ONCOLOGY

Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncologists recommendations

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Although gynecologic cancers account for only 10% of all new cancer cases in women, these cancers account for 20% of all female cancer survivors. Improvements in cancer care have resulted in almost 10 million cancer survivors, and this number is expected to grow. Therefore, determining the most cost-effective clinical surveillance for detection of recurrence is critical. Unfortunately, there has been a paucity of research in what are the most cost-effective strategies for surveillance once 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 is the most effective method for the detection of most gynecologic cancer recurrences. There is very little evidence that routine cytologic procedures or imaging improves the ability to detect gynecologic cancer recurrence at a stage that will impact cure or response rates to salvage therapy. This article will review the most recent data on surveillance for gynecologic cancer recurrence in women who have had a complete response to primary cancer therapy.

Key words: cervical cancer, cytology, endometrial cancer, gynecologic cancer, imaging, ovarian cancer, surveillance

In 2010, gynecologic malignancies were expected to afflict approximately 80,000 women within the United States.[1] Advances within the field of gynecologic oncology have resulted in long-term survivals and a high rate of survivors. Because long-term survival is becoming more common in this patient population, insights into cancer surveillance and detection of recurrence and addressing side-effects from treatment are of utmost importance.

Currently, posttreatment guidelines call for frequent visits immediately after treatment, followed by increasing intervals over time. Typically, after the first 2-3 years, patients are transitioned back to their primary care providers. However, primary care physicians may not be comfortable with guidelines or surveillance for each specific cancer type.[2] This is in part due to a lack of training and in part to unclear expectations for the primary care provider by the oncologist.[2-4] As survivorship continues to grow, coordination of care between gynecologic oncologists, primary care providers, other healthcare providers (such as radiation oncologists), and patients ideally 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.

The role of surveillance 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 costs and the use of resources for conducting these tests. Last, patients should be counseled on the benefits and pitfalls of disease monitoring, which should include the psychologic impact of surveillance programs.[5] Unfortunately, most studies across all cancer sites are based predominantly on retrospective studies and provide limited insight into the true benefit of recommended guidelines for posttreatment surveillance. There is a real need for prospective studies to establish the most cost-effective methods for the detection of recurrent disease. In addition, surveillance tests should be directed at detecting recurrences that are amenable to curative or significant palliative treatment. Therefore, the primary objective of this review is to provide the most recent data on surveillance for cancer recurrence in women who have had a complete response to primary cancer therapy for gynecologic malignancies. Additionally, we have included routine health screen-

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ing guidelines to allow for enhanced communication between oncologists and primary care providers.

Endometrial cancer

Endometrial cancer is the most common gynecologic cancer and the fourth most common cancer in women. Yearly, there are approximately 44,000 new endometrial cancer diagnoses and 8000 deaths in the United States.[1] Commonly, patients experience symptoms such as abnormal or postmenopausal bleeding, which warrant further investigation with ultrasound scanning 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 2–15% and reach as high as 50% in advanced stages or in patients with aggressive histologic condition.[7-10] Many local recurrences from endometrial cancer are curable; therefore, the determination of 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 because many studies have shown that most (70-100%) recurrences occur within 3 years after primary treatment.[11-14] Current guidelines of the National Comprehensive Cancer Network (NCCN) and the American Congress of Obstetricians and Gynecologists recommend physical examination every 3-6 months for 2 years, then every 6 months or annually.[15,16] Further evaluation with vaginal cytologic evidence is recommended every 6 months for 2 years and annually thereafter.[16] 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 35-68% of cases.[11,13,17-19] Even more striking is that the combination of physical examination and symptoms has resulted in rates of detection that exceed 80%.[18,19] In a recent literature review, Sartori et al[20] report that only physical examination has shown utility in the detection of endometrial cancer recurrence. 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 in spite of intensive surveillance, many recurrences are detected based on the presence of symptoms, which occurs in 41-83% of patients.[11-13,18,19,21-24] A common symptom, vaginal bleeding, is indicative of a local recurrence that is often curable if it is an isolated site of disease.[13,18,19] However, other common symptoms include abdominal and/or pelvic pain, lethargy, and weight loss.[13,25,26] Even in the face of monitoring for recurrence, patients who experience a distant recurrence are symptomatic in 70% of cases, such as coughing or headaches.[13,21] Therefore, patient education about the signs and symptoms is a critical component of posttreatment care and may lead to the detection of recurrent disease.

Survival outcomes have been evaluated on the basis of the presence or absence of symptoms at the time of recurrence. In a report by Sartori et al,[11] 52% of patients were diagnosed with recurrence after they had symptoms; these patients had a median postrecurrence survival of 7 months. This was significantly less than the 20-month survival that patients experienced if they were diagnosed with recurrence in an asymptomatic state that was based on examination or imaging. Several other series have evaluated the role of routine surveillance for the follow up evaluation of patients with stage I endometrial cancer and reported no difference in survival based on the presence or absence of symptoms.[13,21-23,26,27] Of note, even patients who had symptoms were undergoing the recommended follow-up evaluations, which provided an argument against the use of routine surveillance. 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 cytologic evaluation has been advocated. However, many gynecologic oncologists challenge this recommendation. Rates of recurrence detection on vaginal cytologic evidence range from 0–6.8%, even in asymptomatic patients.[11,17-25,28] Although Berchuck et al[19] and Owen and Duncan[28] report that cytologic evaluation detected 25% of all recurrences and that cytologic evaluation alone detected only 3 of the 44 (7%) recurrences. Furthermore, in addition to a low yield of detection, Agboola et al[13] reported that the use of vaginal cytologic evaluation at each visit resulted in a cost of $27,000 per case detected. Because most recurrences at the vaginal cuff can be found on examination, vaginal cytologic evaluation adds only significant healthcare costs without added benefit.

Similarly to ovarian cancer, the use of cancer antigen 125 (CA125) level has been investigated as a marker for recurrence. In asymptomatic patients with endometrial cancer, the use of CA125 levels accounted for 15% of detections.[12] Rose et al[29] reported that CA125 levels were elevated in more than one-half of the patients with advanced stage and/or high-grade histologic evidence and that of these patients most had an elevated pretreatment level. However, one must be aware of elevated CA125 levels because of other conditions or even previous radiotherapy. In addition, the role of CA125 levels for the detection of recurrence was negligible in patients with low-risk disease.[26,29] At present, the use of CA125 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 a CA125 level that is elevated before treatment.

The use of radiographic imaging has been suggested for the detection of re-

TABLE 1
Sensitivity/detection rate of the methods that were used to detect recurrence in patients at routine visits after treatment

	Type of cancer, %		
Method of detection	Endometrial	Ovarian	Cervical
Symptoms	41-83	—	46-95
Physical examination	35-68	15-78	29-75
Cytologic evidence	0-7	—	0-17
Chest radiograph	0-20	—	20-47
Cancer antigen 125 level	15	62-74	—
Computed tomography scan	0-20	40-93	0-45[a]
Positron emission test–computed tomography scan	100[a]	45-100	86

[a] Limited data.

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current 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 for asymptomatic chest recurrences that are found on chest radiographs ranges from 0–20%.[14,19] In another series, chest radiograph detected 7 asymptomatic pulmonary recurrences and accounted for 0.34% of all chest radiographs that were performed for surveillance, which indicates low utility for this tool.[13] 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.[25,30]

In further evaluation of radiographic imaging for endometrial cancer surveillance, Fung Kee Fung et al[14] conducted a review of the literature and found that only 5-21% of asymptomatic recurrences were found by computed tomography (CT) scans. Other studies have agreed that the role of CT scanning for asymptomatic patients is not warranted, because survival of patients with disease that is detected on CT scan, compared with clinical examination, did not differ significantly.[25,27] To increase the detection of local recurrence, the use of pelvic ultrasound scans has also been reported. Although detection rates for local recurrence range from 4–31%, many of these recurrences were also detected on other diagnostic methods, which included physical examination.[11,14,21,25,26] 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% of cases.[27]

More recently, attention has been focused on positron emission test (PET) ± CT scans for endometrial cancer recurrence. Park et al[31] reported 100% sensitivity and 83% specificity when PET-CT scanning was used for suspected recurrence and 100% diagnostic accuracy in 64 asymptomatic patients. However, its use for routine screening has not been well studied, and larger prospective studies will determine whether PET/CT will have a role in endometrial cancer surveillance. In addition, the high cost of PET/CT may limit its use in routine surveillance (Table 1).

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 through symptoms alone. 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. This approach may save valuable healthcare dollars. Cytologic evaluation and chest radiographs in asymptomatic women are not clearly beneficial. If patients do have a suspected recurrence, generally a CT scan of chest, abdomen, and pelvis or PET/CT scans may be performed to assess the extent of the disease (Table 2).[32,33]

Ovarian cancer

Ovarian cancer affects almost 22,000 women each year in the United States and results in >13,000 deaths yearly.[1] Although responsible for <30% of all gynecologic malignancies, ovarian cancer accounts for >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] Since the 1970s, the median overall survival of patients with advanced ovarian cancer has increased from 20 months up to 65 months because of advances in surgery and chemotherapy.[34,35]

Despite the achievement of a complete clinical response, recurrence rates remain high, occurring in 25% of patients with early-stage disease and >80% of patients with advanced disease.[35,36] Although patients with recurrent ovarian cancer rarely are cured, patients can have significant responses to salvage treatments.

To detect recurrences, the NCCN guidelines for epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer recommend follow-up visits every 2-4 months for the first 2 years, followed by 6-month intervals for the next 3 years. At each visit, physical examination and identification of the CA125 level or corresponding tumor marker are recommended.[37] Additionally, these guidelines advocate the use of radiographic imaging and laboratory testing, as clinically indicated. However, the impact of surveillance and guidelines are based predominantly on retrospective studies and expert opinions.

Because 26-50% of recurrences occur within the pelvis, a thorough physical examination is an important part of a patient's follow-up care and should include a bimanual pelvic and rectovaginal ex-

TABLE 2
Endometrial cancer surveillance recommendations

	Months			Years	
Variable	**0-12**	**12-24**	**24-36**	**3-5**	**>5**
Review of symptoms and physical examination					
Low risk (stage IA grade 1 or 2)	Every 6 mo	Yearly	Yearly[a]	Yearly[a]	Yearly[a]
Intermediate risk (stage IB-II)	Every 3 mo	Every 6 mo	Every 6 mo[b]	Every 6 mo[b]	Yearly[a]
High risk (stage III/IV, serous or clear cell)	Every 3 mo	Every 3 mo	Every 6 mo	Every 6 mo	Yearly[a]
Papanicolaou test/cytologic evidence	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated
Cancer antigen 125	Insufficient data to support routine use	Insufficient data to support routine use	Insufficient data to support routine use	Insufficient data to support routine use	Insufficient data to support routine use
Radiographic imaging (chest x-ray, positron emission tomography/computed tomography, magnetic resonance imaging)	Insufficient data to support routine use	Insufficient data to support routine use	Insufficient data to support routine use	Insufficient data to support routine use	Insufficient data to support routine use
Recurrence suspected	Computed tomography and/or positron emission tomography scan ± cancer antigen 125	Computed tomography and/or positron emission tomography scan ± cancer antigen 125	Computed tomography and/or positron emission tomography scan ± cancer antigen 125	Computed tomography and/or positron emission tomography scan ± cancer antigen 125	Computed tomography and/or positron emission tomography scan ± cancer antigen 125

[a] May be followed by a generalist or gynecologic oncologist; [b] Consider alternating visits with a generalist and gynecologic oncologist.

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amination.[36,38] However, the rates of detection by physical examination vary significantly from 15-78%.[39,40] Although physical examination is one of the most commonly used tools and is associated with low cost, the reproducibility is low and may not detect other common sites of disease recurrence, such as the retroperitoneal lymph nodes, upper abdominal organs, or lungs.[41,42] Thus, in a patient with symptoms or tests that are concerning for recurrence, physical examination alone may not be sufficient.

Historically, second-look surgeries have been used to assess disease response to primary treatment. Despite negative findings, recurrence rates that range from 35-50% have been reported, and no benefit in overall survival was noted. Thus, this procedure fell out of favor and is used rarely today.[42,43]

Since its discovery in 1981, the use of CA125 level for tumor recurrence has been evaluated extensively. Approximately 80% of epithelial tumors will have an elevated CA125 level at the time of diagnosis. Studies have shown that CA125 level correlates with disease status in most cases and is often elevated 2-5 months before clinical detection of relapse.[38] Generally, the sensitivity and specificity for CA125 level and disease recurrence ranges from 62–94% and 91–100%, respectively.[41,42,44,45] In 255 patients who had completed primary therapy, a CA125 level twice the upper limits of normal was consistent with disease progression in almost all patients who were evaluated.[46] Santillan et al[46] reported that CA125 levels with a persistently low level of increase, even within normal values of the test, were often consistent with tumor recurrence. However, other reports found that the detection of recurrent disease by CA125 level alone yielded no prognostic benefit and advocate the use of CA125 level for surveillance only after a discussion that would explain the interpretation of the test.[47] Furthermore, in a recently completed prospective randomized trial, the European Organization for Research and Treatment of Cancer assessed the outcome of 527 patients who were treated for recurrent ovarian cancer based on CA125 level alone vs clinically evident recurrence. The overall survival outcome did not differ for either group, and the investigators concluded that routine measurement of CA125 level is not warranted for disease surveillance.[48]

To improve early detection of recurrent disease, the role of radiographic imaging modalities has been investigated. In a 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 recurrence detected asymptomatically, compared with the symptomatic recurrence.[49] 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. 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%), CA125 level (23%), and CA125 level and imaging in (35%). However, the authors did not find a difference in survival, regardless of

TABLE 3
Ovarian cancer surveillance recommendations

	Months			Years	
Variable	**0-12**	**12-24**	**24-36**	**3-5**	**>5**
Review of symptoms and physical examination	Every 3 mo	Every 3 mo	Every 4-6 mo	Every 6 mo	Yearly[a]
Papanicolaou test/ cytologic evidence	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated
Cancer antigen 125	Optional	Optional	Optional	Optional	Optional
Radiographic imaging (chest x-ray, positron emission tomography/ computed tomography, magnetic resonance imaging)	Insufficient data to support routine use	Insufficient data to support routine use	Insufficient data to support routine use	Insufficient data to support routine use	Insufficient data to support routine use
Recurrence suspected	Computed tomography and/or positron emission tomography scan	Computed tomography and/or positron emission tomography scan	Computed tomography and/or positron emission tomography scan	Computed tomography and/or positron emission tomography scan	Computed tomography and/or positron emission tomography scan
	Cancer antigen 125	Cancer antigen 125	Cancer antigen 125	Cancer antigen 125	Cancer antigen 125

[a] May be followed by a generalist or gynecologic oncologist.

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the modality that was used.[50] Ideally, prospective studies will help to determine the true role of interval CT scans in ovarian cancer surveillance.

Because CT scans may lack the ability to detect a small volume of disease, other imaging modalities have been reviewed. The use of magnetic resonance imaging has also been evaluated for its role in ovarian cancer surveillance. Although sensitivity ranges from 62-91% and specificity ranges from 40-100%, comparable detection rates to CT scans and increased costs have limited its generalized acceptance.[41] Ultrasound scanning has also been investigated for ovarian cancer surveillance. Studies have shown sensitivity that ranged from 45-85% and specificity that ranged from 60-100%.[41] However, because of user variability and limited visibility, this modality typically is not used for the evaluation of recurrent disease.

More recently, the use of PET-CT scans has been reported. Sensitivity varies from 45-100% and specificity ranges from 40-100%, although diagnostic accuracy rates approach as high as 95%.[41,42,51] In patients with normal CA125 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.[52] 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.[53] However, the potential use of this modality for surveillance is limited, and currently the role of radiographic imaging is best reserved as a supplement to abnormalities in physical examination, CA125 levels, or symptoms.

Although improvements in primary treatment of ovarian cancer have occurred, outcomes after recurrence remain disappointing. Many physicians hypothesize that the detection of recurrence early potentially may improve the benefit of available treatments, especially surgery. Second-line therapies are rarely curative and often result in short-term progression-free survival. However, some patients, especially those who are good candidates for secondary surgical cytoreduction and/or those who remain platinum sensitive will have high response rates to salvage treatments. 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 CA125 level monitoring should be discussed with patients. The pros and cons of imaging should be discussed with the patients who do not have an elevated CA125 level at the time of diagnosis. When a recurrence is suspected based on symptoms, examination, or CA125 level, a CT scan of the chest, abdomen, and pelvis should be obtained to determine the extent of the disease. PET scans are a useful adjunct when CT scans are indeterminate (Table 3).[54]

Low malignant potential (LMP) tumors

Tumors of LMP, also called borderline tumors, account for 10-20% of epithelial ovarian tumors; approximately 4000 cases are diagnosed annually.[55] 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.[55] In general, the prognosis for women with LMP tumors is quite good, and most women (especially those with stage I disease) are at a very low risk of recurrence.[2,3] Recurrences tend to occur late, and, even in advanced stages, 70% of recurrences will be after 5 years, and 30% will be after 10

years.[3] Many patients with recurrent LMP tumors can be salvaged with additional surgery, and <5% eventually progress to invasive cancers.[55-57]

Current NCCN guidelines recommend physical examination, including pelvic examinations, CA125 level (if initially elevated), every 3-6 months and pelvic ultrasound scans for those women with fertility-sparing surgery. Complete hysterectomy with bilateral salpingo-oophorectomy is recommended once fertility is completed.[37] However, there are no studies that suggest that this aggressive surveillance improves prognosis for women with LMP tumors.

Retrospective studies suggest that, in women who have undergone a complete hysterectomy with bilateral salpingo-oophorectomy and resection of all gross disease, surveillance should be similar that used for those women with invasive ovarian cancer. For patients who have undergone fertility-sparing surgery, either a unilateral salpingo-oophorectomy or a cystectomy, the risk of recurrence ranges from 7–30%.[58] Current surveillance recommendations for women who have undergone fertility-preserving surgery are to undergo serial pelvic sonography because this is the most sensitive method of detection of recurrent disease in residual ovary.[59] Ultrasound scanning with or without tumor markers is recommended on an every 6-month basis.

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,[56,57] 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.

Germ cell and sex-cord stromal tumors of the ovary

Malignant germ cell tumors of the ovary are rare and account for 2.6% of all ovarian cancers.[60] Most patients have abdominal pain and a palpable mass. Malignant germ cell tumors can produce serum tumor markers that can prove helpful in the diagnosis and posttreatment surveillance if they are elevated at the time of diagnosis. Alpha-fetoprotein can be produced by yolk sac tumors, embryonal carcinomas, polyembryomas, and immature teratomas. Human chorionic gonadotropin can be produced by choriocarcinomas, embryonal carcinomas, polyembryomas, and, in low levels, in some dysgerminomas. Lactate dehydrogenase can be a marker for dysgerminoma.[61-63] Because these tumors tend to occur in young women and most are unilateral, fertility-sparing surgery has been used to include pelvic washings, unilateral salpingo-oophorectomy, peritoneal biopsies, omentectomy, and pelvic and paraaortic lymph node dissection. NCCN guidelines recommend observation for low-risk tumors such as stage I dysgerminomas and stage IA, grade 1 immature teratomas.[37,61-63] All other malignant ovarian germ cell tumors in this country receive postoperative chemotherapy with bleomycin, etoposide, and platinum with excellent survival rates. However, in Europe some healthcare providers advocate observation of all stage I germ cell tumors.

Sex cord stromal tumors are rare and account for 1.2% of ovarian cancers.[60] Sex cord stromal tumors of the ovary can also produce serum tumor markers such as estradiol, inhibin, Müllerian inhibitory substance, and testosterone.[63,64] Granulosa cell tumors also have the possibility of late recurrence of disease, with a reported median time to recurrence of 4-6 years.[62] Pelvic recurrence accounts for 30-45% of cases.[64,65] Surveillance should include a thorough physical examination and serum tumor markers for an extended period of time because of reports of recurrence even 20 years after the initial diagnosis. The utility of imaging in sex-cord stromal tumors has not been proven, so imaging should be limited to patients with symptoms or concerning findings on physical examination.[64,65]

Studies that have evaluated surveillance strategies for ovarian germ cell tumors and sex cord stromal tumors have not been performed; therefore, recommendations are based on expert opinion. NCCN guidelines for surveillance recommend tumor markers every 2-4 months for 2 years if the markers were elevated originally. Physical examination that includes bimanual examination may be less helpful than serum tumor markers, especially in adolescent patients. Although recurrences are rare and data about them in the gynecologic oncology literature are small in number, they typically occur in the first 2 years after treatment. Although prognosis for recurrent germ cell tumors is usually poor, there are potentially curative treatment options that are available with multiagent chemotherapy regimens and high-dose chemotherapy with autologous stem cell support. Recently, the American Society of Clinical Oncology issued guidelines for surveillance using serum tumor markers for men with testicular cancer.[66] The recommendations were similar to the current NCCN guidelines for germ cell tumors of the ovary in the first 2 years, with the exception that the surveillance continues for 10 years after treatment because of a reported incidence of 50% of the recurrences occurring 5 years after treatment in men.[66] The timing of surveillance imaging in ovarian germ cell tumors is less well-characterized. NCCN guidelines for germ cell testicular tumors recommend CT scans every 3-6 months for the first 2 years then every 6-12 months until 6 years after treatment for those who received chemotherapy alone.[67] Because germ cell tumors of the ovary occur in young women, because serum tumor markers are very sensitive for the presence of disease, and because repeated CT scans can lead to significant radiation exposure over time, the argument could be made that imaging is not indicated without evidence of the elevation of serum tumor markers, clinical symptoms, or concerning findings on physical examination. In addition, in those patients without elevated tumor markers, radiologic assessment in the first 2 years can be helpful (Table 4).

Cervical cancer

More than 12,000 women are diagnosed with cervical cancer each year in the United States.[1] Patients are diagnosed with stage I disease in 50% of cases, and the 5-year survival rate for this group ex-

TABLE 4
Nonepithelial ovarian cancer (germ cell and sex-cord stromal tumors) surveillance recommendations

	Months			Years	
Variable	**0-12**	**12-24**	**24-36**	**3-5**	**>5**
Review of symptoms and physical examination					
Germ cell tumors	Every 2-4 mo	Every 2-4 mo	Yearly	Yearly	Yearly
Sex-cord stromal tumors	Every 2-4 mo	Every 2-4 mo	Every 6 mo	Every 6 mo	Every 6 mo
Serum tumor markers					
Germ cell tumors	Every 2-4 mo	Every 2-4 mo	Not indicated	Not indicated	Not indicated
Sex-cord stromal tumors	Every 2-4 mo	Every 2-4 mo	Every 6 mo	Every 6 mo	Every 6 mo
Radiographic imaging (chest x-ray, computed tomography, magnetic resonance imaging)					
Germ cell tumors	Not indicated unless tumor marker normal at initial presentation	Not indicated unless tumor marker normal at initial presentation	Not indicated	Not indicated	Not indicated
Sex-cord stromal tumors	Insufficient data to support routine use	Insufficient data to support routine use	Insufficient data to support routine use	Insufficient data to support routine use	Insufficient data to support routine use
Recurrence suspected	Computed tomography scan	Computed tomography scan	Computed tomography scan	Computed tomography scan	Computed tomography scan
	Tumor markers	Tumor markers	Tumor markers	Tumor markers	Tumor markers

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ceeds 90%.[6] However, recurrence rates for this group of patients are high, ranging from 10–20%.[68] The treatment of recurrent cervical cancer depends greatly on the primary therapy that is used and the location of recurrence. Patients with locally recurrent disease can be offered salvage treatments with the potential for cure. Distant metastases are rarely salvageable. In efforts to detect disease at curable states, surveillance has been advocated in patients who have successfully completed primary treatment.

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.[68-72] 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. These recommendations include cytologic evaluation at each visit and recommend annual chest radiographs, although optional.[71] Use of other imaging is advocated on the basis of clinical indications. Similarly to most cancer surveillance, these recommendations are based on retrospective studies.

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 26–36% of cases.[69,72] Despite surveillance, presentation with symptoms is common, ranging from 46–95% of patients.[73,74-81] 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.[68,73] Additionally, the presence of symptoms or suspicion of recurrence prompted unscheduled evaluation in approximately 40% of patients.[77,78] 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 29–75%.[11,68] Physical examination accounted for the highest detection rate when compared with cytologic evaluation and imaging modalities.[11,68,77] The evaluation should include a complete assessment of areas that are susceptible to the human papilloma virus and a thorough speculum, bimanual, and rectovaginal examination. Although there is insufficient evidence in cancer surveillance, cytologic evaluation may have value in the detection of other lower genital tract neoplasia. Along with symptoms, physical examination will detect most cases of recurrent cervical cancer.[76]

In efforts to detect patients with a vaginal/local recurrence, surveillance with cytologic evaluation has been recommended.[64,70-73] Unfortunately, retrospective studies have shown cytologic evaluation to be consistently low yield, with detection rates that range from 0–17%.[68] In addition, other studies have found that rarely was cytologic evidence the only abnormality and that clinical ev-

idence of disease was often or soon thereafter apparent. These low rates of detection have led to the recommendations by authors to eliminate the use of cytologic evaluation or to limit its use to once a year.[68,74,75] Furthermore, the role of cytologic evaluation in patients who have undergone pelvic radiation therapy may be limited, and the elimination of its use from routine surveillance may be acceptable. Thus, the reduction of unnecessary cytologic 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 the asymptomatic patient. In regards to chest radiographs, rates of detection range from 20–47%.[68,69,74] Because of a higher distant failure rate, Salmal et al[69] advocated its use, particularly in patients who had received radiotherapy. However, because many of these cases are not salvageable, others have questioned its use.[75,76] Although some studies have reported successful treatments for patients with isolated pulmonary recurrence, there is little evidence to support its use at this time.[68,69,74] Other studies have evaluated the use of radiographic imaging modalities (such as CT scan and magnetic resonance imaging), pelvic ultrasound scans, and intravenous pyelograms.[11,69] 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.

PET ± CT scans have also been used for the evaluation of recurrent cervical cancer. In patients with clinical suspicion of recurrence, PET scans detected disease with high sensitivity (86%) and specificity (87%).[77] More recently, its use as a surveillance tool has been studied with promising results. In this series, PET-CT showed locoregional disease in 8 of the 9 asymptomatic patients, compared with 4 of the 21 with symptoms that were being evaluated.[78] Because pelvic recurrences may be amenable to salvage therapy, with radiation or exenteration, this modality may have potential benefit; further investigations are ongoing.

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 8–53 months and 8–38 months, respectively.[68] Several studies have reported improved median survival in patients who were detected with asymptomatic recurrence, regardless of the method of diagnosis, and advocate the need for surveillance programs.[69,74,77-80] Other reports have noted similar survival regardless of symptoms and have questioned the effectiveness of routine surveillance.[72,76]

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 locoregional recurrence. The potential of newer modalities, which includes PET/CT scanning, must be investigated further in prospective studies, especially given the high 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, a CT scan of the chest, abdomen, and pelvis 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 (Table 5).[81]

Vulvar cancer

With 3900 new cases and 920 deaths annually in the United States, vulvar cancer is uncommon and represents approximately 4% of malignancies of the female genital tract and 0.6% of all cancers in women.[1] Radical local excision of the vulva and inguinofemoral lymphadenectomy has 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 investigation of the sentinel lymph node technique. 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. 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.[82] 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. There are no NCCN practice guidelines to address this issue. Thus, surveillance strategies for patients with definitively treated vulvar cancer are extrapolated from other disease sites, mainly cervix cancer. A report from the Mayo Clinic on 330 patients with primary squamous cell carcinoma of the vulva, >95% of whom underwent bilateral inguinofemoral lymphadenectomy, underscores the significant correlation between lymph node status and the risk of treatment failure in the first 2 years after initial therapy: 44.2% overall recurrence rate with positive vs 17.5% with negative lymph nodes. After 2 years, patients with positive and patients with negative nodes had similar recurrence rates. Importantly, more than one-third of relapses occurred ≥5 years after the initial therapy. In other words, nearly 1 in 10 patients had a late (>5 years) reoccurrence of disease (same site recurrence or second primary vulvar site), which demonstrates the need for long-term surveillance. More than 95% of those late relapses had local reoccurrences; 13% of the relapses also demonstrated evidence of distant disease.[83] This pattern of predominantly local recurrence is confirmed by another study of 399 patients with node-negative

TABLE 5
Cervical, vulvar, and vaginal cancer surveillance recommendations

	Months			Years	
Variable	**0-12**	**12-24**	**24-36**	**3-5**	**>5**
Review of symptoms and physical examination					
Low risk (early stage, treated with surgery alone, no adjuvant therapy)	Every 6 mo	Every 6 mo	Yearly[a]	Yearly[a]	Yearly[a]
High risk (advanced stage, treated with primary chemotherapy/ radiation therapy or surgery plus adjuvant therapy)	Every 3 mo	Every 3 mo	Every 6 mo	Every 6 mo	Yearly[a]
Papanicolaou test/cytologic evidence	Yearly[b]	Yearly[b]	Yearly[b]	Yearly[b]	Yearly[b]
Routine radiographic imaging (chest x-ray, positron emission tomography/computed tomography, magnetic resonance imaging)	Insufficient data to support routine use	Insufficient data to support routine use	Insufficient data to support routine use	Insufficient data to support routine use	Insufficient data to support routine use
Recurrence suspected	Computed tomography and/or positron emission tomography scan	Computed tomography and/or positron emission tomography scan	Computed tomography and/or positron emission tomography scan	Computed tomography and/or positron emission tomography scan	Computed tomography and/or positron emission tomography scan

[a] May be followed by a generalist or gynecologic oncologist; [b] Insufficient evidence for cancer recurrence but may have value in the detection of other lower genital tract neoplasia.

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squamous cell carcinoma of the vulva, 23% of which recurred with >90% of the recurrences in the vulva.[84]

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. 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. Patients whose symptoms or review of systems suggests the possibility for distant failure should undergo additional imaging and may be evaluated similarly as with patients with cervical cancer. If exenterative surgery is considered for local recurrence, PET-CT should be performed to rule out distant disease that would alter management (Table 5).[84]

Vaginal cancer

Primary cancer of the vagina is an uncommon malignancy. With approximately 2300 cases diagnosed annually in the United States, vaginal cancer comprises approximately 3% of all malignant neoplasms of the female genital tract.[1] Given the rarity of the disease, there is a paucity of information to guide posttreatment surveillance for patients with vaginal cancer. There are no data to support the routine use of follow-up vaginal cytologic evaluation or imaging in the asymptomatic patient. Posttreatment surveillance relies primarily on the careful assessment of symptoms and physical examination, which should survey not only for vaginal recurrence or multifocal vaginal cancer but also for cervical, vulvar, and perianal neoplasia. Patients with a suspicion of recurrent disease should undergo additional imaging for the evaluation of disease extent that may help guide treatment options (Table 5).[85]

Comment

Although gynecologic cancers account for only 10% of all new cancer cases in women, the number of survivors from these malignancies approaches 20%.[1,86] Improvements in cancer care have resulted in almost 10 million cancer survivors, and this number is expected to grow at an even faster rate than ever before.[86] Thus, the determination of the most clinically and cost-effective surveillance for the detection of recurrence is critical.

As survivorship increases, 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.[86] However, primary care providers generally are willing to assume cancer follow-up care, typically after 2 years from treatment. In a survey, primary care providers believed the transition of oncology patients could be improved with an individualized treatment summary, guidelines for surveillance, and expedited routes of rereferral for suspected recurrence.[2-4,86-88] Thus, the provision of up-to-date information and the education of both patients and physicians are mandatory.

However, a recent evaluation of cancer survivorship care demonstrated a significant discordance among primary care providers, oncologists, and patients. This discrepancy was seen with primary cancer surveillance and with the recommendation of cancer screening and preventative healthcare management.[3] Therefore, 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. As rates of the development of a second cancer approach 10% within 30 years,[4] communication between providers and with patients will improve adherence to guidelines and reduce repetitive testing.[3] Despite its association with cancer and comorbidities, almost one-quarter of cancer survivors continue to use tobacco after the first year of diagnosis; rates, which exceed 37%, are highest in patients with a history of gynecologic malignancies.[89] Thus, both oncologists and primary care providers should advocate for smoking cessation in these patients. In addition, the promotion of exercise and weight reduction (if indicated), of the monitoring of bone density, and of breast and colorectal screening is important.

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 popula-

FIGURE
Checklist for surveillance of gynecologic malignancies

Patient name_____
Visit date_____
Disease site and stage_____
Date of diagnosis/surgery_____
Date treatment completed_____

Symptoms review and treatment side-effects

- •Pain (abdominal or pelvic, hip or back)
- •Abdominal bloating
- •Vaginal bleeding (also rectum, bladder)
- •Weight loss
- •Nausea and/or vomiting
- •Cough or shortness of breath
- •Lethargy/fatigue
- •Swelling of abdomen or leg(s)
- •Depression
- •Sexual dysfunction
- •Neuropathy
- •Fatigue

Physical examination

- •General physical examination targeted to symptoms
- •Lymph node assessment (axillary, supraclavicular, and inguinal)
- •Pelvic examination (evaluation of lower genital tract, speculum, bimanual, rectovaginal examination)

Laboratory

- •Tumor markers_____

Disease status

- •No evidence of disease
- •Suspect recurrence
  - ••Radiographic imaging _____
  - ••Biopsy_____
  - ••Refer to gynecologic oncologist

Routine health maintenance

Breast cancer screening

- •Yearly clinical breast examination _____
- •Mammogram _____

Every 1-2 years starting with ages 40-49 years, then yearly

Colon cancer screening

- •Colonoscopy or flexible sigmoidoscopy _____

Every 5-10 years beginning at age 50 years

Genetic screening

- •Not indicated
- •Recommended/completed _____

Consider if patient is diagnosed at a young age, strong family history, multiple primaries (see specific surveillance guidelines)

Menopausal assessment

Osteoporosis prevention

Calcium (1200-1500 mg) and vitamin D (800 IU)
Bone mineral density testing

Begin at age 65 years (sooner if high risk factors)

Smoking cessation

Weight maintenance (exercise, diet)

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tion. 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. 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.[90]

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 will result in cost-savings.[86-91] 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 (Figure). 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; the incorporation of cost-effective follow-up plans into the design of clinical trials will help to establish the ideal regimens. ■

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The Society of Gynecologic Oncologists' (SGO) Clinical Practice Committee has developed a series of Clinical Documents that are designed in part to improve the overall quality of women's cancer care, to reduce the use of unnecessary, ineffective, or harmful interventions, and to facilitate the treatment of patients with a goal to maximum the chance of benefit with a minimum risk of harm and at an acceptable cost.

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This Clinical Document has met SGO's criteria of an Expert Clinical Opinion Document.

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