Role of Imaging in Fertility-sparing Treatment of Gynecologic Malignancies

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Abstract: Treatments for gynecologic cancer usually result in loss of fertility due to surgery or radical radiation therapy in the pelvis. In countries with an established screening program for cervical cancer, the majority of gynecologic malignancies occur in postmenopausal women. However, a substantial number of affected women are of childbearing age and have not completed their families. In these younger women, consideration of fertility preservation may be important. This article describes the fertility-sparing treatment options that are currently available and outlines the role of imaging in the selection of eligible patients on the basis of a review of the literature. In the setting of cervical cancer, magnetic resonance (MR) imaging is used to delineate the size, position, and stage of the tumor for selection of patients who are suitable for radical trachelectomy. In patients with solitary complex adnexal masses, diffusion- and perfusion-weighted MR imaging sequences are used to categorize the likelihood of invasive or borderline malignancy for consideration of unilateral ovarian resection, with fertility preservation when possible. In patients with endometrial cancer, MR imaging is used to rule out signs of invasive disease before hormone therapy is considered. Imaging is also used at patient follow-up to detect recurrent disease; however, evidence to support this application is limited. In conclusion, imaging is an essential tool in the care of patients with gynecologic malignancies who are considering fertility-preserving treatment options.

Introduction

It is important that each woman with cancer receive personalized care. The plan for eradication of the tumor must be optimized to ensure excellent treatment outcomes. However, the plan also needs to be tailored to the patient’s survivorship wishes, when possible. As more women delay the onset of childbearing, gynecologic malignancy during the reproductive years will pose a greater treatment dilemma because many patients will wish to preserve their fertility (1). Several...
MR imaging is the imaging modality of choice when staging the primary cervical tumor or assessing eligibility for fertility-sparing procedures, treatment response, tumor recurrence, and potential complications. In the presence of an ovarian mass, the key role of CT is in the identification of measurable disease beyond the mass, which would make fertility preservation unacceptable and allow appropriate planning of radical cytoreductive surgery. Invasive malignant masses are typically characterized as complex solid cystic lesions whose solid components have intermediate T2 signal intensity and, when compared with the adjacent myometrium, demonstrate a rapid wash-in rate and more intense enhancement during dynamic contrast-enhanced MR imaging. In most patients with endometrial cancer, MR imaging is used at initial staging to help exclude cervical and myometrial invasion and thus ensure suitability for fertility-sparing treatment. It is also performed for surveillance and posttreatment follow-up.

Transvaginal Doppler US is the mainstay of diagnostic imaging for gestational trophoblastic disease, with further imaging performed according to clinical need.

TEACHING POINTS

- MR imaging is the imaging modality of choice when staging the primary cervical tumor or assessing eligibility for fertility-sparing procedures, treatment response, tumor recurrence, and potential complications.
- In the presence of an ovarian mass, the key role of CT is in the identification of measurable disease beyond the mass, which would make fertility preservation unacceptable and allow appropriate planning of radical cytoreductive surgery.
- Invasive malignant masses are typically characterized as complex solid cystic lesions whose solid components have intermediate T2 signal intensity and, when compared with the adjacent myometrium, demonstrate a rapid wash-in rate and more intense enhancement during dynamic contrast-enhanced MR imaging.
- In most patients with endometrial cancer, MR imaging is used at initial staging to help exclude cervical and myometrial invasion and thus ensure suitability for fertility-sparing treatment. It is also performed for surveillance and posttreatment follow-up.
- Transvaginal Doppler US is the mainstay of diagnostic imaging for gestational trophoblastic disease, with further imaging performed according to clinical need.

Cervical Cancer

Worldwide, cervical cancer accounts for 9% of cancer deaths (4) and is the second most common cancer that affects women (5). In the United Kingdom, cervical cancer is the second most common cancer in women younger than 35 years (6). The early incidence of cervical cancer is largely attributed to women becoming sexually active in their late teens or 20s, with an accompanying risk of human papilloma virus infection, which is the key underlying cause of disease. The peak incidence of this malignancy occurs in women between the ages of 25 and 39 years (7).

Clinical Background

Fertility-preserving surgical techniques such as conization and trachelectomy are suitable for patients who have early-stage cervical cancer—that is, International Federation of Gynecology and Obstetrics (FIGO) stage IA1, IA2, or IB1 disease without any myometrial invasion. Stage IA cancer includes microscopic disease, whereas stage IB1 lesions are clinically visible but smaller than 4 cm in maximal diameter (8). In patients who have more advanced stages of disease for which chemoradiation therapy is considered the initial treatment of choice, ovarian transposition, whereby the ovaries are moved out of the radiation field in an attempt to preserve ovarian function, is an option.

Conization, or cone biopsy of the cervix, can be performed as the primary treatment of diagnosed and histologically staged IA1 disease without lymphovascular space invasion. The reported risk for recurrent adenocarcinoma at this stage is approximately 1.5% (9). Cone margins must be clear at histologic analysis to avoid further radical treatment. When lymphovascular space invasion is identified, lymphadenectomy and radical trachelectomy may be necessary if fertility preservation is desired (10,11). Stage IA2 cervical adenocarcinoma and stage IA2 cervical squamous cell carcinoma are treated more aggressively, with no set approach. Management can include large-cone biopsy and pelvic nodal dissection; however, in some cases, a more radical surgical approach such as trachelectomy (9) is undertaken. If invasion is suspected clinically, magnetic resonance (MR) imaging may be performed before cone biopsy.
Figure 1. Appearance of the cervix before and after conization. (a) Sagittal T2-weighted MR image shows the normal appearance of the cervix, with no visible tumor. (b) Sagittal T2-weighted MR image obtained at the same level after conization shows a substantial reduction in the size of the cervix. A small high-signal-intensity focus (arrow) in the endocervical canal is seen posteriorly and is consistent with the changes typically seen after cone biopsy. This focus did not show restricted diffusion at diffusion-weighted (DW) MR imaging and thus was not considered to be residual disease.

Table 1: Eligibility Criteria for Vaginal Radical Trachelectomy

<table>
<thead>
<tr>
<th>Disease limited to cervix</th>
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<tr>
<td>Tumor diameter ≤ 2 cm (or ≤2.5 cm if exophytic lesion)</td>
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<tr>
<td>Squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma found at histologic analysis</td>
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<tr>
<td>Unaffected cervix with an estimated length of ≥1 cm from the proximal aspect of the tumor to the internal os</td>
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<tr>
<td>Absence of parametrial invasion</td>
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<td>Absence of lymph node metastasis or metastatic spread</td>
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or loop excision to avoid difficulties in interpreting the findings of subsequently performed MR imaging that is indicated after biopsy—if histologic analysis results indicate the need to proceed to radical trachelectomy or hysterectomy. A stage IA tumor is not visible at MR imaging (Fig 1a); however, once biopsy is performed, the cervix usually has an altered shape on MR images (Fig 1b).

Vaginal radical trachelectomy (VRT) with laparoscopic pelvic lymphadenectomy is the most widely evaluated fertility-sparing technique in patients who have cervical cancer, with more than 1500 cases reported in the literature (12). This technique involves surgical removal of the cervix to the level of the internal os, with en bloc resection of the vaginal fornix and a cuff of parametrial tissue. The vagina is then sutured to the lower uterine body, and a cerclage suture is placed at the level of the internal os to prevent miscarriage during a future pregnancy. VRT can be performed in patients with stage IIA disease and lymphovascular space invasion, in those with stage IIA2 disease, or in select patients with stage IB1 disease in whom the suitability criteria have been met (Table 1). The absence of isthmic invasion is crucial for trachelectomy to be feasible, and MR imaging is very accurate for making this determination (13–15). Although lymphovascular space invasion is a feature associated with recurrence and nodal metastatic disease, VRT can still be considered in patients with solely lymphovascular space invasion if other suitability criteria are met (16,17).

VRT performed in conjunction with laparoscopic lymphadenectomy to treat patients who have early-stage cervical cancer that is less than or equal to 2 cm in diameter is reportedly associated with a recurrence-free survival rate higher than 90.8% and a 5-year disease-free overall survival rate of 97%–98% (18). Similar recurrence rates of 2.9% and 3.1%, respectively, were reported in two other studies (19,20). Despite the prudent selection criteria, 10%–12% of patients who undergo trachelectomy require adjuvant therapy owing to recurrence or histologic findings perceived to be associated with a high risk for recurrence (2).

 Higher tumor grade, tumor size larger than 2 cm, lymphovascular space invasion, and a histologic tumor type associated with a poor prognosis
appear to be predictive of VRT being abandoned during the surgery. A tumor diameter larger than 2.5 cm and suspicion of parametrial invasion based on the MR imaging appearance are strongly associated with a higher risk of parametral invasion at surgery, a lower 5-year progression-free survival rate, and a higher risk of recurrence (21,22).

Abdominal radical trachelectomy, as compared with VRT, involves a wider or complete dissection of the parametrium, is not limited by the strict eligibility criteria, and has been used to address larger tumors with a better success rate. It can be performed in patients with a distortion of the vaginal anatomy, with a tumor diameter larger than 2 cm, or in whom a vaginal approach is not possible. It also has been performed in women in their first trimester of pregnancy (9,11).

However, very limited outcome data have been published, and it is not yet clear which patient groups will benefit most from abdominal radical trachelectomy in the longer term (23–25).

Patients who have small cervical tumors that are amenable to fertility-sparing treatment should be counseled thoroughly so that they have realistic expectations and understand that the trachelectomy procedure may need to be abandoned if metastatic nodal or parametrial disease is identified intraoperatively and thereby necessitates radical hysterectomy. They also need to be made aware of the recurrence rates, fertility outcomes, and follow-up regimen (21,22,26).

With ovarian transposition, the ovaries are detached from the uterus with their vascular pedicles intact and then reattached inside the abdomen—away from the proposed radiation field in the pelvis (Fig 2). This procedure may be performed in women who are undergoing primary radiation therapy or chemoradiation therapy, or it may be performed before radical hysterectomy with adjuvant chemoradiation therapy in an attempt to preserve fertility for in vitro fertilization and surrogacy (1,11,27–30).

Role of Imaging in Cervical Cancer Staging and Fertility-sparing Surgery

In the 2009 revised FIGO staging system, imaging is acknowledged as being complementary to the established clinical staging of cervical cancer and helpful in assessing prognostic factors. MR imaging is the imaging modality of choice when staging the primary cervical tumor or assessing eligibility for fertility-sparing procedures, treatment response, tumor recurrence, and potential complications. Satisfactory patient preparation, imaging protocols, and MR imaging reporting are key to achieving diagnostic accuracy (31).

Before any fertility-sparing surgery is performed, careful selection of patients with use of a multidisciplinary approach is required to ensure a successful outcome. The important MR imaging parameters used to determine patient eligibility are included in Table 2 and shown in Figure 3. In particular, MR imaging is accurate for evaluating the proximity of a tumor to the internal cervical os to ensure clear surgical resection margins (Fig 3b). At MR imaging, the internal os is defined as the waist of the uterine contour and the entrance of the uterine vessels, at the point of transition from the low-signal-intensity cervical stroma to the intermediate-signal-intensity myometrium. On oblique axial MR images, the internal os is defined as the point of transition from the low-signal-intensity cervix to the intermediate-signal-intensity myometrium (15).

In a number of recent studies involving patients who had early-stage cervical cancer with histopathologic correlation, MR imaging was shown to be an accurate imaging modality for assessing the size and position of the tumor within the cervix and evaluating parametrial spread. Investigators in a 1999 study reported that MR imaging could be used to determine the relationship of a tumor to the internal cervical os with 100% sensitivity and 96% specificity (15).
Figure 3. Assessment of eligibility for trachelectomy. (a) Sagittal T2-weighted MR image shows soft tissue with intermediate signal intensity (arrow), consistent with a cervical tumor, in the anterior lip of the cervix. The tumor is smaller than 2 cm in diameter and more than 1 cm from the internal os, with no evidence of extrauterine extension. (b) Sagittal T2-weighted MR image shows the measurements that must be recorded before trachelectomy is considered. Initially, the position of the internal os (dotted line) needs to be defined. Then, the length of the cervix from the internal os to the external os (solid white line), the length of the endometrial cavity from the fundus to the internal os (gray line), and the distance from the leading edge of the tumor to the internal os (red line) should be measured.

<table>
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<tr>
<th>Table 2: MR Imaging Findings Used to Assess Eligibility for Trachelectomy</th>
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<tr>
<td>Length of the cervix from the external os to the internal os</td>
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<tr>
<td>Length of the endometrial cavity from the fundus to the internal os</td>
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<tr>
<td>Diameter of the tumor on three axes</td>
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<td>Position of the tumor in the cervix</td>
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<tr>
<td>Tumor growth pattern (exophytic or diffusely infiltrating)</td>
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<tr>
<td>Distance of the proximal edge of the tumor to the internal os, parametrium, or vaginal fornix</td>
</tr>
<tr>
<td>Nodal enlargement (pelvic or para-aortic)</td>
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<tr>
<td>Incidental finding in other organs (ovaries, rectum, or bladder)</td>
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In a more recent study involving 150 patients with early cervical cancer (IB1 or earlier stage), the sensitivity, specificity, and positive and negative predictive values of MR imaging in the assessment of internal os involvement were 90%, 98%, 86%, and 98%, respectively (32). In the assessment of parametrial invasion, the specificity and negative predictive value of MR imaging were 97% and 100%, respectively. In the evaluation of myometrial invasion, the sensitivity, specificity, and negative and positive predictive values of MR imaging were 100%, 99%, 88%, and 100%, respectively (32). The accuracy of MR imaging in determining the relationship of the tumor to the internal os was supported by findings in a meta-analysis involving 366 patients; estimates of specificity, sensitivity, and negative and positive predictive values were 91%, 97%, 99%, and 79%, respectively (14). The accuracy of MR imaging in the selection of patients for trachelectomy has been supported by the results of a number of studies (33–36).

Nodal Disease

Many studies have been performed to evaluate the accuracy of MR imaging in the diagnosis of nodal disease. A review of the literature revealed sensitivities as low as 40%; however, a sensitivity of 80% was achieved in some studies (37–39). In the study involving 150 patients cited earlier (32), the prevalence of nodal metastases was 2.9%. On a node-by-node basis, the sensitivity and specificity of MR imaging in the detection of nodal involvement were 27% and 99%, respectively, and on a per-patient basis, 37% and 92%, respectively (32). The main difficulty is in detecting small metastases in normal-sized nodes. Reported specificities of MR imaging in the diagnosis of nodal metastatic disease are high when a short-axis tumor diameter larger than 10 mm is used as the threshold size (40,41).

Although the lymph node status is not considered in and does not alter the FIGO stage (38), nodal metastases are an independent prognostic indicator. The presence of nodal disease substantially alters the treatment plan because chemoradiation is required for patients with
node-positive disease. When imaging reveals that all nodes are smaller than 10 mm in short-axis diameter, the sensitivity is too low to be reliable, and if a fertility-sparing surgical approach is being considered, pelvic lymphadenectomy will be warranted in most patients (32,38). Fluorine 18 ($^{18}$F) fluorodeoxyglucose positron emission tomography (PET)/computed tomography (CT) has not been found to be reliable in the detection of nodal metastases in patients with early-stage (FIGO stage IA or IB1) cervical cancer; its sensitivity was as low as 10% in one series (42). In a large series, Plante et al (21) assessed 125 trachelectomy cases and found that the most frequent reason that VRT was abandoned was the finding of nodal metastases rather than threatened endocervical margins.

Follow-up
At our institution, patients who undergo cone biopsy or trachelectomy will undergo pelvic MR imaging annually for the first 2 years after the procedure. In other centers in the United Kingdom, follow-up MR imaging has been performed 3 and 6 months after treatment and only if clinically indicated beyond that point (43).

It is important to be aware of posttrachelectomy MR imaging findings (Fig 4) and complications that could be mistaken for findings of recurrent disease (Fig 5) (43). The following posttrachelectomy findings have been described (43): posterior vaginal wall outpouching that mimics a vaginal fornix and has low T2 signal intensity like the normal vaginal wall. This was seen in 56% of cases in the 2005 study by Sahdev and colleagues (43). This appearance could be mistaken as being indicative of recurrent disease, which has intermediate or high T2 signal intensity. Diffuse vaginal wall thickening with intermediate T2 signal intensity may persist for up to a year after trachelectomy and gradually resolves without treatment; this was seen in 7% of cases. Slow-resolving hematoma in the vaginal wall has intermediate to high T1 signal intensity and low or intermediate T2 signal intensity; this was seen in 4% of cases. Anastomotic suture artifacts from a cerclage or uterovaginal anastomosis also are observed; thus far, however, they have not impaired the diagnostic capability of follow-up MR imaging (44). The most likely site of recurrent disease is the uterovaginal anastomosis, which must be carefully evaluated with clinical or MR imaging examination at each follow-up (Fig 6). However, other local sites of recurrence can be seen in the pelvis (Fig 7). When recurrent disease is suspected clinically, $^{18}$F fluorodeoxyglucose PET/CT may be needed to delineate the extent of disease before further treatment is initiated (45,46).

Ovarian Cancer
The majority of patients with ovarian cancer have advanced disease when they present and no options for fertility preservation. However, fertility preservation may be considered for some patients with early-stage ovarian cancer or borderline ovarian tumors. The potential for fertility preservation is related to the perceived lack of dissemination of the tumor at the time of presentation or the low potential for malignancy. Ultrasonography (US) is the most important first step in determining whether an adnexal mass is benign or potentially malignant before surgery. When US findings are indeterminate, MR imaging may be used. Careful use of imaging is required, as biopsy of a solitary complex adnexal mass is not advocated owing to the associated potential for dissemination of a tumor confined within a cystic mass. Ovarian tumors that are potentially suitable for fertility-preserving surgery include borderline ovarian tumors, stage I epithelial ovarian cancers, malignant ovarian germ cell tumors, and sex cord–stromal tumors. These tumors are more prevalent in women of child-bearing age. In a comprehensive Swedish study involving women with ovarian tumors, the median age of women who had borderline ovarian tumors was 55.2 years. However, in the women with an
Figure 5.  Posttrachelectomy appearances in a woman before, during, and after pregnancy. (a) Sagittal T2-weighted MR image obtained before the pregnancy shows a normal uterovaginal anastomosis, consistent with findings seen after trachelectomy. (b–d) During the pregnancy, images were obtained when there was symptomatic vaginal bleeding (b, c) and when the bleeding resolved (d). (b) Sagittal T2-weighted MR image shows the uterus at 16 weeks of pregnancy, with an intermediate- to high-signal-intensity abnormality (arrow) in the upper-third region of the vagina. Although there was concern that this abnormality could be a recurrent tumor, the structure of the mass conformed smoothly to the vaginal lumen, and only blood was seen at clinical examination of the vagina. (c) Axial T1-weighted MR image shows an area of intermediate signal intensity (arrow). (d) Sagittal T2-weighted MR image obtained 2 months later shows complete resolution of the abnormality, which enabled confirmation of the diagnosis of hematoma at the anastomosis site.

Figure 6.  Cervical cancer recurrence at the uterovaginal anastomosis in a woman who previously underwent trachelectomy. (a) Sagittal T2-weighted MR image shows a large soft-tissue mass (arrow) with central necrosis at the site of the uterovaginal anastomosis. (b) Axial T1-weighted MR image through the recurrent malignant mass shows intermediate signal intensity (arrow).
ovarian tumor who were younger than 40 years, 34% of the ovarian tumors were of the borderline histologic type (47).

Clinical Background

Borderline Ovarian Tumors.—Borderline ovarian tumors have histologic features of malignancy but no evidence of ovarian stromal invasion (48). The most common histologic subtype is serous, followed by mucinous. Borderline ovarian tumors tend to affect younger patients and account for 10%–15% of all ovarian neoplasms (1,11,48,49). Fifty percent of serous borderline tumors and 80%–90% of mucinous borderline tumors are unilateral at the time the patient presents; 60% and 90% of these neoplasms, respectively, are confined to the ovary and thus associated with a good prognosis (11). In the majority of studies, reported oncologic and obstetric outcomes after fertility-preserving surgery have been good; however, there are limited data thus far (50).

In a study involving 360 women with borderline ovarian tumors, recurrence rates in the fertility-sparing group (n = 184) and radically treated group (n = 176) were comparable (4.9% vs 5.1%, respectively). In the fertility-sparing group, tumor recurrence occurred predominantly in the remaining ovarian tissue (48).

Stage I Invasive Cancer.—The standard of care for stage I invasive epithelial ovarian cancer is total abdominal hysterectomy and bilateral salpingo-oophorectomy followed by surgical staging of the peritoneum and omentum and lymph node sampling or dissection. However, stage I disease may be an unexpected histologic finding after resection of an adnexal mass or cyst that was thought to be benign at US. The question that then arises is to what extent should completion surgery and staging be undertaken. In a 2010 study performed by Satoh et al (51) in which 211 patients who underwent fertility-sparing surgery were examined, favorable oncologic and obstetric outcomes were demonstrated in those patients who had stage IA disease of non–clear cell histologic types (ie, serous, endometrioid, or mucinous), with 5-year overall survival and recurrence-free survival rates of 100% and 97.8%, respectively. Patients at higher risk—that is, those with stage IA disease of the clear cell histologic type or unilateral stage IC disease of the non–clear cell histologic type—also have fared well, with adjuvant chemotherapy administered in these two groups (39). In the study by Satoh et al (51), both the 5-year overall survival rate and the 5-year recurrence-free survival rate were 100% for patients with stage IA disease of the clear cell histologic type, and these rates were 96.9% and 92.1%, respectively, for patients with stage IC disease of the non–clear cell histologic type (51).
Surgical-pathologic tumor stage and grade are the biggest predictors of the prognosis in patients with early-stage disease, and the dilemma regarding resection of the contralateral ovary and uterus persists. Surgical staging of the peritoneum and omentum is critical to ensuring the stage I status of disease (48,49). In the majority of studies, however, it has been shown that recurrence rates generally are slightly higher (3%-5% higher) in patients who undergo fertility-sparing procedures than in those patients who undergo radical surgery. This discrepancy is thought to be due to microscopic, nonvisible malignant involvement of a macroscopically normal contralateral ovary (50,52,53). It is important for patients to understand that retaining the contralateral ovary involves a small but real risk for recurrence (54).

**Malignant Germ Cell Tumors.**—Malignant germ cell tumors account for approximately 5% of all ovarian malignancies and are most common in children and young women; thus, fertility preservation is a high priority in patient care. These tumors can be divided into two categories, dysgerminomas and nondysgerminomas, and most of them are diagnosed preoperatively owing to the secretion of typical tumor markers such as the beta subunit of human chorionic gonadotropin (β-hCG). Most cases are unilateral—although dysgerminomas can be bilateral in up to 15% of cases—and treatment consists of unilateral cystectomy or salpingo-oophorectomy followed by surgical staging (1,11,49). The contralateral ovary can be retained—even in patients with advanced disease—because of the good response to chemotherapy, with no alteration in the prognosis (55). Adjuvant chemotherapy is standard practice, except in the treatment of stage I dysgerminoma or stage IA-grade I immature teratoma, for which chemotherapy is not required. Patients should be made aware of the reported risk (up to 30%) of failed ovarian function associated with chemotherapy (1,11).

**Malignant Sex Cord–Gonadal Stromal Tumors.**—Granulosa cell tumors of the ovary are rare, but they are the most common subtype of sex cord–gonadal stromal tumor. Patients with the adult form of this disease have an excellent prognosis when it is confined to one ovary and found to be stage IA or IB disease, which is amenable to fertility-sparing treatment (1,11), after the patient presents. The juvenile form, which occurs predominantly in patients younger than 20 years, may be more aggressive; however, fertility-sparing surgery remains the standard treatment.

### Role of Imaging in Ovarian Cancer Staging and Fertility-sparing Surgery

**US Staging.**—US is the first-line imaging modality in the identification and characterization of adnexal masses (Table 3) (56). When an adnexal mass has features that suggest malignancy but there is a normal contralateral ovary and no other site of disease, fertility preservation may be

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<th>Table 3: Ten Simple US-based Rules for Predicting Malignancy or Benignity in an Adnexal Mass (IOTA Group)</th>
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<tr>
<td><strong>Rules for predicting a benign tumor (B rules)</strong></td>
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<tr>
<td>B1: Unilocular cyst</td>
</tr>
<tr>
<td>B2: Presence of solid components, where the largest solid component has a largest diameter of &lt;7 mm</td>
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<tr>
<td>B3: Presence of acoustic shadows</td>
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<tr>
<td>B4: Smooth multilocular tumor with a largest diameter &lt;100 mm</td>
</tr>
<tr>
<td>B5: No blood flow (color score, 1)</td>
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<tr>
<td><strong>Rules for predicting a malignant tumor (M rules)</strong></td>
</tr>
<tr>
<td>M1: Irregular solid tumor</td>
</tr>
<tr>
<td>M2: Presence of ascites</td>
</tr>
<tr>
<td>M3: At least four papillary structures</td>
</tr>
<tr>
<td>M4: Irregular multilocular solid tumor with a largest diameter ≥100 mm</td>
</tr>
<tr>
<td>M5: Very strong blood flow (color score, 4)</td>
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<td>Note.—Adapted and reprinted, with permission, from reference 56. If one or more M rules apply in the absence of a B rule, the mass is classified as malignant. If one or more B rules apply in the absence of an M rule, the mass is classified as benign. If both M rules and B rules apply, the mass cannot be classified. If no rule applies, the mass cannot be classified. IOTA = International Ovarian Tumor Analysis.</td>
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considered. Staging of the peritoneum should be performed and includes CT in most cases and surgical staging at the time of resection.

CT Staging.—When a mass is considered to be overtly malignant on the basis of US findings, identification of other sites of disease in the pelvis and peritoneum becomes critical. CT is the current reference standard for this identification, as recommended by the National Institute for Health and Care Excellence, the European Society of Urogenital Radiology, and the American College of Radiology (57,58). Although CT is commonly used to assess advanced disease, it has low sensitivity for the detection of small-volume peritoneal disease and limited accuracy in the staging of early peritoneal dissemination; thus, surgical staging is necessary. In the presence of an ovarian mass, the key role of CT is in the identification of measurable disease beyond the mass, which would make fertility preservation unacceptable and allow appropriate planning of radical cytoreductive surgery.

MR Imaging Characterization and Staging of Adnexal Masses.—If the nature of an adnexal mass is indeterminate at US, MR imaging can be used, as it has been shown to increase specificity in the determination of malignant disease and can be used to very accurately rule out malignancy and thereby decrease the chance of inadvertent removal of the contralateral ovary (59,60).

The correct MR imaging technique needs to be chosen to ensure the highest possible diagnostic accuracy. The MR imaging sequences used to characterize adnexal masses, as well as the rationales for and value of these sequences, are listed in Table 4. The addition of DW MR imaging and dynamic contrast-enhanced MR imaging to morphologic sequences has been reported to aid in diagnosis of benign and likely malignant ovarian lesions (Figs 8, 9). An algorithmic evaluation of the adnexal mass can be used to determine the associated risk for malignancy (Table 5) (59).

MR imaging features that are highly predictive of benignity include purely cystic, purely endometriotic, and purely fatty masses; absence of wall enhancement; and masses that have solid components with low T2 signal intensity (59,61–63). Solid components with low T2 signal intensity have been reported to be related to fibrous tissue, such as that in benign ovarian fibroma or cystadenofibroma. There is emerging evidence that when a solid enhancing component is seen, a slow wash-in rate or a time–signal intensity curve showing slow gradual enhancement—that is, a type 1 curve—is predictive of benignity (Fig 8) (59,64).

In patients with borderline ovarian tumors, the solid tumor components often have a papillary appearance and a slower enhancement curve compared with that of the myometrium—but with a shouldered curve shape (Fig 9) (59,65).

The MR imaging features of overtly malignant masses are well established. Invasive malignant masses are typically characterized as complex solid cystic lesions whose solid components have intermediate T2 signal intensity and, when compared with the adjacent myometrium, demonstrate a rapid wash-in rate and more intense enhancement during dynamic contrast-enhanced MR imaging (Figs 10, 11) (59,64,66,67). A time–signal intensity curve that shows earlier and more rapid enhancement compared with that of the adjacent myometrium is considered a type 3 curve (Fig 11).

| Table 4: MR Imaging Sequences Used to Characterize Adnexal Masses |
|----------------------|-----------------------------------------------|
| **Sequence**         | **Use or Value of Sequence**                  |
| T2 weighted          | Determine origin of mass (ovarian or uterine) |
|                      | Measure size of lesion                        |
|                      | Determine signal intensity characteristics of lesion |
|                      | Perform complete evaluation of pelvic organs, lymph nodes, and bone marrow |
| T1 weighted          | Identify high signal intensity                |
| T1-weighted fat saturated | Perform complete evaluation of lymph nodes and bone marrow (in conjunction with T2-weighted MR imaging) |
| Three-dimensional isotropic dynamic contrast material enhanced, with subtraction | Evaluate the perfusion time–signal intensity curves for the solid components |
| DW                   | Mass is highly likely to be benign if there is no residual high signal intensity on high–$b$-value image |
DW MR imaging has been reported to be a useful adjunctive tool for ruling out malignant change. DW images should always be interpreted in conjunction with the morphologic data available on conventional MR images and should not be used as the sole diagnostic tool. Many benign masses (ie, cystic teratomas, endometriotic cysts) and malignant masses demonstrate restricted diffusion, with high signal intensity on high–b-value images, and quantitative apparent diffusion coefficient measurements cannot be used as the differentiating parameters. DW imaging has value in cases in which no residual high signal intensity in the solid component is viewed on high–b-value images. In these cases, the positive likelihood ratio for benignity has been reported to be 10.9 (68). When a mass demonstrates solely low signal intensity on the T2-weighted MR image and a complete loss of signal on the high–b-value image, there is a high likelihood that the lesion is benign. The use of DW imaging and dynamic contrast-enhanced MR imaging is being evaluated, and further data are needed to determine the accuracy and reproducibility of these techniques.

In the case of an isolated sonographically indeterminate ovarian mass with US features that have a high positive predictive value for cancer, the decision to consider fertility preservation requires full discussion between the patient and physician. When the MR imaging findings also are indeterminate, fertility preservation by means of initial cystectomy or oophorectomy with contralateral ovarian preservation undergo US, clinical assessment, and tumor marker measurement every 3 months in the 1st year, at 4-month intervals in the 2nd year, and at 6-month intervals in the 3rd year for assessment of possible recurrence and suitability for further fertility-sparing treatment, if it is required. There is no defined consensus in the current literature as to when surveillance imaging should begin—and how often it should be performed—after treatment. In the face of possible recurrence, additional imaging is individualized and may include MR imaging, CT, or PET/CT (57,72).

**Follow-up**

At our institution, patients who undergo fertility-sparing treatment (eg, cystectomy or oophorectomy with contralateral ovarian preservation) undergo US, clinical assessment, and tumor marker measurement every 3 months in the 1st year, at 4-month intervals in the 2nd year, and at 6-month intervals in the 3rd year for assessment of possible recurrence and suitability for further fertility-sparing treatment, if it is required. There is no defined consensus in the current literature as to when surveillance imaging should begin—and how often it should be performed—after treatment. In the face of possible recurrence, additional imaging is individualized and may include MR imaging, CT, or PET/CT (57,72).

**Endometrial Cancer**

Endometrial cancer is relatively uncommon in women of reproductive age. Nulliparity is a known risk factor associated with this disease (44). Premenopausal patients with endometrial cancer may have background polycystic ovarian syndrome, which further confounds the problem of subfertility and should be considered when selecting patients for fertility-sparing treatment.
Figure 8. Ovarian fibroma. (a) Sagittal T2-weighted MR image shows a large well-defined relatively low-signal-intensity mass (white arrow). The uterus is seen inferiorly to the mass (black arrow). (b) Axial DW image ($b = 1000 \text{ sec/mm}^2$) shows high signal intensity, consistent with restricted diffusion. (c, d) Axial contrast-enhanced fat-saturated T1-weighted subtracted MR images without (c) and with (d) color mapping. In d, regions of interest are outlined on the outer myometrium (1) and enhancing solid tissue of the mass (2). (e) Time–signal intensity curve for the mass (green line, 2) is slow and gradual compared with that for the myometrium (red line, 1), indicating a type 1 curve. X-axis values indicate time, in milliseconds. Y-axis values indicate relative signal intensity. A right oophorectomy was performed, and histologic analysis revealed an ovarian fibroma.

The standard treatment and staging procedure for women with endometrial cancer consist of hysterectomy and bilateral salpingo-oophorectomy. In women who wish to preserve their fertility and have a reasonable chance of becoming pregnant, hysteroscopy, dilation, and curettage with progesterone hormone therapy can be offered if important clinical parameters are acceptable. No consensus or established guidelines regarding eligibility for this treatment exist; however, patients who meet certain criteria are believed to be suitable candidates (Table 6) (49). The initial challenge for the pathologist is to determine whether the histologic findings represent...
Figure 9. Borderline ovarian tumor in the right ovary. (a) Axial T1-weighted MR image shows a large multiseptated cystic mass. (b) Time–signal intensity curve for the thickened septa indicates moderate enhancement, with the shoulder typical of a type 2 curve (two lower curves, 2 and 4), compared with the enhancement of the myometrium (two upper curves, 1 and 3). (c) Findings on an axial MR image with color mapping correspond to the data in b. A right oophorectomy was performed, and histologic analysis revealed a borderline ovarian tumor.

Figure 10. Immature germ cell tumor. (a) Axial T2-weighted MR image shows a large cystic lesion that contains a papillary mural nodule (arrow). (b, c) Axial DW image (b) shows high signal intensity in the solid-component areas (arrow) of the solid nodule; the high signal intensity correlates with the low b value on the corresponding apparent diffusion coefficient map (c). The patient underwent a right oophorectomy, and histologic analysis of the mass revealed an immature germ cell tumor.
complex atypical hyperplasia or cancer. If an aggressive cancer such as serous carcinoma, clear cell carcinoma, or carcinosarcoma is found at histologic analysis, fertility preservation cannot be recommended. If the presence of a well-differentiated endometrioid cancer is confirmed, several progesterone regimens are available and have been described, the most common of which involve high doses of oral medroxyprogesterone acetate or megestrol. Repeated endometrial curettage is then performed at 3-month intervals to monitor tumor regression. An intrauterine device that contains levonorgestrel or medroxyprogesterone acetate may be used as a maintenance therapy and is an alternative to oral progesterone therapy for women who have complex atypical hyperplasia (54,73). The intrauterine device provides topical treatment without the associated systemic side effects. In one study, when the efficacy of an intrauterine device was compared with that of oral progesterone therapy at 6, 56, and 108 months after treatment, the intrauterine device was found to be superior (74). In the event of disease progression, hysterectomy is recommended (44). With disease regression, continuation of hormone therapy is permitted for another 6–9 months, and at the completion of treatment, the patient can attempt to become pregnant (49). The tumor response rate with high-dose progesterone is approximately 75%; however, nearly half of patients who are treated with this therapy experience a relapse, so the prolonged response rate is approximately 50%.

Live-birth rates of 22%–47% have been reported for women with endometrial cancer—but with relatively high (28%–41%) relapse rates.
Table 6: Criteria for Fertility Preservation Eligibility in Patients with Endometrial Cancer

<table>
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<tr>
<td>Curettage specimen that enables confident diagnosis</td>
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<td>Well-differentiated histologic grade 1 endometrioid tumor</td>
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<tr>
<td>Positive expression of progesterone receptor on immunohistochemically</td>
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<tr>
<td>stained endometrial biopsy or curettage specimen</td>
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<td>No evidence of myometrial invasion at MR imaging</td>
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<tr>
<td>No evidence of extrauterine disease at staging MR imaging or CT</td>
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<tr>
<td>No CT or US evidence of adnexal mass associated with concurrent ovarian</td>
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<td>malignancy*</td>
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*It has been reported that as many as 29% of premenopausal women with endometrial cancer may be at risk for ovarian malignancy (49).

Hormone therapy is unsuccessful in 18% of patients, and poor outcome is seen in fewer than 1% of patients (49,75). Hysterectomy is recommended after childbearing (54).

Role of Imaging in Treatment Selection

In most patients with endometrial cancer, MR imaging is used at initial staging to help exclude cervical and myometrial invasion and thus ensure suitability for fertility-sparing treatment. It is also performed for surveillance and posttreatment follow-up. Although MR imaging is relatively accurate in local disease staging, very early myometrial invasion can be difficult to identify. Comprehensive MR imaging evaluation should include the acquisition of T2-weighted sagittal, axial, and oblique datasets, with the oblique images oriented perpendicular to the long axis of the uterus. Although DW imaging may be used to determine the tumor grade, there is substantial overlap between grades; therefore, it cannot be used confidently to raise a tumor’s classification to a higher grade (76–78). Benign concomitant disease, such as adenomyosis or fibroid tumors, can make staging difficult. Hemorrhage within the endometrial cavity from a dilation and curettage procedure also may pose difficulties in tumor staging (44). MR imaging may be used to follow the tumor’s response to progesterone therapy if clinical or US findings are equivocal (Fig 12) (79).

At our institution, follow-up for women who undergo fertility-sparing treatment consists of US performed at 3-month intervals during the 1st year after treatment, at 4-month intervals in the 2nd year, and at 6-month intervals in the 3rd year to check for recurrence and assess the patient’s suitability for further fertility-sparing treatment, if it is desired. Hysteroscopy or Pipelle biopsy is performed intermittently.

Gestational Trophoblastic Disease

Gestational trophoblastic disease is an umbrella term that encompasses benign and malignant neoplastic disease and includes hydatidiform mole; invasive mole, which has malignant potential; choriocarcinoma; and placental site trophoblastic...
tumor, which is a rare form of malignant gestational trophoblastic disease that is associated with a 20% mortality rate (80). Gestational trophoblastic disease is relatively uncommon. Because it is a neoplasia of placental tissue, it invariably affects women of reproductive age, in whom fertility preservation is an important consideration (1). The diagnosis is usually made by using a combination of US and MR imaging findings (Fig 13), and histologic confirmation is achieved by evacuating the products of conception (81).

In the majority of patients, gestational trophoblastic disease can be managed conservatively with single- or multiagent chemotherapy regimens. Before treatment commences, assessment with use of the FIGO prognostic scoring system is performed to determine a suitable course of therapy. For disease with a score of 7 or higher, the use of multiagent chemotherapeutic regimens with methotrexate, etoposide, cyclophosphamide, vincristine, and dactinomycin is warranted (81,82). Chemotherapy is continued until levels of β-hCG normalize and for 6 weeks thereafter (81). According to the Royal College of Obstetricians and Gynaecologists (81), follow-up should be tailored to the individual patient and normally includes measurement of the level of β-hCG. Fertility is usually preserved, with good outcomes, in the majority of patients despite the use of various chemotherapeutic regimens; pregnancy rates of up to 83% of cases after treatment have been reported (83).

Placental site trophoblastic tumor is an aggressive form of gestational trophoblastic disease and is often resistant to chemotherapy. Hysterectomy is often advocated in this patient group, unless there is a strong desire to preserve fertility. Results of a number of case studies (80,84–88) have shown that term pregnancies are possible after conservative therapy with chemotherapeutic agents for women with placental site trophoblastic tumors; however, metastatic disease and a pregnancy that occurred 4 or more years previously are factors of poor outcome (87).
The standard management for placental site trophoblastic tumors is radical hysterectomy with pelvic lymph node sampling. Although the modified Strassman procedure is an alternative fertility-sparing technique performed to address a presumed solitary uterine placental site trophoblastic tumor, in two studies, fertility was preserved in only one of five patients owing to suspected incomplete excision in the uterus, which was treated with hysterectomy (89,90). Further development of this new technique may be seen in the future.

Imaging
To our knowledge, no specific follow-up imaging regimen for gestational trophoblastic disease has been documented in the literature owing to the lack of data on this relatively rare condition. Transvaginal Doppler US (Fig 13b) is the mainstay of diagnostic imaging for gestational trophoblastic disease, with further imaging performed according to clinical need. Pelvic MR imaging also can be useful if resection is being considered (Fig 13c) (91,92). For low-risk disease, chest radiography is used for assessment of possible lung metastases. For patients with high-risk disease, such as those with vaginal or lung metastases, full staging CT including brain imaging is recommended. The retroperitoneal lymph nodes are another typical site for recurrent disease (Fig 14). For patients with placental trophoblastic tumors who have undergone fertility-sparing surgery, the policy at our institution is to perform pelvic MR imaging every 3 months in the 1st year after the procedure.

Conclusion
For patients with gynecologic malignancies, the use of fertility-sparing treatment procedures, as compared with established surgical techniques, has led to favorable live-birth rates and is now a viable option for many women who have not completed their families. Imaging is of paramount importance in determining which patients are suitable for fertility-sparing treatment and thus ensuring the best possible obstetric and oncologic outcomes. Imaging is also used for follow-up assessment of possible disease recurrence and evaluating suitability for additional fertility-sparing procedures, if these are warranted.

In patients with cervical cancer, MR imaging is used to assess possible local disease spread; this information is essential for selecting patients who are eligible for fertility-sparing treatment. Trachelectomy is now a well-established treatment for early-stage cervical cancer, and MR imaging of the cervix is vital for safe patient selection. However, owing to the low sensitivity of MR imaging
in the detection of nodal metastases, imaging of the cervix is combined with surgical nodal staging for complete confidence in patient selection.

Surgical stage and tumor grade are the most important prognostic indicators in patients who have early-stage invasive ovarian malignancies, with traditional surgical techniques advocated. However, current literature data indicate that patients who undergo fertility-sparing treatment and those who choose traditional surgical options have comparable recurrence rates. MR imaging is used to select women who are unlikely to have invasive disease or who have, at most, FIGO stage IA disease. Borderline ovarian tumors and malignant germ cell tumors tend to affect younger patients, and fertility-sparing treatment is a higher priority in the care of these patients.

In patients with endometrial cancer, MR imaging is used to rule out disease extending beyond the endometrial lining. Hormone therapy regimens are established treatments for low-risk endometrial cancer and have acceptable outcomes. Chemotherapy can be used in patients with gestational trophoblastic disease, with the uterus preserved in many of them.

The radiologist has an important role in terms of the use of these important advances in the care of young women, which offer survivorship options in the face of gynecologic cancer. If fertility preservation is chosen, careful patient counseling is vital to ensuring that these women have full knowledge of the potential risks. In addition, these patients need to understand the requirements for careful follow-up and subsequent definitive treatment after attempted pregnancy.

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References


