A Nuanced Defense

By Christopher P. DeSimone, M.D., and Andrew DeSimone

A delayed cancer diagnosis case in particular requires an intimate knowledge of the cancer involved, as well as significant legal principles.

Endometrial Cancer—A Primer in Medicine and the Law

Few words inspire such terror, fear, and sadness as the word cancer. Almost everyone has had friends and family suffer from this insidious disease. However, few people have more than a lay knowledge of cancer. This article will discuss endometrial cancer, how it is treated, and some nuances related to the defense of malpractice claims for failure to diagnose.

Endometrial Cancer

What is a cancer? In essence, it is the unrestricted growth of a host’s own cells. The growth is exponential, and the cells mutate from their original histologic appearance as they divide.

In addition to growth, cancer has other unique characteristics that differentiate it from a benign growth. Normal cells don’t abide exponential growth; they don’t thrive being piled on top of each other. Normal cells also lack the ability to recruit new blood vessels and nutrients, which would support their growth. Cancers have no inhibition about being piled on top one another. They continue to expand beyond their origin by forming new blood vessels, which support their exponential growth.

Finally, cancers are able to metastasize. They are able to separate from the original mass, infiltrate the vascular network, and then extricate themselves from the vascular network in distant organs such as the liver, lungs, or bone. Identifying the source of the metastasis is important for an oncologist because it helps define treatment. Patients often proclaim that they have a cancer of the uterus and cancer of the lung and cancer of the liver. In reality, they have endometrial (uterine) cancer, metastatic to the liver and lungs.

Dr. Christopher P. DeSimone is an associate professor in the Division of Gynecologic Oncology at the University of Kentucky. He serves as associate chief medical officer, Perioperative Services and is the director of Robotic Surgery for the UK Medical Center. His interests include resident and fellow education, perioperative risk assessment, and clinical optimization, as well as robotic surgery. Andrew DeSimone is a member of Sturgill Turner Barker and Moloney PLLC in Lexington, Kentucky. Mr. DeSimone defends physicians, multi-specialty practice groups, and hospitals against allegations of medical malpractice. He is the publications chair of the DRI Trial Tactics Committee and is on the steering committee of the DRI Medical Liability and Health Care Law Committee.
Endometrial cancer or cancer of the uterus is the most common gynecologic cancer with an estimated 60,050 cases diagnosed in 2016. However, the death rate is relatively low (10,470). Since 1997, the incidence has nearly doubled from 33,000 to 60,000 cases a year. Soon, endometrial cancer will overtake colorectal cancer as the third most common malignancy in women. Sadly, this cancer is largely preventable. The meteoric rise in the incidence of endometrial cancer is attributed to obesity due to the increased dietary sugar intake commonly found in first-world countries.

The endometrium is the innermost lining of the uterus. Its function is to support an early pregnancy. The lining thickens during a woman’s menstrual cycle to accommodate a fertilized ovum. If the patient is not pregnant, the endometrium is sloughed, or shed, by the body. The sloughing of the endometrium is known as menses (menstrual blood). This process of thickening to sloughing is known as the menstrual cycle. The endometrium is under hormonal regulation, and estrogen causes the lining to thicken; progesterone causes the lining to regress and slough. Obese women produce estrogen by converting androgens to estrogen through an enzyme located in adipose (fat) tissue. The excessive estrogen production in obese women leads to overstimulation of the endometrium and eventually progresses to cancer.

There are two types of endometrial cancer. Type 1 cancer is prevalent among premenopausal and postmenopausal obese women. This group tends to have an excess of estrogen, hypertension, and diabetes. The cancer is low-grade and minimally invasive, meaning that it does not spread rampantly throughout the body. Few patients have metastatic spread to the pelvic lymph nodes, and the five-year survival is excellent (85 percent). Even with a delay in diagnosis, a patient typically does well. Type 2 cancer is prevalent in thin, postmenopausal women. These cancers occur due to genetic alterations, which occur with advancing age. The cancers are poorly differentiated, deeply invasive, and often metastatic to the pelvic lymph nodes and elsewhere (chest, liver, brain). The five-year survival rate reflects the invasive nature of this cancer (58 percent).
Grade and Stage
Various organizations publish guidelines for the treatment and management of cancer. These are designed to help practitioners and patients understand the survivability of their cancer. This is typically accomplished through grade and stage. Few things confuse a patient as much as understanding the difference between these two concepts. The grade of the tumor describes how closely the cancer resembles the normal tissue of its origin. Grade 1 tumors look the most similar: in the case of endometrial cancer, it will closely resemble the lining of the endometrium itself. A grade 3 tumor has become so distorted that it no longer looks like endometrium. Grade 3 cancers can become so abnormal that the site of origin is difficult or impossible to determine. For example, a grade 3 adenocarcinoma obtained from a lung biopsy might have originated from the breast, colon, uterus, ovary, pancreas, and lung. Determining the origin of the tumor (apart from a direct biopsy of the organ) relies upon immunohistochemistry (IHC), which stains the tumor with specific antibodies to determine its origin.

The nomenclature of grade is also confusing since the written description is often interposed with the ordinal description. Well-differentiated cancer is a grade 1 cancer; well-differentiated simply means that the tumor looks most like the tissue of its origin. Moderately differentiated cancer is a grade 2 cancer, and poorly differentiated cancer is a grade 3 cancer.

The grade of the cancer (1) determines how likely the cancer will invade local tissue and spread to distant organs (metastasis); (2) affects doubling time (the amount of time it takes for the cancer to double in size); and (3) determines how resistant the cancer can be to adjuvant therapy—radiation and chemotherapy. Patients often misinterpret the grade of the cancer as the stage. They also equate advanced grade as an “aggressive cancer.” Since grade is hard to describe, most oncologists reinforce this simplistic description.

The stage of a cancer, on the other hand, predicts patient survival. Most academic journals publish survival statistics as a five-year survival rate (though two- and 10-year survival rates exist, depending upon the type of cancer). Almost all patients erroneously equate the five-year survival rate to cure. Unfortunately, the survival rate simply states whether the patient is alive five years from the initial therapy. For example, a woman with recurrent endometrial cancer dies from her disease eight years after her initial surgery. If enrolled in a study or cancer database, she is included among the x number of patients alive at the five year mark.

Most patients are also aware of staging criteria provided by the American Joint Committee on Cancer (AJCC). The AJCC uses the TNM classification system, which assesses tumor, (lymph) node, and metastasis. The “T” stands for tumor size or invasion. The “N” stands for tumor size or invasion. Nodal status is “N,” which assesses whether the cancer has spread into the lymph nodes. N0 is defined as no metastases to the regional lymph nodes (breast cancer spreads to the axillary lymph nodes; endometrial cancer spreads to the pelvic lymph nodes). Distant metastases are defined by “M.” Metastatic spread is M1; no metastatic spread is M0. Once you have all the data, the TNM system defines the stage. For instance, a 1 cm breast cancer with metastatic spread to the axillary lymph nodes (fixed) and no evidence of metastatic spread by CT scan is a T1 N2 M0, which is a stage IIIA breast cancer. This system is complex, but easy to calculate.

However, gynecologic cancers are staged with a different system from the International Federation of Gynecology and Obstetrics (FIGO). See Table 1. There is no TNM system. Endometrial cancer is primarily staged by surgical excision, which determines a stage by the size of the tumor and gross or microscopic observation of regional invasion. Endometrial cancer starts in the uterus and spreads to the cervix, ovaries, and pelvic lymph nodes before metastasizing to the paraaortic lymph nodes, mediastinal lymph nodes, and lungs. In other words, it spreads through the lymphatic system from the pelvis up to the chest cavity. Surgery removes the uterus, ovaries, and cervix to allow the pathologist to analyze for microscopic metastases. Early-stage endometrial cancers (stage IA) have a high percentage of patients alive at five years (99 percent). Late-stage endometrial cancers (Stage IVB) have a low percentage of patients alive at five years (10 percent).

Diagnosis
The diagnosis of endometrial cancer is made by performing a biopsy of the endometrial lining. The typical patient presents with post-menopausal spotting or heavy irregular bleeding for a pre-menopausal woman. As a result of this history, an office procedure (endometrial biopsy) or minor surgical procedure (dilatation and curettage of the uterus) is performed. The pathology from the biopsy specifies the type and grade of the endometrial cancer. There are four types of epithelial adenocarcinoma—endometrioid (the most common), serous, clear cell, and mucinous. A typical report will state that the patient has a grade 2, endometrioid adenocarcinoma (typically type 1). The type of cancer has prognostic implications as well. Serous and clear cell cancers are always grade 3, and they have a propensity for metastatic spread. These types usually require chemotherapy or radiation following a surgery. Serous and clear cell adenocarcinomas are found in patients with type 2 endometrial cancer.

Table 1

<table>
<thead>
<tr>
<th>Carcinoma of the Endometrium</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Tumor confined to the uterus, no or &lt; ½ myometrial invasion</td>
</tr>
<tr>
<td>IB</td>
<td>Tumor confined to the uterus, &gt; ½ myometrial invasion</td>
</tr>
<tr>
<td>II</td>
<td>Cervical stromal invasion, but not beyond uterus</td>
</tr>
<tr>
<td>IIIA</td>
<td>Tumor invades serosa or adnexa</td>
</tr>
<tr>
<td>IIIB</td>
<td>Vaginal and/or parametrial involvement</td>
</tr>
<tr>
<td>IIIC1</td>
<td>Pelvic node involvement</td>
</tr>
<tr>
<td>IIIC2</td>
<td>Para-aortic involvement</td>
</tr>
<tr>
<td>IVA</td>
<td>Tumor invasion bladder and/or bowel mucosa</td>
</tr>
<tr>
<td>IVB</td>
<td>Distant metastases including abdominal metastases and/oringuinal lymph nodes</td>
</tr>
</tbody>
</table>
Treatment

There are three initial treatments for endometrial cancer. The most common treatment is surgery. The physician, typically a gynecologic oncologist, will remove the uterus, cervix, fallopian tubes, ovaries, and pelvic and para-aortic lymph nodes. This can be performed through an abdominal incision, known as a total abdominal hysterectomy (TAH). Minimally invasive procedures can be performed with laparoscopic instruments or with the aid of a robot—total laparoscopic hysterectomy (TLH) or robotic total laparoscopic hysterectomy (rTLH). Each approach has its benefits and risks. Success rate does not vary between the surgeries listed above.

Primary pelvic radiation is an alternative to surgery. Historically, it has an 80 percent success rate for early stage endometrial cancers. This treatment is best in patients who are too ill to undergo surgery. Patients with cirrhosis or oxygen-dependent, chronic obstructive pulmonary disease are difficult to manage post-operatively. Radiation spares this morbidity, albeit radiation has less of a chance for curing the patient.

Finally, progestin or hormonal therapy can be utilized to treat young women with endometrial cancer. This therapy is designed to shed the endometrial lining and thus the cancer. The patient usually takes three months of hormone treatment and then has another endometrial biopsy to document cancer regression. If the cancer has not regressed, surgery is the next best option. The benefit to this therapy is that the patient retains her fertility. The success rate for this therapy ranges from 50–70 percent. However, this therapy is temporary only. The typical patient who develops endometrial cancer in her 20–30s is obese and infertile. Obesity is the cause of the cancer and infertility. Weight loss is the best therapy for both issues. Without it, neither condition will resolve.

Surgery is performed for greater than 90 percent of women diagnosed with endometrial cancer. The standard therapy for the late 1980s and 1990s was total abdominal hysterectomy (TAH), bilateral salpingooophorectomy (BSO), and pelvic and para-aortic lymph node sampling, performed through a vertical midline incision. This route provided a surgeon with great visualization and exposure to the entire abdominal cavity. Most endometrial cancers are confined to the uterus, but they can spread from the uterus and invade the pelvic sidewall, block the pelvic ureter, or metastasize to the upper abdomen (omentum). This incision is ideal to deal with this unexpected invasion. The obvious downside to this incision is cosmetic and increased pain, but it also has an increased risk for wound separation, seroma, ventral hernia formation, and infection. These risks are less frequent among normal weight women but occur commonly in obese and morbidly obese patients.

As technology improved, gynecologic oncologists shifted their approach to minimally invasive surgery. Laparoscopic assisted vaginal hysterectomy (LAVH) used laparoscopic instruments to remove the ovaries, upper uterine blood supply, and pelvic and para-aortic lymph nodes before the surgeon began a vaginal surgery to remove the remaining cervical and uterine attachments. This approach avoided the traditional vertical incision and wound complications. The downside to this surgery is a lengthy surgery and increased blood loss. As surgeons became more facile with the surgery, the length of the surgery and blood loss declined. Eventually, surgical technology improved to the point that the entire procedure was completed through laparoscopy (TLH). Thermal devices such as the Harmonic scalpel and the Ligasure device allow a surgeon to cauterize and cut vascular structures reliably. Once the surgeon has removed the uterus and cervix, the specimens are removed through the vagina to avoid a large abdominal incision.

Finally, Intuitive Surgical introduced the DaVinci robot in 2005. This machine incorporated laparoscopic techniques with three-dimensional vision, enhanced optics, and instruments that mimic the natural movement of a surgeon’s hand. Robotic total laparoscopic hysterectomy (rTLH) has become the surgery of choice for most gynecologic oncologists.

Despite the changes in surgical technique, the complications caused by the surgery remain relatively constant. Urologic injuries to the bladder and ureter are rare (<1 percent), but can occur with spread of tumor to the bladder or pelvic sidewall. The small bowel and colon can be injured when encased in cancer or with laparoscopic trocar placement. Finally, injury to the iliac veins or inferior vena cava can occur with removal of the lymph nodes. Large, metastatic lymph nodes can adhere to the surface of these veins, making excision difficult and hazardous. Tedious dissection is a must. Injury may result in excessive blood loss and deep vein thrombosis (DVT). Surgery experience is important. Multiple studies have shown that high-volume surgeons have better outcomes and fewer complications.

Adjuvant Therapy and Recurrence

For patients who have had surgery for endometrial cancer, the need for adjuvant therapy (radiation or chemotherapy) is determined by stage, grade, and histologic cell type. These therapies are employed to decrease the recurrence rate of the cancer. The recurrence rate is opposite of the survival rate. If a stage I endometrial cancer has a 90 percent five-year survival rate, a stage I cancer also has a 10 percent recurrence rate. Recurrence of any cancer is lethal, with few exceptions. The average span of life from recurrence to demise is variable. Patients diagnosed with a recurrent gynecologic cancer live on average one to three years. Because a recurrent cancer is a terminal process, every effort is made to maximize primary and adjuvant therapy. Aggressive primary treatment with long-lasting side effects is acceptable to most patients as long as the therapy increases a chance for a cure. Once a recurrence has occurred, additional treatment (palliative/salvage chemotherapy) is used to prolong survival. At best, these therapies might add an additional three to nine months to a patient’s life.
Endometrial cancer recurrence is categorized into low-, intermediate-, and high-risk categories. Low-risk endometrial cancer is often stage IA or IB, low to moderate grade, and endometrioid adenocarcinoma cell type that occurs among young women (50 years or less). In fact most of endometrial cancer is an early stage, with low risk of recurrence (80 percent). This patient is marked to show where the radiation will be concentrated. Photons of energy are delivered for short periods (10 seconds), daily for five weeks. Brachytherapy is a procedure during which a radioactive pellet is placed into a vaginal cylinder. The naturally occurring radioactive element delivers a low dose of radiation to the local tissues for one to three hours. The radiation and device is removed once the calculated dose of radiation has been achieved. This procedure is repeated weekly for one to three weeks. For some patients, both external beam radiation and brachytherapy are used. Recent studies have shown that vaginal brachytherapy is just as effective as external beam radiation for endometrial cancer; it has fewer side effects; and it costs less. Unfortunately, brachytherapy is not offered in many local communities since it is a minor surgical procedure.

High-risk endometrial cancer (stage III, IV cancer, serous endometrial adenocarcinoma) is often treated with chemotherapy plus or minus pelvic radiation. The current chemotherapy of choice is intravenous (IV) Carboplatin and Paclitaxel (Taxol) administered every 21–28 days for six cycles. Chemotherapy is distributed throughout the body so that a cancer cell in the lung, liver, and left supraclavicular lymph node (neck lymph node) will all be treated with one dose. The current treatment regimen for stage III endometrial cancer is “sandwich” treatment. Here, three cycles of chemotherapy are given to treat distant metastatic disease. Then pelvic radiation is given (both external beam and brachytherapy). Finally, another three cycles of chemotherapy finishes the treatment.

**A Case Study**

Armed with a basic amount of information, here is the case of a fictitious patient, Ms. Johnson. Ms. Johnson is a 56-year-old, postmenopausal, with a hematocrit (HCT) of 29. Dr. Sallee informed Ms. Johnson that she would need either an endometrial biopsy or a dilatation and curettage (D&C) of the uterus. Ms. Johnson wanted to avoid surgery, so she consented to an office endometrial biopsy. The pathology from the biopsy revealed a grade 3, endometrioid adenocarcinoma of the endometrium.

Dr. Sallee discussed the diagnosis with Ms. Johnson and referred her to a gynecologic oncologist, Dr. Smith, for further therapy. The referral of Ms. Johnson to Dr. Smith is the standard of care for endometrial cancer, given the complexity of managing endometrial cancer, surgery, and adjuvant therapy. After Dr. Smith took Ms. Johnson’s history and performed her physical exam, she recommended surgery to remove Ms. Johnson’s uterus, cervix, tubes, ovaries, and pelvic and para aortic lymph nodes. Dr. Smith discussed robotic, laparoscopic, and abdominal approaches to the surgery. The risks of each surgery were explained and discussed. Ms. Johnson elected to have a robotic total laparoscopic hysterectomy (rTLH), bilateral salpingo-oophorectomy (BSO), and pelvic and para aortic lymphadenectomy.

Her final pathology revealed a stage IIIC2, grade 3, endometrioid adenocarcinoma of the endometrium. The cancer measured 4.5 cm and was deeply invasive to the myometrium (19/20mm). There was evidence of metastatic spread to the cervix, right tube and ovary, and 4/16 pelvic and 3/6 para aortic lymph nodes. The upper abdomen was visually normal. After the surgery, Dr. Smith recommended a surveillance CT scan, followed by adjuvant chemotherapy (three cycles of Carboplatin and Paclitaxel). However, Dr. Smith failed to order radiation therapy, and then failed to order another three cycles of che-
motherapy. Standard of care required the radiation therapy and the extra three cycles of chemotherapy.

Ms. Johnson’s CT scan before adjuvant therapy revealed no evidence of metastatic disease. Following the treatment, she had another negative CT scan. Dr. Smith informed Ms. Johnson that she was in remission. She also told Ms. Johnson that her five-year survival rate was 50 percent. Ms. Johnson initially attended her first surveillance exam at six months and then elected to see her primary care provider, Dr. Ambrose, for continued cancer surveillance. Dr. Smith was unaware of this decision. Dr. Ambrose saw her periodically for acute care issues. Eighteen months after surgery, Ms. Johnson developed shortness of breath and chest pain. Dr. Ambrose ordered a CT scan that revealed numerous pulmonary lesions consistent with recurrent, metastatic endometrial cancer. Ms. Johnson responded to palliative chemotherapy (the cancer shrinks), but she eventually passed away nine months later. What patients fail to understand is that even if Ms. Johnson had been diagnosed with the recurrence six months after surgery, her overall survival remained the same: 27 months following the initial surgery.

Based on this case study, two different allegations of negligence exist: (1) the failure to provide all adjuvant therapy by Dr. Smith; and (2) failure by Dr. Ambrose to order surveillance CT scans after the adjuvant therapy.

**Legal Considerations**

Delay in diagnosis cancer cases can be difficult to defend and can carry with them significant damage exposure. On the one hand, these cases can be emotionally charged and very sympathetic to the patient, especially if the patient endured multiple hospitalizations, surgery, radiation, and chemotherapy, only to pass away eventually from the cancer. On the other hand, almost all jurors will have known a friend, loved one, or family member who has suffered or passed away from cancer when no lawsuit was filed.

Standard of care, as in all medical malpractice lawsuits, is of paramount importance in mounting a successful defense. The standard of care will need to be assessed through expert testimony of physicians of the same specialty as the defendant medical provider, and potentially the specialist in that particular cancer. This is essential to educate the defense attorney on the medicine.

In most jurisdictions, if the patient does not have expert testimony to testify to a breach of the standard of care, the case cannot proceed to the jury. See, e.g., Higginbotham v. D’Amico, 741 S.E.2d 668, 671 (N.C. App. 2013); Becker v. Mayo Foundation, 737 N.W.2d 200, 216 (Minn. 2007). There are a few exceptions to this general rule: (1) when the negligence is apparent to a lay person (wrong-site surgery) or (2) when res ipsa loquitur applies (retained sponge). See Hubbard v. Mellion, 302 P.2d 1084, 1092 (Kan. App. 2013).

An expert is also essential to educate the attorney on the potential standard of care criticisms that may develop against the defendant medical provider. These potential criticisms should be addressed in deposition preparation of the defendant medical provider.

However, the defense of causation warrants particular attention in delay of cancer diagnosis cases. Generally, causation—did the breach of the standard of care cause an injury—must be proved within a reasonable degree of medical probability. See Kilpatrick v. Bryant, 868 S.W.2d 594, 603 (Tenn. 1993). Causation must also be proved by expert testimony. Morris v. Hoffman, 551 S.W.2d 8, 9 (Ky. 1977). Expert testimony on causation based upon “possibility” or “could” is insufficient to meet the legal causation standard. In other words, is it “more likely than not,” or is the probability 51 percent or greater, that the failure to provide chemotherapy or to take appropriate CT scans caused Ms. Johnson’s death? In Ms. Johnson’s case, even if she had received the additional adjuvant therapy, her five-year survival rate would have remained only 50 percent. Therefore, she could never have proved, more likely than not, that negligence was the cause of her death.

However, many jurisdictions allow for a claim of lost or diminished chance. See, e.g., Crosby v. United States, 48 F. Supp. 2d 924, 926 (D. Ark. 1999). This claim allows a patient to recover damages for the reduction in the odds of recovery attributable to the medical provider, even if it is more likely than not that the patient would pass away regardless. In essence, this is an equitable doctrine that attempts to provide some recourse for the patient. See also Roberts v. Ohio Permanente Med. Group, Inc., 668 N.E.2d 480, 482 (Ohio 1996). In these cases, the expert testimony can be as generic as the patient’s “chance of survival would have been significantly improved.”

---

**Generally, causation—did the breach of the standard of care cause an injury—must be proved within a reasonable degree of medical probability.**

---

**Conclusion**

Defense of a delayed diagnosis case of cancer requires an intimate knowledge of the cancer involved, as well as significant legal principles. Early expert review is essential to appreciate fully the potential standard of care and causation defenses.