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Endometrial Cancer: Screening, Diagnosis, and Surgical Staging

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Abstract

Environmental and hereditary factors contribute to increased risk of developing endometrial cancer. An understanding of risk factors can guide screening modalities in premenopausal and postmenopausal women. Attention is drawn to certain anatomic abnormalities that prevent vaginal bleeding—the most common symptom related to cancer. Diagnostic tests that are available to pursue various aspects of the diagnosis in a sequential fashion are described, the most important of which is the endometrial biopsy. Recommendations for screening and diagnosis in the asymptomatic as well as the symptomatic patients are summarized. Surgical staging represents the final event in the diagnostic workup. Instances when such staging can be modified to deal with various comorbidities are delineated.

Keywords

Endometrial cancer • Heredity • Screening • Endometrial biopsy • Surgical staging

Screening

Case Report 1 *A 32-year-old thin, nulliparous woman presented with menorrhagia. The bleeding was unresponsive to birth control pill use. She had no other medical conditions. There was no family history of malignancies. She underwent an endometrial ablation. An endometrial biopsy was not performed prior to the ablation. Six months later, a hysterectomy was performed because of persistent bleeding. Her pathology showed a deeply invasive grade 2, endometrioid endometrial adenocarcinoma with metastases to a para-aortic lymph node.*

Endometrial cancer is the most common gynecologic malignancy in North America with an estimated 60,650 new cases and 10,470 deaths in 2016 and is the fourth most common cancer in women in the developed world [1, 2]. Routine

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screening is not recommended as symptoms of endometrial cancer develop at an early stage and the female genital tract allows easy access to the uterus for diagnostic evaluation. Therefore, the focus has been on efficient evaluation in the setting of symptoms.

There are certain groups of women who have an increased risk for the development of endometrial cancer. Evaluation of the endometrial cavity should be considered and a higher index of suspicion for the development of endometrial cancer should be entertained even in the absence of symptoms for these women. The decision to screen an individual, asymptomatic woman will be based on her risk factors, age, and physical examination findings.

Since the 1980s, two distinct types of endometrial cancers have been described, Type I and Type II [3]. Type I endometrial cancer makes up 80–90 % of all sporadic endometrial cancers [4]. Histologically, these tumors can be endometrioid adenocarcinoma with or without squamous differentiation and often are well differentiated. A multistep carcinogenic process of Type I endometrial malignancies starts with simple endometrial hyperplasia, then develops complex atypia hyperplasia followed by progression into the precursor lesion, endometrial intraepithelial neoplasia (EIN) [5]. The remaining 10–20 % of endometrial cancers, Type II, are mainly composed of two rarer histologies: uterine papillary serous carcinoma (UPSC) and clear-cell carcinoma. Both cancers appear to progress from an atrophic endometrium to the precursor lesion, endometrial glandular dysplasia [6].

Table 1 summarizes the groups of women who are at increased for the development of endometrial cancers. For this group, any factor that increases the exposure to unopposed estrogen increases the risk of endometrial cancer [7]. Premenopausal women who have had chronic anovulation will develop a buildup of the endometrial lining [8]. Women with polycystic ovarian syndrome will present with years of anovulation since their teenage years [9]. Other causes of anovulation include thyroid disease, hyperprolactinemia, and certain exogenous drugs such as antipsychotics [10]. Metabolic syndrome has been linked with endometrial cancer [11, 12]. Diabetes (both type 1 and type 2) has also been related to an increased risk of endometrial cancer [13]. Further, other metabolic risk factors, such as hypertension and hyperglycemia, have also been associated with increased endometrial cancer risk, especially among overweight and obese women. Estrogen-secreting ovarian tumors such as granulosa cell tumors and thecomas can lead to stimulation of the endometrial lining [14].

Morbid obesity is a risk factor at all ages as these women have higher endogenous estrogens

Table 1 Factors associated with increased risk of developing Type I endometrial cancer

Premenopausal women
Endogenous estrogen exposure
Anovulatory cycles
Polycystic ovarian syndrome
Morbid obesity
Estrogen secreting tumors
Sex cord stromal tumors Adrenal adenomas
Metabolic Syndrome
Hereditary syndromes
Hereditary Nonpolyposis Colorectal Cancer (HNPCC), Lynch Syndrome
BRCA 1 mutation
Cowden syndrome
Li–Fraumeni syndrome
Peutz–Jeghers syndrome
Postmenopausal women
Endogenous estrogen exposure
Morbid obesity
Estrogen secreting tumors
Cirrhosis of the liver
Exogenous hormonal exposure
Exogenous estrogens without progestins
Tamoxifen
History of pelvic radiation
Hereditary syndromes
Hereditary Nonpolyposis Colorectal Cancer (HNPCC), Lynch Syndrome
BRCA 1 mutation
Cowden syndrome
Li–Fraumeni syndrome
Peutz–Jeghers syndrome

due to aromatization of androgens to estradiol and the conversion of androstendione to estrone in peripheral adipose tissue [15]. The epidemic of obesity has led to a 50 % increase in the incidence of endometrial cancer [1, 16]. Use of exogenous estrogens without the balance of progesterone is associated with endometrial cancer [17]. Women with liver disease who cannot adequately metabolize their endogenous or exogenous estrogens are also at risk for the development of endometrial malignancies [18].

Tamoxifen increases the risk of endometrial cancer two- to threefold but the effects are not seen before 2 years of use [19]. However, the absolute risk of developing endometrial cancer while taking tamoxifen is 1.2/1000 per year. Currently, the American College of Obstetrician Gynecologists (ACOG) does not recommend routine screening in asymptomatic women taking tamoxifen [20]. Given the current obesity epidemic and factoring in long-term adverse effects, ACOG guidelines suggest consider of aromatase inhibitors instead of tamoxifen because of the reduced incidence of thrombosis, endometrial cancer, and vaginal bleeding.

Pelvic radiation for other malignancies such as lymphoma, cervical or rectal cancers will increase the risk of uterine corpus cancer. The most common post-radiation pelvic malignancy is adenocarcinoma of the endometrium [21].

Women with breast or colon cancer may have a higher genetic risk of gynecologic malignancies. A careful family history will help guide the decision to evaluate the endometrium. Hereditary nonpolyposis colon cancer (HNPCC) or Lynch syndrome, an autosomal dominant syndrome, confers a 40–60 % risk of endometrial cancer and makes up about 5 % of all cases of endometrial cancer [22]. The molecular basis for Lynch syndrome is a heritable functional deficiency in the DNA mismatch repair system, typically due to a germ line mutation. In contrast to the general population, the high lifetime risk of endometrial cancer in women with Lynch syndrome has led to consensus guidelines recommending annual or biennial endometrial sampling beginning at age 30–35 years and risk-reducing hysterectomy and bilateral salpingo-oophorectomy in women who have completed childbearing [23].

BRCA 1 gene mutation, in addition to the well-known risk of ovarian cancer, has been associated with an increased endometrial cancer risk [24]. Other genetic syndromes associated with endometrial cancer have now been identified [25]. Increased risk of endometrial cancer is caused by mutation in the phosphatase and tensin homolog (PTEN) gene in Cowden syndrome. Ovarian, uterine, and cervical cancers related to Peutz–Jeghers syndrome are due to liver kinase b1 (LKB1/STK11) gene mutation. Ovarian and endometrial cancers also occur excessively in patients with Li–Fraumeni syndrome, which has an inherited germ line mutation in p53.

Even in the absence of personal or family risk factors for endometrial cancer, all women with abnormal bleeding need to be evaluated for malignancy. Any vaginal bleeding in postmenopausal women regardless of the quantity needs to be evaluated. The risk of endometrial cancer in a 50-year-old woman with postmenopausal bleeding is 9 %, 16 % foe a woman in her sixties, 28 % for a woman in her seventies, and 60 % for a woman in her eighties [26]. Irregular bleeding in premenopausal women needs to be thoughtfully worked up. While hormone irregularities, complications of pregnancy, and pelvic infection are other causes of premenopausal bleeding; the possibilities of malignancy must be taken seriously. Twenty-five percent of all endometrial cancers occur in premenopausal women and 5 % are found in women less than 40 years old [27].

Table 2 lists certain anatomical changes that may prevent the development of the warning sign of vaginal bleeding or impair the examiner's ability to fully evaluate the pelvic tract. Women who have developed cervical stenosis because of postmenopausal atrophy, or previous cervical procedures such as cryotherapy, loop electrosurgical excision procedures (LEEP), or cervical cone biopsies may not have an open cervical canal. On physician inspection, the examiner will see that a cutip or cytobrush cannot pass

Table 2 Anatomic abnormalities that prevent vaginal bleeding

Abnormality	Causes
Agglutinated vagina	Dermatologic conditions
	Lichen planus
	Lichen sclerosis
	Postmenopausal atrophy
	Pelvic radiation
	Sequelae of infection
	Toxic shock syndrome
	Stevens–Johnson syndrome
	Use of exfoliating chemicals
	Intravaginal 5-fluoro-uracil cream
	Trauma
	Sexual assault
Cervical stenosis	Sequelae of therapy for CIN
	Cryotherapy
	LEEP
	Cone biopsy
Vaginal septum	Congenital
Intrauterine synechiae	Asherman's syndrome
	Endometrial ablation

CIN cervical intraepithelial neoplasia
LEEP loop electrosurgical excision procedure

through the cervical os. Some women develop agglutination of the upper vagina secondary to atrophy, radiation, trauma, or infection. Certain congenital duplications of the lower genital tract such as a vaginal septum can be a barrier to egress of blood from the uterus. Women who have had an endometrial ablation may develop a malignancy deep to the scar of ablation, which may not be amenable to detection by biopsy [28]. For all these women, it is important to evaluate the upper genital tract, especially if they also have other risk factors (Table 1).

Comment on Case Report 1

The 32-year-old woman had no known risk factors for endometrial cancer. However, she had unexplained abnormal bleeding that was not fully evaluated before the intervention of endometrial ablation. It is crucial to perform an endometrial biopsy when bleeding is unexplained [29]. Only 10 % of all gynecologic cancers are associated with a known genetic risk. Endometrial cancers that are not associated with hyperestrogenism have a more aggressive behavior.

Diagnostic Tests

Case Report 2 *A 49-year-old woman presented with mid-cycle spotting. She has had several abnormal pap smears showing atypical glandular cells over the past 5 years. Colposcopy and cervical biopsies had been normal. An endometrial biopsy showed a grade 2 endometrioid adenocarcinoma. She underwent a laparoscopic assisted hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic node dissection. Her final pathology showed a superficially invasive endometrioid adenocarcinoma. All staging biopsies were negative.*

Evaluation of the uterus occurs with physical examination, which includes a visual inspection of the vagina and cervix and palpation of the uterus by vaginal and rectovaginal digital examination, cervical cytology, endometrial tissue sampling, and radiologic imaging. Table 3 summarizes the different diagnostic tests that are available to study the uterus.

Physical examination includes visual inspection of the external genitalia. In the setting of abnormal bleeding, it is important to rule out the possibility of an extrauterine lesion. The vulva, periurethral region, and anus are examined. The vagina and cervix are evaluated. The cervix is assessed for stenosis, friability, and gross lesions. The vagina should also be palpated circumferentially to make sure that there are no nodules that may have been missed on visual examination. Palpation of the uterus gives information about uterine size, tenderness, and irregularities of shape. A rectovaginal examination can evaluate the cul-de-sac, back wall of the uterus, adnexa, and the pelvic floor compartments: parametrial and uterosacral ligaments and the pelvic sidewall. There are some women who will be unable to tolerate an

Table 3 Diagnostic tests for uterine corpus disease

Office procedure	*Type of information*
Physical examination	Origin of bleeding
	Cervical stenosis
	Uterine size
	Pelvic mass
Pap smear	Cytologic abnormalities of cervix, vagina
	Occasional information about upper genital tract
Endometrial biopsy	Endometrial lining
Hysteroscopy	Endometrial lining
Radiologic Procedures	*Type of Information*
Transvaginal ultrasound	Endometrial stripe
	Uterine size
	Adnexal size, presence of cysts, masses
Sonohysterogram	Endometrial stripe
	Submucosal fibroids
	Endometrial polyps, masses
Pelvic MRI	Myometrial abnormalities, fibroids
	Depth of myometrial invasion
	Adnexal structures
	Invasion into parametria, vagina, bladder
	Pelvic lymphadenopathy
Abdominopelvic CT scan	Ascites
	Lymphadenopathy
	Intraparenchymal organ abnormalities
	Peritoneal and omental disease
PET CT scan	Same as CT scan
	Metabolic activity suggestive of metastatic disease
Operative procedures	*Type of information*
Examination under anesthesia	Same as physical examination
Dilation and curettage	Endometrial lining
Hysteroscopy	Endometrial lining
Hysterectomy	Full pathologic analysis of the uterus
Sentinel Node Biopsy	Identification of first lymphatic bed from uterus
Lymphadenectomy	Lymphatic involvement by cancer

office exam due to discomfort or due to psychological reasons such as a history of past sexual assault [30].

While Papanicolaou (Pap) smears were developed for screening lower genital tract neoplasia, an occasional asymptomatic woman with endometrial carcinoma will present with abnormal cytology. Cervical cytology is not a reliable screening test for endometrial cancer. In a recent review of 54,179 women who underwent pap smear screening, 14 were identified as having endometrial cancer based on abnormal glandular cytology [31]. However, endometrial cells identified on cervical cytology in women over 40 years of age can signify endometrial cancer [32]. Human papillomavirus (HPV) testing for high-risk subtypes can be a triage test to determine a cervical or endometrial origin to atypical glandular cytology [33]. HPV is not associated with endometrial neoplasia and therefore a positive HPV test will indicate a premalignant or malignant cervical glandular lesion.

Any abnormal uterine bleeding needs to be evaluated by endometrial biopsy. The accuracy of an office biopsy will depend on the size of the endometrial lesion, the examiner's skills, the anatomy of the patient, and patient comfort. A lesion that occupies less than 10 % of the uterine cavity, cervical stenosis with inability to enter the uterine cavity, distorting uterine fibroids, and patient factors such as vaginismus will all reduce the yield of an office biopsy. Premedication with a nonsteroidal anti-inflammatory drug, and the use of a paracervical block can help facilitate an office evaluation. An office hysteroscopy can also increase the yield for diagnostic abnormalities. Many different types of office biopsy devices are thought to be effective for diagnosis of endometrial pathology [34]. Currently, the office Pipelle biopsy device is thought to be as accurate as a dilation and curettage when the previously mentioned challenges are not a factor [35].

If it is not possible to obtain an adequate sampling in the office due to patient distress, anatomic factors, or a discrepancy between normal office biopsy results and an abnormal imaging study (see below), an outpatient surgical procedure should be scheduled. Under

anesthesia, vaginal adhesions can be gently opened up. If cervical stenosis is present, an ultrasound-guided dilation can prevent uterine perforation. Hysteroscopy in combination with endometrial curettage is recommended to avoid missing small lesions.

Imaging studies are a useful adjunct in the evaluation of endometrial pathology. In asymptomatic women, a transvaginal ultrasound finding of an abnormally thickened endometrial lining will guide the practitioner to performing a biopsy. Endometrial stripe width will vary with the menstrual cycle in premenopausal women. Thickness varies between the proliferative phase (4–8 mm) and the secretory phase (8–14 mm); the 8-mm cutoff value is used for recommending a biopsy in perimenopausal women unless they present with other risk factors [36]. After menopause, an endometrial stripe thickness greater than 4 mm is considered abnormal [37]. Tamoxifen can increase the incidence of a falsely thickened endometrial stripe due to tamoxifen-induced subendometrial edema [38]. In addition, about 30 % of women taking tamoxifen will develop endometrial polyps [39]. A sonohysterogram is a more sensitive and specific than transvaginal ultrasound in detection of intra cavity abnormalities [40]. Sterile saline is instilled into the endometrial cavity and then a transvaginal ultrasound is performed. The saline will reveal subtle irregularities such as small polyps and will reduce inaccuracies of endometrial stripe measurement.

A pelvic MRI is useful preoperatively to help determine depth of myometrial invasion in a known invasive endometrial cancer. When compared to the findings of surgical pathology, there was concordance on the depth of myometrial invasion and pathology 64 % of the time [41]. CT scan and PET CT scans can help evaluate for intraperitoneal and nodal metastatic disease and is recommended for women with high risk features such as poorly differentiated tumors and serous and clear cell subtypes [42]. Table 4 summarizes screening and diagnostic recommendations.

Table 4 Endometrial cancer: Recommendations for screening and diagnosis

Asymptomatic patient
No risk factors and normal physical examination: routine yearly follow-up
Risk factors for estrogen excess: transvaginal ultrasound
Tamoxifen use for greater than 2 years: annual sonohysterogram
Genetic risk factors: annual endometrial biopsy; consideration of risk reducing hysterectomy after completion of family
Cervical stenosis, enlarged uterus: transvaginal ultrasound
Symptomatic patient
Office endometrial biopsy and transvaginal ultrasound
Dilation and curettage and hysteroscopy if unable to perform office biopsy

Comment on Case Report 2

This patient had repetitively abnormal glandular cells of cytology. She also had unexplained mid-cycle bleeding. When her cervical evaluation with colposcopy and cervical biopsies was normal, she should have undergone an endometrial biopsy and transvaginal ultrasound.

Surgical Staging

Case Report 3 *A 35-year-old G3P3 woman with menorrhagia underwent a total vaginal hysterectomy. The final pathology revealed a grade 3 endometrioid adenocarcinoma of the endometrium with inner one half myometrial invasion. She is taken back to surgery and undergoes a laparoscopic bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node dissection. All staging biopsies are negative for cancer. She has a stage Ia Grade 3 endometrioid endometrial cancer.*

The staging of a cancer serves three main purposes. An internationally agreed upon numeric classification of extent of disease allows the collection of statistics and

worldwide interpretation of treatment outcome and survival. A stage assignment for a particular cancer gives information about prognosis. Third, a particular evidence-based treatment by staging and risk factors can be assigned. A stage is assigned for the cancer at initial presentation and this stage assignment never changes. For instance, a woman who develops lung metastases after an initial diagnosis of stage II endometrial cancer does not now have stage IV endometrial cancer. Her cancer is described as stage II with lung metastases.

The endometrial cancer is staged surgically and the most recent revision of the International Federation of Gynecology and Obstetrics (FIGO) staging system was published in 2009 [43]. Table 5 summarizes surgically staged categories for endometrial cancer. The endometrioid adenocarcinoma, the degree of differentiation is included in staging information. A grade 1 or well-differentiated tumor has less than 5 % solid growth pattern of the glandular component. A grade 2 or moderately differentiated tumor has between 6 and 50 % solid growth pattern. Grade 3 or poorly differentiated tumors have greater than 50 % solid component. Endometrioid adenocarcinomas of the endometrium usually spread in a predictable pattern [44]. At first there is direct extension into the myometrium. Spread can also progress into the cervix and vagina. Tumor cells can migrate trans-tubally with implantation on the ovaries and uterine serosa. Involvement of lymphovascular spaces can lead to lymphatic spread and distant metastases to the upper abdomen, inguinal nodes, and lungs. Surgical staging reflects this predictable behavior. While the rare histologic subtypes have less predictable behavior, they are included in the FIGO endometrial cancer staging system. Clear cell and serous histologies commonly spread by trans-tubal route and follow the peritoneal fluid circulation in a manner similar to epithelial ovarian cancers [45]. Spread frequently occurs with serous tumors while the primary cancer is small and noninvasive.

Operative Techniques for Staging

Laparoscopic Hysterectomy

The surgical approach chosen for removal of the uterus, tubes, and ovaries will be based on many factors. If a patient has had multiple prior surgeries, a history of peritonitis, diverticulitis, or abdominal radiation, an open laparotomy approach may be judicious. However, laparoscopic removal either by conventional laparoscopic techniques or with the robotic platform has become the standard of care [46]. Usually, a central port in the periumbilical is placed for the camera. The abdomen is insufflated with carbon dioxide gas. Two ports on the right and left sides of the mid to lower abdomen are placed for instrumentation. A uterine manipulator is placed transvaginally into the uterus to allow manipulation of the uterus during the surgical dissection. After all the pedicles have been developed, a colpotomy is made and the uterus, cervix, fallopian tubes, and ovaries are delivered through the vagina. The vagina cuff is then sutured using laparoscopic suturing techniques. Minimally invasive hysterectomy techniques, as described here, do not appear to compromise long-term survival for women with endometrial cancer [47]. Uterine morcellation should not be performed because of the theoretical risk of seeding and spread of viable cancer cells [48].

Laparotomy

The choice of an incision can be based on the patient's body habitus, previous incisions, and what surgery is planned. The classic incision for abdominal exploration is the low vertical incision, which can be extended into the upper abdomen as needed for greater surgical exposure. A modification to the low vertical is a paramedian incision, which avoids compromising the structural integrity of the umbilicus. A low transverse incision is reasonable for grade I cancers when high para-aortic nodal dissection is not planned. The transverse incision can be modified by the

muscle splitting Maylard incision if more exposure is needed. It is important not to compromise the blood supply to the skin by making a parallel incision to an old incision. As the skin and subcutaneous tissue is supplied by the superficial epigastric vessels that come in from the lateral position, a skin bridge between two old incisions has a risk of necrosis. Preoperative knowledge of previous breast reconstruction with a myofascial flap is important. Commonly, a mesh is placed after a TRAM (transverse rectus abdominus muscle) flap. It is helpful to obtain advice about where to place the new fascial incision from the plastic surgeon, who has performed the flap, to reduce postoperative devascularization of the abdominal wall and hernia formation. This information is also important for the laparoscopic approach.

Vaginal Approach

For patients who have multiple comorbidities, a simple vaginal hysterectomy without comprehensive surgical staging should be considered. The purpose of this surgery is to remove the uterus and stop bleeding. This surgery can be performed under spinal anesthesia. Vaginal hysterectomy with bilateral salpingo-oophorectomy is also appropriate for women with grade 1 minimally invasive tumors. It is not always technically possible to remove the ovaries through the transvaginal approach. As synchronous primary cancers of endometrium and ovaries can be found in up to 10 % of women, it is important to remove the ovaries if technically feasible and surgically safe to do [49].

Lymphadenectomy

Most patients with endometrial cancer present at an early clinical stage with low risk for nodal metastases, estimated at 3–5 % for well-differentiated tumors with only superficial invasion of the myometrium [44]. Therefore, performing routine lymphadenectomy (LND) on all women with endometrial cancer may lead to a large number of patients being "surgically overstaged" despite having disease confined to the uterus. Consequently, no consensus has been reached as to the role of LND in the management of early-stage cases. The different approaches range from omission of LND under most circumstances to routine LND for all patients.

Practices opting for a selective LND approach typically rely on algorithms to identify patients in which LND may be safely omitted. The most commonly used algorithm for lymphadenectomy, the "Mayo algorithm", exempts from full staging all patients with International Federation of Gynecology and Obstetrics (FIGO) grade 1–2 tumors of endometrioid histology, with greatest surface dimension $\leq$2 cm, myometrial invasion $\leq$50 % and no intraoperative evidence of macroscopic disease [50]. Current studies on the use of sentinel node biopsy suggest that this minimally invasive nodal evaluation may be another useful tool in surgical staging [51].

Comment on Case Report 3

The gynecologic oncology group demonstrated that 22 % of women with clinical stage I disease but high risk features had extrauterine spread of disease [44]. The patient had undergone a vaginal hysterectomy because of menorrhagia but without a preoperative endometrial biopsy. With the discovery of grade 3 cancer, it was crucial to perform a second surgery to remove her adnexa and evaluate her lymph nodes. Her final surgical stage of stage Ia grade was reassuring and she did not need postoperative adjuvant therapy with chemotherapy or whole pelvic radiation. She still was at higher risk for vaginal cuff recurrence and vaginal brachytherapy was recommended.

Conclusions

- An endometrial biopsy is the key diagnostic test for abnormal bleeding.
- Any positive findings on biopsy should be pursued further beyond physical examination and

Table 5 Surgical staging of endometrial cancer

Stage	Site of tumor involvement	Substages
I	uterine corpus	Ia: no or < one half myometrial invasion
		Ib: > one half myometrial invasion
II	cervix	II: cervical stromal invasion
III	pelvic structures	IIIa: invades serosa or adnexa
		IIIb: vaginal and/or parametrial involvement
	Lymph nodes	IIIc1: pelvic node involvement
		IIIc2: para-aortic node involvement
IV	Pelvic viscera	Iva : invades bladder and/or bowel mucosa
	Distant structures	IVb: abdominal metastases, inguinal nodes Lung, brain

cytologic evaluation, selecting from a number of radiologic and operative procedures.

– With a diagnosis of invasive endometrial cancer, treatment includes the surgical removal of uterus, cervix, and adnexa. Surgical staging requires a lymphadenectomy. Algorithms have been developed to determine which patients are at highest risk for lymph node metastases. Another approach is to consider sentinel node biopsies on all patents (Table 5).

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