regimen to include a thorough history and physical examination, which would include a speculum and pelvic examination, at scheduled intervals with further testing indicated to evaluate symptoms and abnormalities that are detected on examination. As recurrence rates vary based on presence of risk factors and stage of disease, surveillance may be tailored based on this risk assessment and recommendations are listed in Table 1. Cytology evaluation and chest radiographs in asymptomatic women are not beneficial and imaging should be reserved for patients with suspected recurrence. This approach is unlikely to compromise clinical outcomes and may save valuable healthcare dollars.

3. Uterine sarcomas

Uterine sarcomas are malignant mesenchymal tumors and include endometrial stromal sarcoma (ESS), undifferentiated uterine sarcoma (UUS), and uterine leiomyosarcoma (uLMS). Though only accounting for 1–2% of uterine malignancies, these tumors are often associated with a poor prognosis [24]. uLMS are the most common subtype of uterine sarcoma and even when confined to the uterus, recurrences are common, occurring in over 50% of patients [24,25]. The more common sites of recurrence include the lungs, pelvis, and liver. Due to these high rates of recurrence and distant sites, CT scans of the chest, abdomen, and pelvis are advised every 6 to 12 months (or as clinically indicated). Similar recommendations can be followed for USS. Endometrial stromal tumors are the second most common and account for <10% of all uterine sarcomas. These tumors are usually indolent with a favorable prognosis; however, they have a tendency for late recurrences, which often affect the abdomen/pelvis or lungs [26]. Though long term follow up is recommended, long term surveillance with imaging is of low yield and may be omitted in the absence of clinical suspicion.

Table 1
Endometrial cancer surveillance recommendations.

	Follow up recommendation intervals			
Time from completion of primary therapy	Year 0–1	Year 1–2	Years 2–5	Years >5
Symptom review and examination				
Low risk	6 months	6–12 months	Yearly[a]	Yearly[a]
High risk[b]	3 months	3 months	6 months	Yearly[a]
Pap test/cytology	Not indicated			
CA 125	Insufficient data to support routine use			
Radiographic imaging[c]	Insufficient data to support routine use			
Recurrence suspected	CT scans or PET/CT scans ± CA 125			

[a] May be followed by a gynecologic oncologist or generalist.
[b] High risk is defined as advanced stage or high risk histologies.
[c] May include chest X-ray, PET/CT scans, MRI, ultrasound.

4. Epithelial ovarian cancer

It is estimated that 22,440 women will be diagnosed with ovarian cancer in the United States in 2017 [1]. Although responsible for <30% of all gynecologic malignancies, ovarian cancer accounts for over 50% of deaths. These results stem from a lack of accurate screening tools and symptoms that are vague and often not specific, which result in approximately 75% of patients being diagnosed with advanced disease [6]. Though the overall median survival of ovarian cancer has increased since the 1970s, the average 5 year survival is only 46.2% [6]. Despite the achievement of a complete clinical response following primary treatment, recurrence rates remain high, occurring in 25% of patients with early-stage disease and >80% of patients with advanced disease [6]. Although recurrent ovarian cancer is rarely curable, patients can have significant responses to salvage treatments and surveillance can play a key role.

Because 26–50% of recurrences occur within the pelvis, a thorough review of symptoms and physical examination (with a bimanual pelvic and rectovaginal examination) are an important part of follow-up care [27]. In a review of 144 patients with ovarian cancer, in addition to CA-125 levels, the authors noted that recurrence was detected by symptomatology in 49% and physical exam findings in 60% of patients; emphasizing the importance of these tools for tumor progression detection in this population [28]. Although physical examination is one of the most commonly used tools and is associated with low cost, the reproducibility is low (ranges from 15 to 78%) and it may not detect other common sites of disease recurrence, such as the retroperitoneal lymph nodes, upper abdominal organs, or lungs [27,29,30]. Thus, in a patient with symptoms or tests that are concerning for recurrence, physical examination alone may not be sufficient.

Since its discovery in 1981, the use of CA-125 level for tumor recurrence has been evaluated extensively. Approximately 80% of epithelial tumors will have an elevated CA-125 level at the time of diagnosis. Studies have shown that CA-125 level correlates with disease status in most cases and is often elevated 2–5 months before clinical detection of relapse [29]. Generally, the sensitivity and specificity for CA-125 level and disease recurrence ranges from 62 to 94% and 91–100%, respectively, even with subtle rises within the normal values of the test [28,30,31]. On the contrary, in a prospective randomized trial, the European Organization for Research and Treatment of Cancer (EORTC) assessed the outcome of 527 patients who were treated for recurrent ovarian cancer based on CA-125 level alone versus clinically evident recurrence. The overall survival outcome did not differ for either group, and the investigators concluded that routine measurement of CA-125 level is not warranted for disease surveillance [32]. Other tumor biomarkers have also been studied in attempts to improve ovarian cancer surveillance. Though limited data is available, HE4 may be an independent predictive factor of disease recurrence and may improve accuracy when used along with CA-125 [33]. Currently, multicenter studies are ongoing to further elucidate the use of HE4 in the surveillance of ovarian cancer. Other potential tumor markers include evaluating the role of lipid profiles, immune markers, such as CD44, and circulating tumor DNA are being evaluated for early identification of tumor relapse in women with ovarian cancer [34–36]. However, these data are premature and studies are ongoing/under development [36].

To improve early detection of recurrent disease, the role of radiographic imaging modalities has also been investigated. In a

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retrospective analysis, surveillance with CT scans every 6 months for the first 2 years, followed by yearly intervals, demonstrated the ability to detect asymptomatic disease. The authors reported a higher rate of optimal secondary cytoreductive surgery and an improved overall survival in the group with asymptomatic recurrences detected compared with their symptomatic counterparts [37]. Other studies that have evaluated methods of surveillance for ovarian cancer have reported the sensitivity of CT scans to be 40–93% and the specificity to be 50–98% for recurrent disease [3]. On the contrary, in a study of 412 patients, the use of surveillance techniques detected recurrence in 80% of patients with the following evaluations: examination (15%), imaging (27%), CA-125 level (23%), and CA-125 level and imaging in (35%) [38]. However, the authors reported no difference in survival, regardless of the modality in which recurrence was detected. These findings were further supported by a post hoc analysis of the AURELIA trial, in which the progression of disease was noted to be detected earlier by imaging than by CA 125 levels, however, this was not prognostic for overall survival [39]. The authors concluded that the most important part of surveillance is to continue monitoring improvement in patient symptoms, performance status, and clinical need for treatment.

Interestingly, in a prospective study, the use and associated costs of CA125 tests and CT scans were assessed before and after the EORTC study on CA-125 levels and detection of recurrence [5,32]. Among the 1241 women studied, surveillance patterns did not change significantly. The estimated costs of surveillance of CA-125 tests alone were almost $2 million/year and over $16 million when CT scans were added [5]. A review of the SEER database and a cost-effective analysis found that 95% of recurrences were detected by office visit findings or rising CA-125 levels [40]. The authors further noted that the cost of surveillance increased from $32.5 million to $58 million with the use of one CT scan with minimal increase in detection of recurrence [40]. Despite the SGO and NCCN guidelines recommending that CT scans should be used only when clinically indicated, as well as the Choosing Wisely campaign encouraging health care professionals to avoid routine radiographic surveillance, it is still noted that over 75% of ovarian cancer patients were still undergoing unindicated imaging for routine surveillance [5,21].

Because CT scans may lack the ability to detect a small volume of disease, other imaging modalities have been studied. The use of magnetic resonance imaging (MRI) has demonstrated sensitivity ranges from 62 to 91% and specificity ranges from 40 to 100%, which is comparable to CT scans [30]. However, increased costs of this modality have limited its generalized acceptance. Most recently, whole-body MRI with diffusion-weighted sequence was noted to have higher accuracy than CT scans for determining potential operability in women with recurrent ovarian cancer [41]. Future studies regarding this technique's role in surveillance may be forthcoming. Ultrasound scanning has also been investigated for ovarian cancer surveillance and studies have shown sensitivity that ranged from 45 to 85% and specificity that ranged from 60 to 100% [30]. However, because of user variability and limited visibility, this modality typically is not used for the evaluation of recurrent disease.

The use of PET/CT scans for surveillance has also been reported. Sensitivity varies from 45 to 100% and specificity ranges from 40 to 100%, although diagnostic accuracy rates approach as high as 95% [30]. In patients with normal CA-125 levels and clinical suspicion of disease (based on symptoms or surveillance CT scans), PET/CT was slightly more sensitive than CT scans for the detection of recurrent disease [42,43]. Studies have shown that PET/CT will alter treatment in approximately 60% of patients with recurrent disease and many recommend PET/CT before secondary cytoreduction [44]. Therefore, the use of imaging for surveillance is limited and is best reserved as a supplement to abnormalities in symptoms, physical examination, or CA125 levels.

Until the ideal surveillance is determined, individualized patient plans that consist of a thorough assessment of symptoms and physical examination, which includes a pelvic examination, should be undertaken. The role for CA-125 level monitoring should be discussed with patients and the risks and benefits of imaging should be discussed with the patients who do not have an elevated CA-125 level at the time of diagnosis (Table 2). When a recurrence is suspected based on symptoms, examination, or CA-125 level, a CT scan of the chest, abdomen, and pelvis should be obtained to determine the extent of the disease. PET scans may be a useful adjunct when CT scans are indeterminate or in patients who are candidates for secondary cytoreductive surgery.

Table 2
Invasive ovarian cancer surveillance recommendations.

	Follow up recommendation intervals			
Time from completion of primary therapy	Years 0–2	Year 2–3	Years 3–5	Years >5
Symptom review and examination	3–4 months	4–6 months	6 months	Yearly[a]
Pap test/cytology	Not indicated			
CA 125	Optional			
Radiographic imaging[b]	Insufficient data to support routine use			
Recurrence suspected	CT scans or PET/CT scans CA 125			

[a] May be followed by a gynecologic oncologist or generalist.
[b] May include chest X-ray, PET/CT scans, MRI, ultrasound.

5. Low malignant potential (LMP) tumors

LMP tumors, also called borderline tumors, account for 10–20% of epithelial ovarian tumors, with approximately 4000 cases diagnosed annually [45]. The average age of a woman at the time of diagnosis is 40–60 years, but a significant proportion of these tumors occur in women in their child-bearing years [45].

Current guidelines are extrapolated from invasive ovarian cancer and recommend physical examination, including pelvic examinations, CA-125 level (if initially elevated), every 3–6 months, as well as pelvic ultrasounds (as indicated) for those women with fertility-sparing surgery [3]. However, this disease behaves quite differently from invasive ovarian cancer with recurrences occurring late, even in advanced stages. In general, 70% of recurrences will be after 5 years, and 30% will be after 10 years [45]. Furthermore, many patients with recurrent LMP tumors can be salvaged with additional surgery.

Large retrospective studies report that LMP recurrence rate range from 5 to 8% and ~2% of women with LMP will eventually progress to invasive cancers, which is associated with a worse prognosis [45,46]. The risk of recurrence is higher in women who had preservation of one or both ovaries, with the highest risk in women who underwent ovarian cystectomy (~6 fold increased risk) [46]. Other factors that increase the risk of recurrence are residual macroscopic disease, age ≥65 at the time of diagnosis, and advanced stage at the time of diagnosis [45–47]. Therefore, in women who were diagnosed with stage I disease with removal of both ovaries, surveillance is low yield and these patients can be monitored on an annual basis by their gynecologist or gynecologic oncologist. Though no additional surveillance is warranted, further assessment should be based on symptoms/examinations. For patients who have undergone fertility-sparing surgery, either a unilateral salpingo-oophorectomy or a cystectomy, the risk of recurrence ranges from 5 to 7% [45–47]. Current surveillance recommendations for women who have undergone fertility-preserving surgery are to undergo serial pelvic sonography with or without tumor markers [45,46]. Though complete hysterectomy with bilateral salpingo-oophorectomy has been recommended once fertility is completed, there are no studies that suggest that this aggressive surveillance or completion hysterectomy improves prognosis for women with LMP tumors. Even in women with advanced LMP tumors, survival outcomes are favorable and despite an increased risk of recurrence, 5 year progression free survival is approximately 90% and 5 year overall survival rates are ~95% [45,46]. Therefore, in patients with advanced (stage II-IV) LMP tumors, review of symptoms and

physical examination on a yearly basis ± tumor markers (if originally elevated) would be appropriate.

When recurrent disease is suspected, a CT scan of abdomen and pelvis is recommended to assess the extent of the disease. Because most women with LMP tumors can be salvaged with additional surgery, prompt attention to symptoms or physical examination abnormalities is important; however, there is no evidence that routine radiographic surveillance with CT scans is at all beneficial.

6. Germ cell and sex-cord stromal tumors of the ovary

Malignant germ cell tumors of the ovary account for 2.6% of all ovarian cancers and may produce serum tumor markers that can prove helpful in the diagnosis and posttreatment surveillance [48]. Alpha-fetoprotein (AFP) can be produced by endodermal sinus (yolk sac) tumors, embryonal carcinomas, polyembryomas, and immature teratomas. Human chorionic gonadotropin (hCG) can be produced by choriocarcinomas, embryonal carcinomas, polyembryomas, and, in low levels, in some dysgerminomas and lactate dehydrogenase (LDH) can be a marker for dysgerminoma [48]. Because these tumors tend to occur in young women and most are unilateral; fertility-sparing surgery with or without adjuvant therapy can be utilized [48,49]. Although data is limited, recurrences are rare and typically occur within the first 2 years. Though prognosis for recurrent disease is poor, there are potential curative options such as multi-agent chemotherapy regimens and/or high dose chemotherapy with autologous stem cell support. Therefore, surveillance with physical examination and tumor markers is advised every 2 to 4 months for the first two years. After two years, the interval increases to yearly and serum markers may be omitted. For patients with a reliable tumor marker, imaging may be deferred and can be reserved for those without an elevated tumor marker.

Sex cord stromal tumors are rare and account for 7% of ovarian malignancies [49,50]. Sex cord stromal tumors of the ovary can also produce biomarkers such as estradiol, inhibin, Müllerian inhibitory substance, and testosterone [49]. Granulosa cell tumors, the most common subtype, have the possibility of late recurrence of disease with a reported median time to recurrence of 4–6 years [50]. Recurrences tend to occur in the upper abdomen (55–70%) and pelvis (30–45%) and response rates are generally favorable ranging from 63% to 80% [50]. Therefore, surveillance should include a thorough physical examination and serum tumor markers (if applicable). Though some of recommended ultrasound/imaging in those who undergo fertility sparing surgery, the utility of imaging is limited and should be reserved to patients with symptoms, elevated biomarkers, or suspicious findings on physical examination [3,50]. The interval for surveillance visits should be dependent on stage and it would be reasonable to extend to every 6 to 12 months for those with early stage, low risk disease and every 4–6 months for those with high risk disease and evaluations should occur for an extended period of time [3,50].

7. Cervical cancer

Almost 12,820 women will be diagnosed with cervical cancer in 2017 in the United States [1]. Approximately 50% of patients are diagnosed with stage I disease, in which the 5-year survival rate for this group exceeds 90% [6]. However, recurrence rates for this group of patients are high, ranging from 10 to 20% [51]. The treatment of recurrent cervical cancer depends greatly on the primary therapy that is used and the location of recurrence. Surveillance will ideally benefit patients with locally recurrent disease who can be offered potentially curative treatment options. Typically, more than three-fourths of recurrences will occur within the first 2–3 years after the initial treatment, which suggests a role for increased surveillance during this time frame [51,52]. Thus, the NCCN guidelines recommend follow-up evaluation every 3–6 months for the first 2 years, followed by every 6 months for the next 3 years.

Although patients are often observed every 3–4 months during the first 2 years, recurrence is diagnosed during routine follow-up examination in few cases, ranging from 26 to 36% of cases [52]. Presentation with symptoms is common, ranging from 46 to 95% of patients [54–57]. These symptoms often include abdominal and pelvic pain, leg symptoms such as pain or lymphedema, vaginal bleeding or discharge, urinary symptoms, cough, and weight loss [51]. Additionally, the presence of symptoms or suspicion of recurrence prompted unscheduled evaluation in approximately 40% of patients [55,56]. Thus, counseling patients about signs and symptoms remains an important part of survivorship care.

The use of physical examination for cervical cancer surveillance has been well accepted. In a review, this simple method accounted for the highest rate of asymptomatic disease, ranging from 29 to 75% [9,51]. Physical examination accounted for the highest detection rate when compared with cytologic evaluation and imaging modalities [9,51,55]. The evaluation should include a complete assessment of areas that are susceptible to the human papillomavirus and a thorough speculum, bimanual, and rectovaginal examination.

In efforts to detect patients with a vaginal/local recurrence, surveillance with cytologic evaluation has been used [52,53]. Although there is insufficient evidence in cancer surveillance, cytology may help detect other lower genital tract disease. However, retrospective studies have shown cytologic evaluation to be consistently low yield, with detection rates of recurrence that range from 0 to 17% [51]. In addition, other studies have found that rarely was cytologic evidence the only abnormality and that clinical evidence of disease was often or soon thereafter apparent. These low rates of detection have led to the recommendations by investigators to eliminate the use of cytologic evaluation or to limit its use to once a year [51,54].

In women with cervical cancer treated with primary radiation therapy, the incidence of an abnormal Pap test ranges from 6% to 34%, with atypical squamous cells of undetermined significance (ASC-US) findings accounting for most of the abnormalities [58,59]. As fertility-sparing surgery increases, surveillance after radical trachelectomy may be more complicated [60]. Following radical trachelectomy, 18% of Pap tests were noted to be abnormal though no recurrences were noted [60]. Therefore, routine cervical cytology following radical trachelectomy is not likely to impact management or affect outcomes [60]. In a cost analysis of colposcopy for post-treatment abnormal cytology in cervical cancer, it was noted that the evaluation of low grade test results or less was ineffective in detecting recurrence [21]. The SGO Choosing Wisely campaign has also advocated that colposcopy should not be performed if cytology demonstrates changes less than high grade [21,61]. Along these same lines, the persistence of high risk HPV may be a risk factor for disease recurrence, but the role of HPV testing has not been studied well enough for clinical utility at this time [62]. Overall, the reduction of unnecessary cytologic and colposcopic evaluation may provide an opportunity for significant cost-savings while maintaining quality of care in these patients.

Imaging has also been suggested for surveillance in asymptomatic patients with a history of cervical cancer. In regards to chest radiographs, rates of detection range from 20 to 47% [3,51]. Although some studies have reported successful treatments for patients with isolated pulmonary recurrence, there is little support for surveillance chest X-ray and it can be omitted [51]. Other studies have evaluated the use of radiographic imaging modalities, including CT scans, MRI, pelvic ultrasounds, and intravenous pyelograms [9,51]. Unfortunately, the rates of detection are low, and these tests have not proven useful for routine surveillance. However, these tests may be indicated based on patient symptoms or findings on examination, and their use should be individualized (Table 3).

PET/CT scans have also been used for the evaluation of recurrent cervical cancer. In patients with clinical suspicion of recurrence, PET/CT scans detected disease with high sensitivity (86%) and specificity (87%) [55]. As a surveillance tool, PET/CT can detect asymptomatic recurrent disease amenable to additional therapy for curative intent,

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Table 3
Cervical, vulvar, and vaginal cancer surveillance recommendations.

	Follow up recommendation intervals			
Time from completion of primary therapy	Year 0–1	Year 1–2	Years 2–5	Years >5
Low risk	6 months	6–12 months	Yearly[a]	Yearly[a]
High risk[b]	3 months	3 months	6 months	Yearly[a]
Pap test/cytology	Yearly[c]			
Radiographic imaging[d]	Insufficient data to support routine use			
Recurrence suspected	CT scans or PET/CT scans			

[a] May be followed by a gynecologic oncologist or generalist.
[b] High risk is defined as advanced stage or high risk histologies.
[c] Insufficient evidence for detection of cancer recurrence but may have value in the detection of lower genital tract neoplasia and immunocompromised patients.
[d] May include chest X-ray, CT scans, PET/CT scans, MRI, ultrasound.

with 3 year overall survival rates of 59–86% [56]. Because localized recurrences may be amenable to additional radiation or exenteration, this modality may have potential benefit. Cost analysis models show conflicting conclusions, depending on what interventions (e.g. adjuvant hysterectomy) are taken with a positive PET/CT finding [63,64].

One of the major components of surveillance is its ability to impact survival. Survival for women with recurrent cervical cancer has been assessed only in retrospective analyses, which compare those women with or without symptoms at the time recurrence is diagnosed. Median survival rates in asymptomatic and symptomatic patients ranged from 8 to 53 months and 8–38 months, respectively [51]. Surveillance should be focused on recurrent disease that is amenable to treatment and that will result in cure or long-term survival. Unfortunately, in regards to cervical cancer, this is limited predominantly to loco-regional recurrence. The potential of newer modalities, including PET/CT, must be investigated further in prospective studies, with consideration for cost. Although only retrospective data are available, history and physical examination are the only consistent methods that have been reported for the detection of recurrence; and specific follow-up plans should be discussed with patients. If recurrent disease is suspected based on symptoms or examination, imaging is recommended to evaluate the extent of disease, and a biopsy should be obtained to confirm recurrence. PET/CT scanning usually is performed before definitive radiation or exenterative surgery to identify distant disease that would alter management [3].

8. Vulvar/vaginal cancer

With 6020 new cases and 1150 deaths annually in the United States, vulvar cancer is uncommon and represents approximately 4% of malignancies of the female genital tract and 0.7% of all cancers in women [1]. Radical local excision of the vulva and inguinofemoral lymphadenectomy have been the standard surgical therapy for nearly 8 decades. More recent advances have included the introduction of preoperative chemoradiation for large primary tumors that involve the urethra, vagina, or anus and the incorporation of the sentinel lymph node evaluation. Survival of patients with vulvar cancer correlates with International Federation of Gynecology and Obstetrics stage. The prognosis for patients with early-stage disease is generally good and lymph node status is the single most important prognostic factor. Patients with negative lymph nodes have a 5–year survival rate of >80%, which falls to <50% for patients with positive lymph nodes and to as low as 13% for those with >4 positive nodes [65]. Although patients with local recurrences may be salvageable, groin or distant recurrences generally are fatal.

There is no direct evidence to inform surveillance strategies for patients with vulvar cancer after definitive treatment. In 2016, the first NCCN practice guidelines in vulvar cancer were developed to address this issue [66]. Due to the rarity of this disease, surveillance strategies for patients with definitively treated vulvar cancer are extrapolated from other disease sites, mainly cervical cancer. These guidelines recommend monitoring patients with physical examination every 3–6 months for the first two years and then at increasing intervals.

However, in a study of 330 patients with primary squamous cell carcinoma of the vulva, within the first two years, an overall recurrence rate in patients with positive nodes was 32.7% compared to 5.1% in women with negative nodes. Interestingly, after two years, the recurrence rates were similar (~12%) regardless of node status. This finding is similar to the long term follow up reported in the GROINSS-V study in which the local recurrence rate was 27.5% at 5 years and 39.5% at 10 years following primary treatment [67]. Importantly, these findings demonstrate the need for long-term surveillance.

Because of the propensity for local recurrence (regular and long-term), careful examinations of the vulva and groin constitute the cornerstone of posttreatment surveillance for these patients. This should include careful visual inspection of the vulva, skin bridge, and inguinal lymph nodes. Because a significant number of vulvar cancers are human papillomavirus associated, such examination should survey not only for vulvar reoccurrence or multifocal vulvar cancer but also for cervical, vaginal, and perianal neoplasia [68].

In general, groin and distant recurrences are more common in women with initial groin involvement. Compared to local recurrences in which the median time to recurrence is 33 months, median time to groin recurrence is 10.5 months and distant recurrence is 8 months [67]. Whether asymptomatic patients with positive groin nodes benefit from additional imaging for the assessment of distant sites of failure is unproven and generally not recommended because salvage therapies are relative ineffective. However, patients whose symptoms or review of systems suggests the possibility for distant failure should undergo additional imaging and may be evaluated similarly to patients with cervical cancer (Table 3). If exenterative surgery is considered for local recurrence, PET/CT should be performed to rule out distant disease that would alter management [69].

9. Comment

Surveillance and survivorship care often involves the coordination of multiple health care providers and specialists. For example, patients may receive treatment at local facilities with a medical or radiation oncologist and may follow up with these teams for surveillance visits. In these cases, it is important to emphasize the key role of the pelvic exams and symptom review (listed in Table 4), while conveying the limited role of imaging/lab tests with both patients and non-gynecologic oncology providers. This will help ensure that patients are receiving

Table 4
Common symptoms/signs associated with gynecologic cancer recurrence.

	Endometrial	Ovarian	Cervical/vaginal	Vulvar
Local	Vaginal bleeding Vaginal lesion/mass	Pelvic nodularity/mass	Vaginal bleeding	New lesion/mass Pruritus
Distant	Abdominal/pelvic pain Cough Lethargy Abdominal distention	Abdominal distention Pain (abdominal) Weight loss Change in bowel habits Elevated CA 125	Pain (abdominal/pelvic) Leg pain/lymphedema Urinary symptoms Cough Weight loss	Leg or groin pain Urinary symptoms Leg lymphedema Weight loss Cough

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optimal surveillance while minimizing unnecessary testing. Furthermore, as survivorship rates increase, transitioning patients from oncology care to the primary care setting is becoming a common practice. However, this shift results in the burden of care falling on primary care providers who may not be comfortable or trained to deal with follow-up needs or practice standards for patients with cancer. Although the Institute of Medicine's report advocates for open communication between oncologists and primary care providers, almost 50% of primary care physicians did not feel comfortable with cancer surveillance and standard guidelines for cancer recurrence [70–72]. However, primary care providers generally are willing to assume cancer follow-up care and believe the transition of oncology patients could be improved with an individualized treatment summary, guidelines for surveillance, and expedited routes of referral for suspected recurrence [70–72]. Thus, the provision of up-to-date information and the education of both patients and physicians are mandatory.

It is important not only to specify routine cancer surveillance but also to continue routine screening guidelines in cancer survivors and to promote healthy behaviors and reduce repetitive testing [70,71]. Both primary care teams and oncology providers should continue to counsel patients on smoking cessation, promotion of exercise, maintenance of a healthy weight, and health maintenance (bone density screening, etc.).

If not previously done, the surveillance period may provide an opportunity to assess patients who are at a higher risk for cancer than the general population. Obtaining a thorough personal and family history, which would include cancer type and age at diagnosis, may help to identify patients who are at risk and result in a referral to genetic counseling for additional assessment/management. Furthermore, patients and family members with a known or suspected genetic predisposition may require a more intensive screening program. Improving one's awareness of risk will enhance compliance with these recommendations and ultimately decrease preventable cancers.

In conclusion, the goal of follow-up evaluation for the detection of recurrent disease requires both clinical and cost-effectiveness. Failure to adhere to recommended guidelines results in unnecessary tests, and efforts should be made to provide effective surveillance, which minimizes excessive costs [3,70]. Currently, the ideal tests and schedule for gynecologic cancer surveillance have not yet been established; however, a detailed review of symptoms and physical examination at each visit results in the detection of most recurrences. The use of additional modalities has not been well-supported and individualized treatment plans should be made with each patient. The lack of evidence-based guidelines for surveillance can be addressed only with prospective studies and the incorporation of cost-effective follow-up plans into the design of clinical trials will help to establish the ideal regimens.

Conflict of interest statement

No author has any conflicts of interests.

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