# Hormonal Therapy in Oncology: A Primer for the Radiologist

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**OBJECTIVE.** The purpose of this article is to provide a comprehensive imaging review of the common hormonal therapies used in oncology and the side effects associated with them.

**CONCLUSION.** Commonly used hormones in oncology include corticosteroids, somatostatin analogues, progestins, gonadotropin-releasing hormone agonists and antagonists, antiandrogens, aromatase inhibitors, and selective estrogen receptor modulators. Familiarity with these hormones and their side effects can help radiologists to be vigilant for the side effects and complications of these agents.

**Keywords:** aromatase inhibitors, corticosteroids, hormonal therapy, imaging, somatostatin, tamoxifen

DOI:10.2214/AJR.14.13604

Received August 4, 2014; accepted after revision October 9, 2014.

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*AJR* 2015; 204:W620–W630

0361–803X/15/2046–W620



Hormones are chemical messengers produced by specific organs of the endocrine system and act on targets distant from their site of origin. Steroid hormones are powerful regulators of gene expression and cell proliferation. A high level of certain hormones therefore leads to uncontrolled cell proliferation and increases the risk of neoplastic transformation. For example, unopposed action of estrogen on the endometrium causes endometrial cancer. Tumors caused by this hormonal dysregulation are referred to as hormone-dependent malignancies and have a high level of hormone receptor expression [1]. Examples of hormone-dependent malignancies include breast, endometrial, and prostate adenocarcinomas and uterine sarcomas.

Medical management of cancer includes chemotherapy, targeted therapy, and hormonal therapy. Hormonal therapy involves administration of exogenous hormones in a hormone-dependent malignancy to manipulate the endocrine system by interfering either with hormone production or with the activity of receptors (Table 1). In addition, certain hormones, such as corticosteroids, have general antiproliferative effects due to their ability to down-regulate genes and induce apoptosis [2]. Like chemotherapy and targeted therapy, hormonal therapy can be used to manage malignancies at various time points, including the neoadjuvant, adjuvant, and metastatic periods. Imaging is routinely used in the care of cancer patients to monitor response to treatment and detect treatment-related side effects. Response to hormonal therapy, like that to chemotherapy, often results in decreases in tumor size that can be captured at imaging. At the same time, hormones can cause a wide spectrum of complications ranging from mild or moderate, such as thrombosis, hepatic steatosis, endometrial hypertrophy, and osteoporosis, to severe, such as pulmonary embolism, avascular necrosis, bowel perforation, and endometrial cancer (Table 2). Familiarity with the hormones used in cancer therapy, their treatment response patterns, and the spectrum of toxicities associated with their use can help radiologists be vigilant for these specific effects. Accordingly, we present a comprehensive review of the various hormones used in cancer therapy, emphasizing the role of imaging in assessing treatment response and treatment-related complications.

## Classification of Hormonal Therapy Used in Cancer

Hormonal therapy used in cancer treatment can be broadly classified as hormone analogues, inhibitors of hormone synthesis, and inhibitors of hormone receptors (Table 1).

## Hormone Analogues

Hormone analogues are naturally occurring hormones or their derivatives that either have a direct antineoplastic effect or inhibit synthesis of other hormones when administered in supraphysiologic quantities. The most common hormone analogues used in

**TABLE 1: Hormonal Therapeutic Agents in Oncology and Their Target Cancers**

| Hormonal Therapy | Cancer |
|---|---|
| Hormone analogues | |
| Corticosteroids | Lymphoid malignancies |
| Somatostatin analogues | Neuroendocrine tumors, Merkel cell carcinoma |
| Progestins (megestrol acetate, medroxyprogesterone acetate) | Endometrial, breast and prostate cancer, uterine sarcomas |
| Estrogens | Prostate and breast cancer |
| Androgens | Breast cancer |
| Inhibitors of hormone synthesis | |
| Gonadotropin-releasing hormone agonist and antagonists (leuprolide, degarelix) | Prostate cancer (androgen deprivation therapy) |
| Abiraterone | Prostate cancer |
| Aromatase inhibitors | Breast and endometrial cancer, uterine sarcomas |
| Reversible (letrozole, anastrozole) | |
| Irreversible (exemestane) | |
| Inhibitors of hormone receptors | |
| Selective estrogen receptor modulators (tamoxifen, raloxifene, toremifene, fulvestrant) | Breast cancer |
| Antiandrogens (flutamide, bicalutamide, enzalutamide) | Prostate cancer |

**TABLE 2: Hormonal Therapeutic Agents in Oncology and Their Adverse Effects**

| Hormonal Therapy | Adverse Effect |
|---|---|
| Hormone analogues | |
| Corticosteroids | Pneumatosis intestinalis, osteoporosis, osteonecrosis |
| Somatostatin analogues | Gallstones, injection hematomas, abscesses |
| Progestins | Venous and arterial thromboembolism, osteoporosis |
| Inhibitors of hormone synthesis | |
| Gonadotropin-releasing hormone agonists and antagonists | Osteoporosis, fractures, gynecomastia, increase in body fat, subcutaneous hematoma, sterile abscess |
| Abiraterone | Fluid retention, peripheral edema, urinary tract infections |
| Aromatase inhibitors | Osteoporosis, fractures |
| Inhibitors of hormone receptors | |
| Selective estrogen receptor modulators (tamoxifen) | Hepatic steatosis, endometrial polyp, hyperplasia, carcinoma, uterine sarcoma |
| Antiandrogens (flutamide and bicalutamide) | Osteoporosis |
| Antiandrogen (enzalutamide) | Diarrhea |

clinical practice include corticosteroids, somatostatin, and progestins. The less common analogues, such as androgens (fluoxymesterone, danazol) used historically in breast cancer [3, 4], and estrogens (diethylstilbestrol) [5], used uncommonly in prostate cancer, are not discussed further in this article.

*Corticosteroids*

The most commonly used hormones in oncology are corticosteroids. Naturally occurring glucocorticoids in humans include cortisol and corticosterone, both produced by the adrenal glands. Exogenous corticosteroids have an antineoplastic effect due to their ability to induce apoptosis in a variety of cell lines, especially immature thymocytes and acute lymphoid leukemia cells [2] (Fig. 1). Corticosteroids used in oncology can be short acting (hydrocortisone), intermediate acting (prednisone, methylprednisolone), or long acting (dexamethasone).

Because of their selective leukocytolytic action, corticosteroids are included in almost all chemotherapy protocols for lymphoid malignancy [6]. Corticosteroids (methylprednisolone) are part of combination chemotherapy for acute leukemia, especially for CNS prophylaxis. In non-Hodgkin lymphoma, steroids are part of the cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) regimen. High-dose methylprednisolone is used as monotherapy in the care of selected patients with chronic lymphocytic leukemia or lymphoma [7]. Steroids are also part of the vincristine, Adriamycin [doxorubicin], dexamethasone (VAD) regimen used in the management of refractory multiple myeloma.

Corticosteroids are routinely used in primary CNS lymphoma for rapid improvement in neurologic status and for decreasing tumor size, an effect known as vanishing tumor [8] (Fig. 2). However, steroids can interfere with biopsy results and as such are routinely withheld at least 1 week before biopsy. Corticosteroids have been used to decrease cerebral or spinal cord edema secondary to tumor or radiotherapy [6, 9]. Corticosteroid therapy markedly improves clinical status and surgical outcomes in patients with gliomas because it reduces tumor-associated edema [9].

Corticosteroids such as dexamethasone have potent antiemetic properties alone and in combination with other agents and are often used to counter chemotherapy-induced nausea and vomiting [10]. Steroids have been used as front-line therapy since the 1980s in the treatment of acute graft-versus-host disease, a source of great morbidity and mortality after allogenic hematopoietic stem cell transplant [11]. They are also used to treat drug-induced pneumonitis, a rare but well-documented toxicity associated with several antineoplastic drugs, including rituximab, trastuzumab, erlotinib, and inhibitors of the mammalian target of rapamycin (mTOR) [12, 13]. High-resolution CT of the chest in drug-associated pneumonitis can be seen as patchy, multifocal ground-glass opacities predominantly in a subpleural location or as cryptogenic organizing pneumonia (Fig. 3). In some instanc-

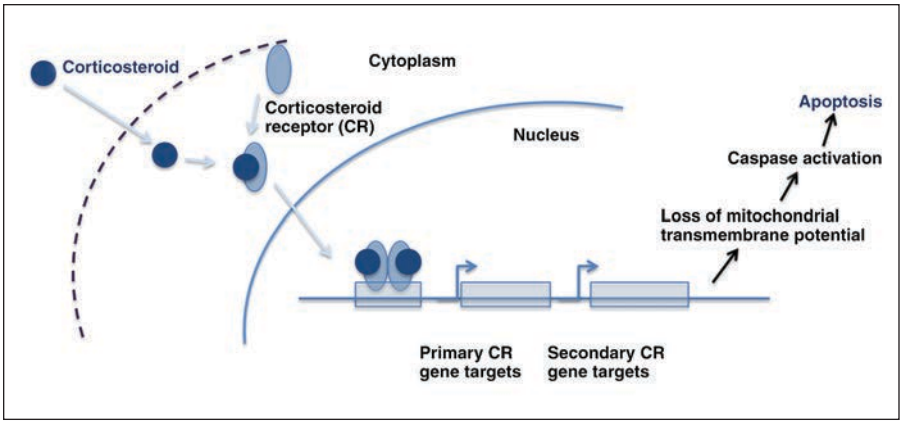



**Fig. 1**—Chart shows mechanism of antineoplastic action of corticosteroids. Corticosteroid enters cell cytoplasm and binds to corticosteroid receptor before being transported into nucleus. In nucleus, corticosteroid binds to DNA, activating and repressing transcription of primary and secondary targets and initiating apoptosis.

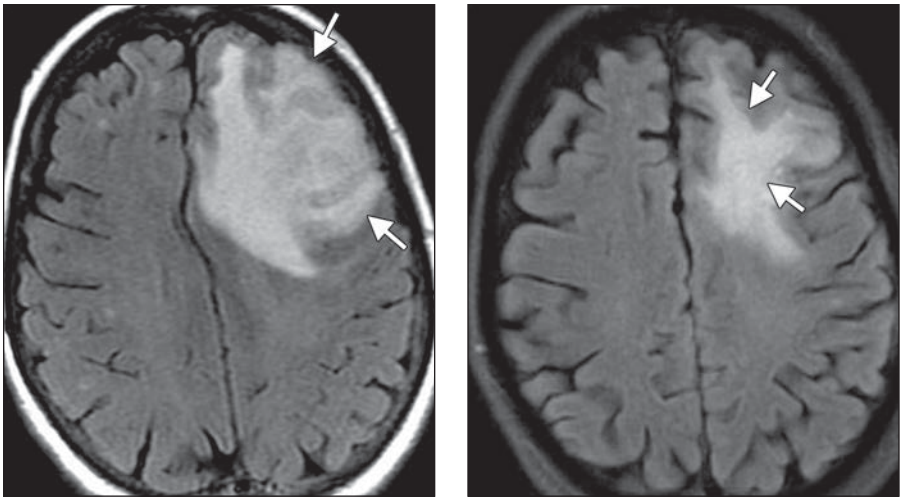



**Fig. 2**—70-year-old woman with primary CNS non-Hodgkin B-cell lymphoma of follicular cell type. **A,** Axial FLAIR MR image at presentation shows large left frontal mass (*arrows*) with surrounding edema. **B,** Follow-up MR image obtained after treatment with steroids for 2 weeks shows considerable reduction in tumor size (*arrows*) known as vanishing tumor effect.

es spontaneous resolution has been reported after discontinuation of the offending agent, but most patients need high-dose steroids for 1–2 months [13] (Fig. 2).

### *Adverse Effects of Corticosteroids*

Although corticosteroids provide a wide range of powerful therapeutic benefits in the treatment of oncology patients, they are not without risk, particularly when used for extended periods. Pneumatosis intestinalis is the presence of gas within the bowel wall and often occurs in patients treated with steroids. Pneumatosis is seen on CT images as intramural air tracking parallel to the mucosal lining (Fig. 4A). Though benign and asymptomatic, the presence of concurrent bowel wall thickening, mesenteric stranding, ascites, and portal and mesenteric venous gas should alert the radiologist to a potentially worrisome cause [14]. Steroid-induced pneumatosis results from shrinkage of Peyer patches secondary to lymphoid depletion and compromise of the structural integrity of the bowel wall [15]. Clinically worrisome pneumatosis occurs in patients within 2 months of steroid administration and necessitates prompt attention by the radiologist. In a study that included 84 patients, Lee et al. [14] found steroid use in 62% of patients with worrisome pneumatosis. Management of steroid-induced pneumatosis is often conservative; surgical intervention is reserved for selected patients with complications.

Glucocorticoid-induced osteoporosis is the most common form of secondary osteoporosis and a source of considerable morbidity for many oncology patients [16]. As many as 30–50% of patients receiving corticosteroids experience a fracture, and the risk is directly proportional to the dose and duration of corticosteroid exposure [16]. Postmenopausal women experience this complication most often, and the most common sites of fractures are the sites of cancellous bone resorption, that is, the vertebrae and femoral neck [16] (Fig. 4B). Thirty-seven percent of postmenopausal women undergoing chronic (> 6 months) oral corticosteroid therapy sustain one or more vertebral fractures, which are often asymptomatic and occur soon after exposure to the corticosteroid [16].

Another complication of corticosteroids is nontraumatic osteonecrosis (avascular necrosis); 9–40% of patients undergoing long-term corticosteroid therapy have osteonecrosis [17] (Fig. 4C). The weight-bearing joints are affected more commonly, the hip most commonly [17]. Approximately 35–50% of patients who experience osteonecrosis of a single joint go on to have contralateral joint involvement (Fig. 4C). Confirmation of osteonecrosis requires imaging or bone biopsy. Radiographs can have normal findings in the early stages or show a subchondral fracture or deformed femoral head in advanced cases. MRI is more sensitive (100%) than bone scintigraphy (90%) and depicts osteonecrosis earlier than any other modality. A double line sign on T2-weighted images is virtually pathognomonic of osteonecrosis. CT scans can show secondary degenerative changes in the hip joint. Management of established osteonecrosis often requires hip arthroplasty. Early osteonecrosis (precollapse stage), however, can be managed with a hip salvage procedure [18].

Secondary adverse effects of steroids include fluid, electrolyte, and metabolic disturbances, such as salt and water retention and gluconeogenesis. Steroids can cause fat redistribution that results in cushingoid habitus (moon facies, buffalo hump, and central obesity) [19]. Chronic steroid administration has been seen as adrenal atrophy, visceral fat deposition, and proximal muscle atrophy on cross-sectional images. Immunosuppression associated with steroids can lead to infections, most commonly by pyogenic bacteria and less commonly by pathogens such as *Listeria* and *Candida* species and herpes virus [20].

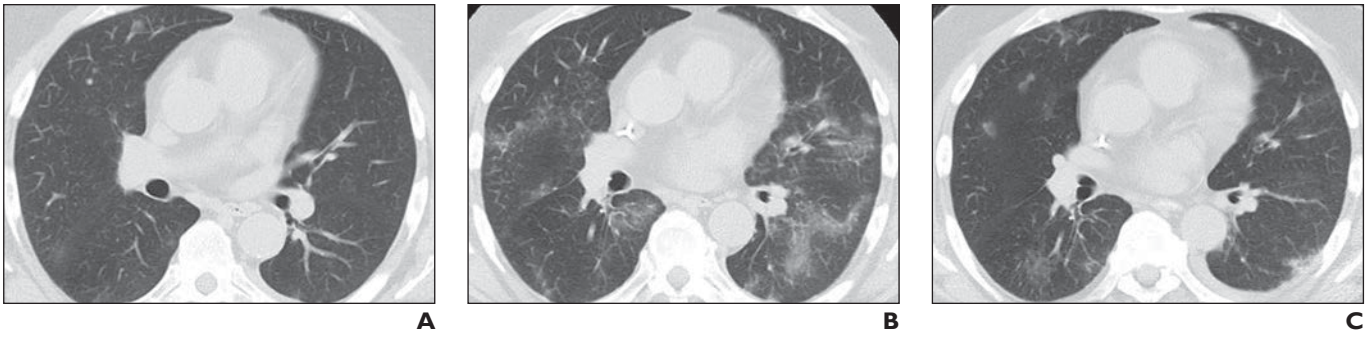


**Fig. 3**—63-year-old man with metastatic renal cell carcinoma, clear cell type, after left nephrectomy and three cycles of temsirolimus (mammalian target of rapamycin [m-TOR] inhibitor) plus bevacizumab.
**A,** Axial CT image of chest at baseline shows no clinically significant abnormality in lung parenchyma.
**B,** Follow-up CT image 8 weeks after start of treatment shows new patchy multifocal ground-glass opacities in both lungs, predominantly along bronchovascular bundles and in subpleural distribution like that of cryptogenic organizing pneumonia compatible with m-TOR inhibitor–associated pneumonitis. Patient had cough and was treated with corticosteroids.
**C,** Axial CT image after steroid therapy shows partial resolution of ground-glass opacities.

*Somatostatin Analogues*

Somatostatin is a peptide hormone produced by the hypothalamus and intestinal mucosa and has negative regulatory effects on several other hormones released by the anterior pituitary gland and intestinal mucosa. It also affects cell proliferation and smooth muscle contraction [21]. The action of somatostatin is mediated by somatostatin receptors 1–5, which activate intracellular signaling pathways. Somatostatin receptors are characteristically expressed by gastroenteropancreatic neuroendocrine tumors, especially the well-differentiated type, which enables targeted therapy for these tumors by somatostatin analogues. Merkel cell carcinoma, an aggressive cutaneous neuroendocrine tumor, also responds to somatostatin analogues [22].

Octreotide and lanreotide are synthetic analogues of somatostatin that have been used to control symptoms of carcinoid syndrome in patients with gastroenteropancreatic neuroendocrine tumors. The long-acting form (long-acting repeatable) of octreotide was approved by the U.S. Food and Drug Administration (FDA) in 1997 and is administered monthly. Both octreotide and lanreotide have higher affinity for somatostatin receptor 2. Although somatostatin analogues are associated with substantial symptom control and

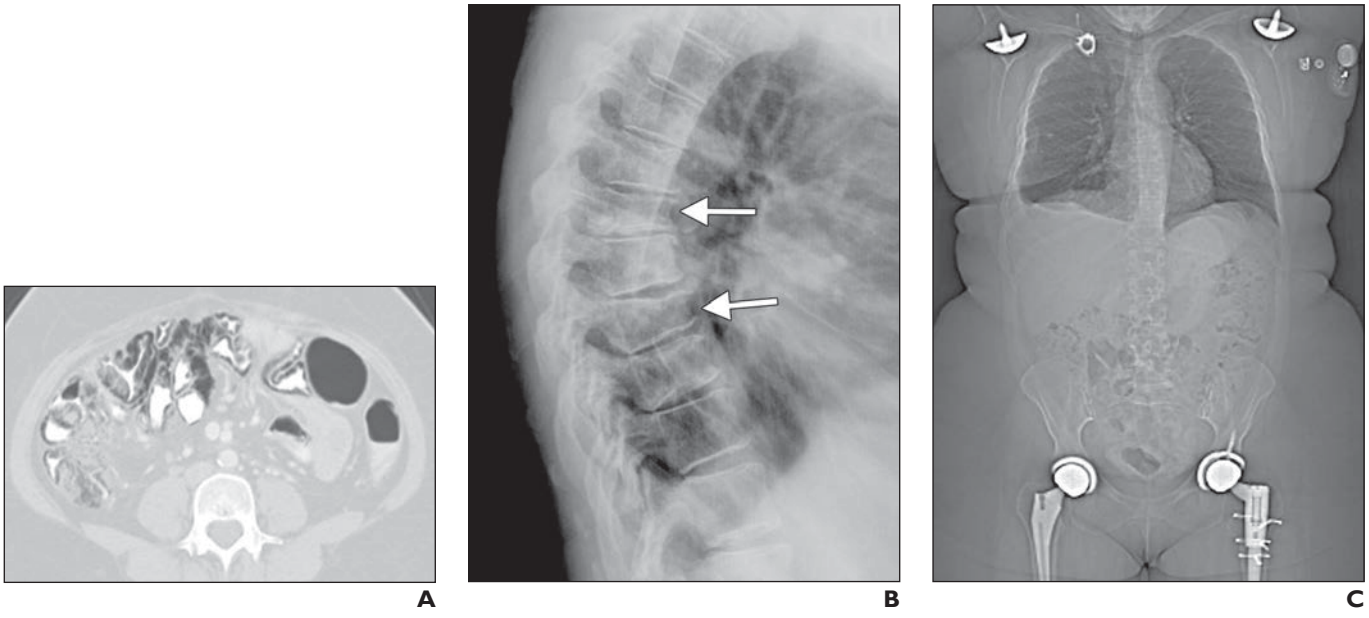


**Fig. 4**— Adverse effects of steroid therapy in three patients.
**A,** 41-year-old woman with chronic lymphocytic leukemia and lymphoma treated with corticosteroid monotherapy. Axial CT image of abdomen (lung window setting) during restaging shows air tracking in small- and large-bowel wall consistent with pneumatosis intestinalis. Pneumatosis, which was asymptomatic, resolved after steroids were withdrawn and new chemotherapeutic regimen was begun.
**B,** 65-year-old woman with history of leukemia treated with corticosteroids. Lateral radiograph of thoracic spine shows compression deformities of thoracic vertebrae (*arrows*) consistent with osteoporotic fractures.
**C,** 47-year-old woman with papillary serous adenocarcinoma of ovary undergoing therapy with cisplatin, paclitaxel, and corticosteroids, which was complicated by osteonecrosis of both humeral and femoral heads. Scout CT image of chest, abdomen, and pelvis shows bilateral shoulder and hip replacements due to osteonecrosis of humeral and femoral heads.

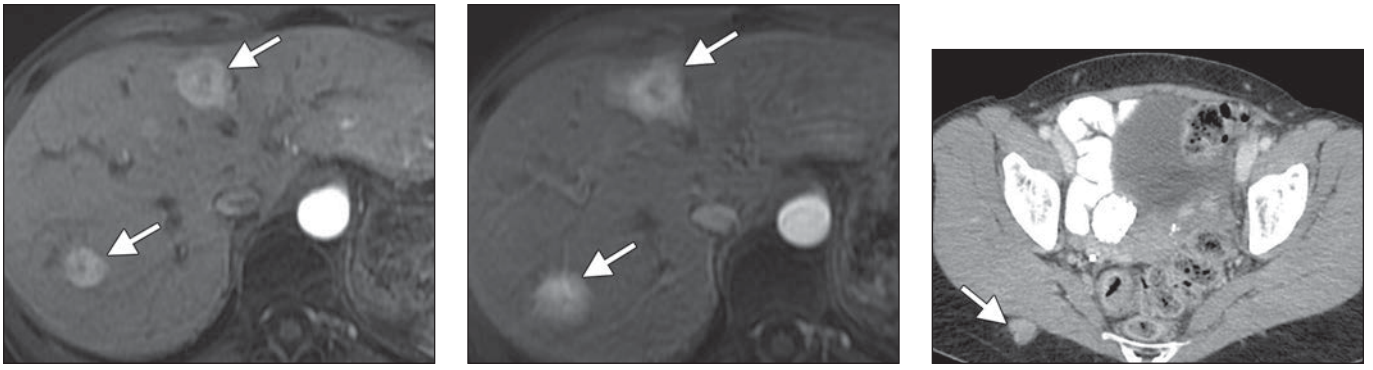


**Fig. 5**—39-year-old woman with von Hippel–Lindau disease after Whipple procedure for metastatic pancreatic neuroendocrine tumor.
**A,** Axial gadolinium-enhanced fat-suppressed T1-weighted MR image of liver shows hypervascular hepatic metastatic lesions (*arrows*).
**B,** Follow-up MR image 6 months after start of treatment shows no clinically significant change in tumor size (*arrows*) consistent with tumor stabilization effect of octreotide.
**C,** Axial CT image through pelvis shows subcutaneous hematoma (*arrow*) related to octreotide injection.

normalization of markers, several studies have shown little radiographic tumor regression [23] (Fig. 5). Restaging imaging typically shows stable size of the metastatic deposits over prolonged periods. In a study that included 35 patients with neuroendocrine tumors, Aparicio et al. [24] found somatostatin analogues were associated with tumor stabilization for 11 months in 60% of patients. The effect of somatostatin analogues usually lasts for a median duration of 12 months owing to development of tachyphylaxis, that is, receptor desensitization [21]. Radiolabeled somatostatin analogues are under research for unresectable and metastatic gastroenteropancreatic neuroendocrine tumors [25].

### *Adverse Effects of Somatostatin Analogues*

Long-acting somatostatin analogues are administered as intramuscular depot injections. These injections are sometimes associated with local hemorrhage, which can cause hematoma formation and be mistaken for intramuscular tumor implants (Fig. 5). In rare instances infection with abscess formation occurs at the injection site [25]. Octreotide increases biliary excretion of calcium, which increases the risk of gallstone formation [26]. Attention to the gallbladder for calculi and biliary obstruction during restaging imaging is recommended.

### *Progestins*

Megestrol acetate and medroxyprogesterone acetate are progesterone derivatives that are predominantly progesterone and androgen receptor agonists with potent antigonadotropic effects. They have antineoplastic effects in estrogen receptor– and progesterone receptor–positive endometrial and breast cancers and uterine sarcomas. Though the standard of care for endometrial cancer is hysterectomy with surgical staging, progestin-based therapy can be used in the care of young patients with low-risk stage IA endometrial cancer who wish to preserve fertility and in the care of patients at poor surgical risk [27]. Because of the risk of stroke, pulmonary embolism, deep venous thrombosis, and myocardial infarction, progestin-based therapy is contraindicated in women with breast cancer and in smokers. The response of endometrial carcinoma to progestin therapy is closely monitored with regular endometrial sampling. Progestational agents either alone or alternating with tamoxifen can also be used in the adjuvant and metastatic settings of the management of endometrial carcinoma [28] (Fig. 6). They are used alone for recurrent and metastatic endometrial stromal sarcoma and estrogen receptor– and progesterone receptor–positive breast cancer. Megestrol acetate is also used as an appetite stimulant in the care of patients with a wide variety of conditions.

### *Adverse Effects of Progestins*

Thromboembolism is a well-described effect of high-dose progesterone treatment, occurring in 4.9% of patients taking megestrol acetate, a sixfold higher risk than in the general population [29]. Yet the gynecologic literature shows that most of the risk of thromboembolism occurs in elderly patients, as opposed to young patients with endometrial cancer who are often treated with high-dose progesterone [30]. Despite this, a high index of suspicion and prudence must be used to evaluate for venous thromboembolism on staging images of this patient population. In addition, arterial thrombus can occasionally be seen in these patients (Fig. 6). Medroxyprogesterone acetate can cause severe osteoporosis due to a hypoestrogenic effect.

## Inhibitors of Hormone Synthesis

Hormone-dependent cancers are sensitive to circulating levels of hormones and respond to suppression of hormone synthesis. Hormone synthesis can be suppressed centrally at the level of pituitary gland or peripherally at sites of hormone production.

### *Gonadotropin-Releasing Hormone Agonists and Antagonists*

Leuprolide acetate and goserelin are agonists of the gonadotropin-releasing hormone (GnRH) receptors in the pituitary gland. By disrupting the normal pulsatile stimulation of these receptors, GnRH agonists desensitize and down-regulate the receptors and decrease secretion of gonadotropins (luteinizing hormone and follicle-stimulating hormone) (Fig. 7). The result is chemical castration, that is, decreased production of estradiol and testosterone by the ovaries and testes [31]. GnRH agonists initially cause increased hormone synthesis due to their agonist action before down-regulating the receptors and therefore can cause transient worsening of disease, especially prostate cancer. In contrast, GnRH antagonists (e.g., degarelix) immediately suppress the receptors with no initial flare [31]. GnRH agonists are used in prostate and breast cancer and in aggressive angiomyxoma.

The mainstay of the management of advanced and metastatic prostate cancer is androgen deprivation therapy (ADT). ADT can be

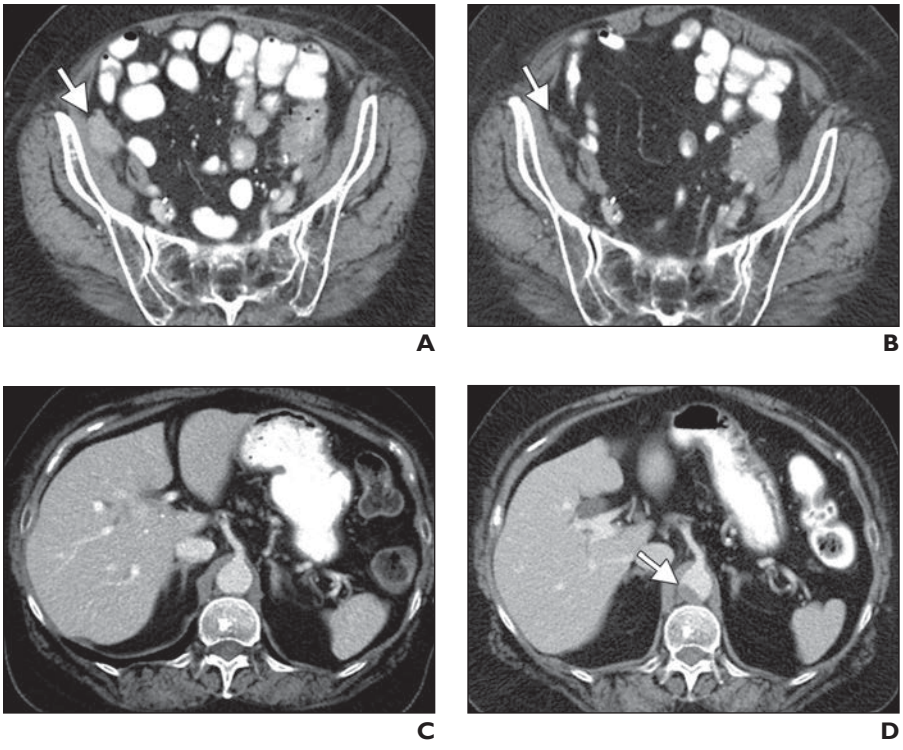



**Fig. 6**—73-year-old woman with metastatic endometrial cancer treated with megestrol acetate. **A,** Axial contrast-enhanced CT image at baseline shows metastatic deposit (*arrow*) in right lower quadrant. **B,** Follow-up CT image obtained 3 months after megestrol therapy shows decrease in size of deposit (*arrow*). **C** and **D,** Axial CT images of upper abdomen at baseline (**C**) and follow-up (**D**) show development of aortic mural thrombus (*arrow,* **D**). Patient continued with megestrol acetate therapy but was also evaluated in vascular medicine department and started aspirin therapy.

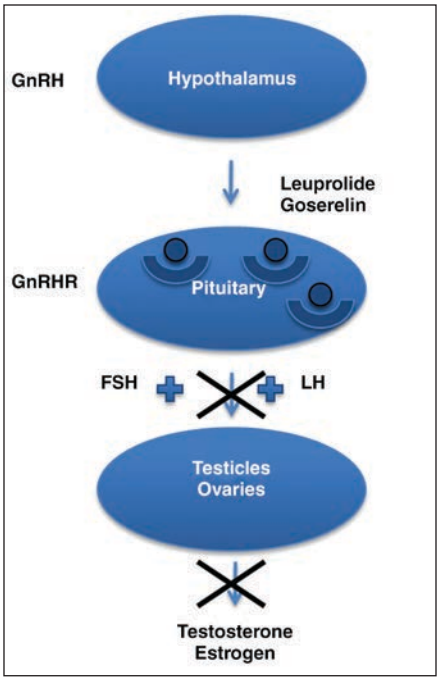



**Fig. 7**—Chart shows mechanism of action of gonadotropin-releasing hormone (GnRH) agonists. GnRH agonists such as leuprolide bind to GnRH receptors (GnRHR) and interrupt their normal pulsatile stimulation. This causes desensitization of GnRHR and down-regulation of secretion of gonadotropins (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]), which decreases production of estrogen and testosterone.

achieved through surgical castration by orchiectomy or medical castration with GnRH agonists and antagonists and antiandrogens [31]. ADT can be used as primary therapy for advanced disease or for neoadjuvant, concomitant, or adjuvant therapy in combination with radiation for locally advanced prostate cancer.

Aggressive angiomyxoma is a rare aggressive benign infiltrative neoplasm commonly occurring in the perineum and vulva of young women. Because of its infiltrative nature, complete excision is often difficult or impossible [32], and local recurrences are common. These tumors are usually hormone receptor positive and respond to hormone therapy. GnRH agonists have been used as neoadjuvant therapy to reduce tumor size and improve resectability (Fig. 8). They are also used in the adjuvant treatment of recurrent tumors [32, 33].

### *Adverse Effects of Gonadotropin-Releasing Hormone Agonists and Antagonists*

GnRH agonists and antagonists cause severe osteoporosis, which increases the risk of fractures in men. ADT has been associated with an increase in relative risk of fractures as high as 20% in some studies [34]. Regular screening for bone mineral density (BMD) is therefore recommended for these patients. Management of ADT-associated osteoporosis includes administration of calcium, vitamin D, and bisphosphonates. GnRH agonists and antagonists increase the risk of cardiovascular disease and diabetes. Gynecomastia, loss of muscle mass, and an increase in body fat can be visualized on cross-sectional images. GnRH agonists can cause transient flare of disease, which can manifest itself as transient worsening of metastatic disease on images. Leuprolide acetate is administered as an intramuscular depot, which in some patients can cause formation of a hematoma or granuloma, which is seen as subcutaneous soft-tissue densities in the gluteal region and mimics metastatic deposits. Similarly, the subcutaneous formulas can incite local indurations, subcutaneous nodules, and sterile abscesses [35].

### *Abiraterone*

Newer ADTs are emerging with evidence of prolonged survival among patients with metastatic castration-resistant prostate cancer previously undergoing chemotherapy. Abiraterone is a selective inhibitor of androgen biosynthesis that blocks cytochrome P450 c17 (encoded by the *CYP17* gene). Because of the risk of adrenal insufficiency, abiraterone was FDA approved in 2011 for use along with steroid replacement in the management of castration-resistant prostate cancer [36]. Abiraterone has been reported to be associated with a higher incidence of paradoxic increase in bone metastases on bone scans during the first 8–12 weeks, when patients are responding to therapy, referred to as the flare phenomenon [37, 38]. This can be confused with disease progression, but a simultaneous decrease in tumor markers and improvement on follow-up images can help in differentiating treatment response from progression.

### *Adverse Effects of Abiraterone*

Abiraterone causes fluid retention and peripheral edema in as many as 28% of patients. Other side effects include hypokalemia, hypophosphatemia, and urinary tract infections, which occur in 12% of patients. Radiologically, urinary infections should be suspected if

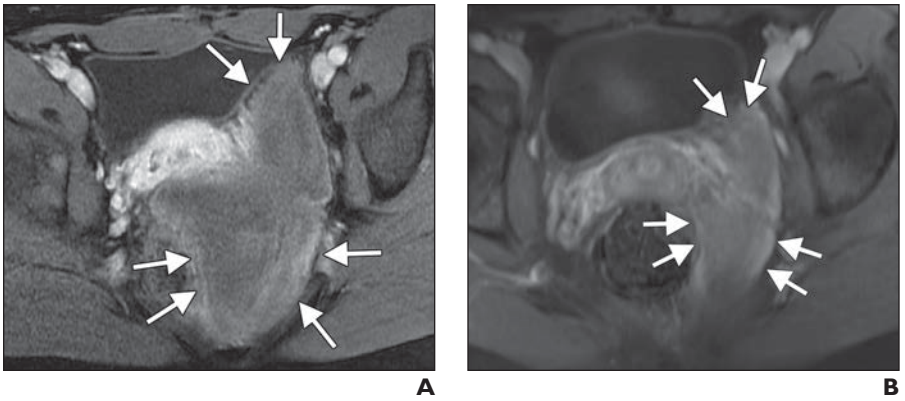


**Fig. 8**—28-year-old woman with aggressive angiomyxoma of pelvis treated with leuprolide.
**A,** Axial gadolinium-enhanced fat-suppressed T1-weighted MR image of pelvis shows enhancing mass (*arrows*) in pelvis.
**B,** Follow-up MR image obtained 6 months after treatment shows decrease in size of tumor (*arrows*).

signs of cystitis, ureteral wall hyperemia, or periureteral fat stranding are seen on staging studies [39].

### *Aromatase Inhibitors*

Endocrine therapy is a cornerstone of breast cancer therapy and consists of three main categories. The first is selective estrogen receptor modulators, of which tamoxifen is the most widely used. Tamoxifen is indicated in the treatment of both premenopausal and postmenopausal women. The second category, aromatase inhibitors, is indicated only for postmenopausal women. Finally, ovarian ablation or suppression can be used for premenopausal women with intact ovarian function. Tamoxifen is discussed later.

Aromatase inhibitors cause antitumor effects by inhibiting the rate-limiting enzyme responsible for the conversion of androgens to estrogens in peripheral tissues. Postmenopausal women derive estrogens from this conversion and are most responsive to inhibition of aromatase. Aromatase inhibitors can be reversible (anastrazole and letrozole) or irreversible (exemestane). Aromatase inhibitors are the first-line drugs for adjuvant and neoadjuvant treatment of postmenopausal women with hormone-sensitive breast cancer [40, 41] (Fig. 9). The duration of adjuvant aromatase inhibitor therapy is uncertain, but treatment is typically continued for 5 years [40].

### *Adverse Effects of Aromatase Inhibitors*

The major adverse effect of aromatase inhibitors is a decrease in BMD. In the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial [42], the risk of fractures was higher in the anastrazole arm (11%) than in the tamoxifen arm (7.7%). Several guidelines call for regular assessment of BMD for patients undergoing aromatase inhibitor therapy, although the frequency is uncertain. BMD can be assessed by several techniques, including dual energy x-ray absorptiometry (DEXA), quantitative CT, and high-resolution microtomography. DEXA is the most widely used modality, and the sites most commonly assessed are the lumbar spine and hip. Before starting aromatase inhibitor therapy, postmenopausal women are usually assessed for risk of fracture according to the World Health Organization T score. A T score of 2.5 or less defines osteoporosis; a score between –1.0 and –2.5 suggests osteopenia; and a score greater than –1.0 is normal BMD [43]. The Fracture Risk Assessment Tool (FRAX) was developed by WHO in 2008 for predicting the 10-year probability of hip fracture in untreated patients 40–90 years old on the basis of clinical risk factors [44]. FRAX-predicted risk varies by country, and the tool is routinely incorporated into DEXA software. Aromatase inhibitor–related bone loss can be prevented and treated with bisphosphonates [40, 45, 46].

## Inhibitors of Hormone Receptors

Inhibitors of hormone receptors compete with physiologic hormones for binding with hormone receptors and blocking them. The two most common classes of hormone receptor inhibitors are estrogen receptor inhibitors and androgen receptor inhibitors.

### *Selective Estrogen Receptor Modulators*

Tamoxifen competitively binds the estrogen receptor with mixed agonist and antagonist actions depending on the target tissue:

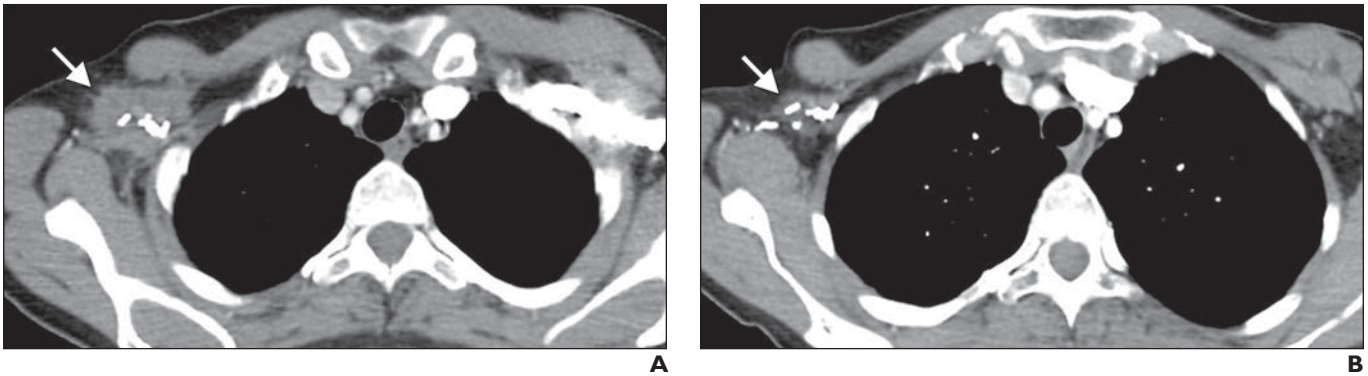


**Fig. 9**—65-year-old woman with recurrent estrogen receptor– and progesterone receptor–positive, *ERBB2* (formerly *HER2* or *HER2/neu*)-negative breast cancer treated with letrozole.
**A,** Axial contrast-enhanced CT image of chest at baseline shows large right axillary nodal mass (*arrow*).
**B,** Follow-up CT scan obtained 3 months after therapy shows decrease in right axillary lymph nodal mass (*arrow*).

antagonist in the breast and agonist in endometrium (Fig. 10). Tamoxifen is the most common form of adjuvant hormone therapy for women with breast cancer. Newer selective estrogen receptor modulators include fulvestrant (pure antiestrogen), raloxifene (antagonist action on the breast and uterus and agonist effects on bones and cardiovascular system), and toremifene (antagonist in the breast and agonist in the uterus and bone). For women with estrogen receptor–positive breast cancer, adjuvant treatment with tamoxifen substantially reduces the recurrence rate beyond the duration of therapy [47, 48].

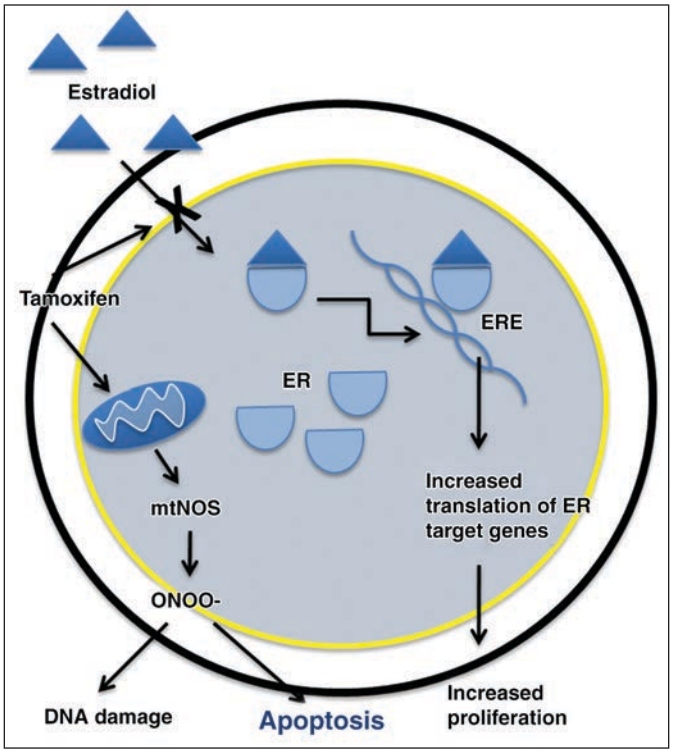



**Fig. 10**—Chart shows mechanism of action of selective estrogen receptor modulator tamoxifen. Estrogen receptor (ER) is ligand-activated transcription factor that binds to specific DNA sequences (ERE). Tamoxifen inhibits estradiol from binding to ER while also increasing oxidative stress (ONOO–), inducing apoptosis and DNA damage. mtNOS = mitochondrial nitric oxide synthase.

*Adverse Effects of Tamoxifen*

Tamoxifen has weak estrogen agonist action in postmenopausal endometrial tissue. The result is a spectrum of benign and malignant endometrial abnormalities within 6–36 months of initiation of therapy [49]. Tamoxifen increases the incidence of endometrial polyps (8–36%), hyperplasia (1.3–20%) (with or without atypia), endometrial carcinoma, leiomyoma, adenomyosis, and uterine sarcomas, including adenosarcoma, endometrial stromal sarcoma, and carcinosarcoma [50, 51] (Figs. 8 and 9). In addition, agonist effects on the ovaries induce ovarian cyst formation without evidence of increased ovarian cancer [52] (Fig. 11). The type of endometrial carcinoma associated with tamoxifen is controversial. Although some authors report less aggressive histologic types, others report more aggressive histologic features, especially in women using tamoxifen for a long time [53].

Tamoxifen-associated endometrial abnormalities are often asymptomatic and can be incidentally detected at routine follow-up CT and PET/CT. They should be further evaluated with transvaginal ultrasound [49]. Ultrasound shows thickened endometrium (> 5 mm) with cystic spaces in postmenopausal women [49]. However, greater than 8-mm thickening is considered abnormal in these patients [54]. Endometrial polyps can present at Doppler ultrasound as nonspecific thickening of the endometrium or as a focal mass within the endometrial canal with a feeding vessel. Tamoxifen-associated polyps tend to be larger than polyps in the general population (mean diameter, 5 cm versus 0.5–3.0 cm) with greater risk of malignant transformation (3–10.7%) than in the general population (0.48%) [52]. Hyperplasia is seen at ultrasound as smooth or focal hyperechoic endometrial thickening (Fig. 11).

At MRI, two endometrial patterns are seen in women undergoing tamoxifen treatment. The first is homogeneous high signal intensity on T2-weighted images, contrast enhancement of the endometrium-myometrium interface, and signal intensity void within the endometrial lumen on T1-weighted images. These findings correspond to endometrial atrophy and proliferative changes. The second pattern is heterogeneous signal intensity on T2-weighted images and latticelike enhancement traversing the endometrial canal on T1-weighted images (Fig. 11). This pattern is associated with polyps [55]. The main utility of MRI in these patients is depiction of myometrial invasion, which suggests endometrial carcinoma and allows staging. Uterine endometrial stromal sarcoma, adenosarcoma, and carcinosarcoma are seen as bulky endometrial masses that can be associated with extrauterine extension (Fig. 12).

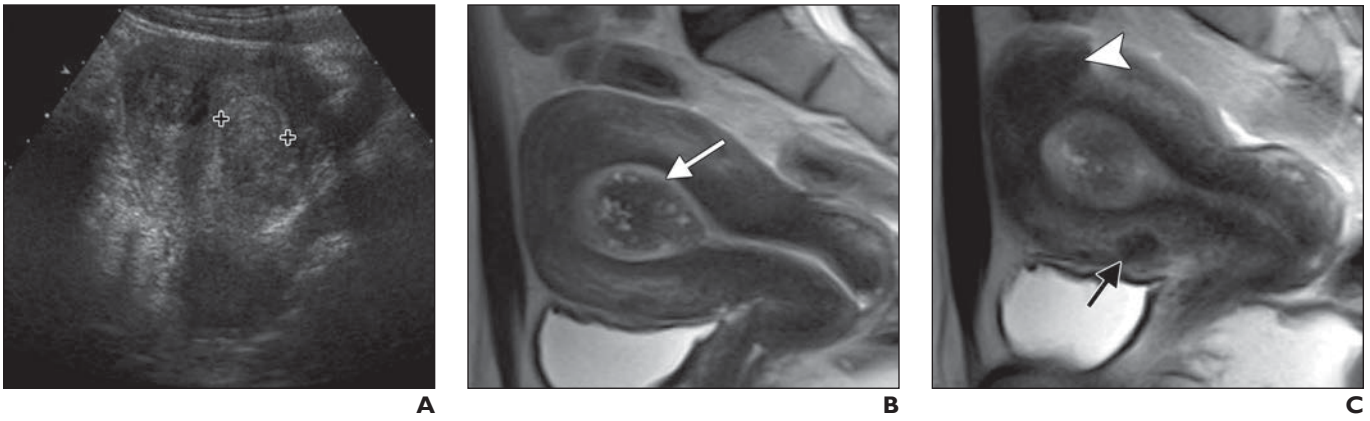
Tamoxifen therapy causes hepatic steatosis, which can mask hepatic metastasis. Nishino et al. [56] reported tamoxifen-associated hepatic steatosis on CT images of 43% of patients within 2 years of initiation of therapy; 79% of those patients had resolution of steatosis within 2 years of cessation of therapy. Use of MRI with in- and out-of-phase techniques can improve detection of liver metastases in this setting. Tamoxifen increases the risk of stroke, deep venous thrombosis, and pulmonary embolism [57, 58], especially in women older than 50 years.

*Androgen Receptor Inhibitors*

Inhibitors of androgen receptors compete with testosterone, block androgen receptors, and are used as part of ADT. Antiandrogens are frequently combined with GnRH agonists or surgical castration in a therapy referred to as combined androgen blockade [59]. Antiandrogens are particularly useful for controlling the flare of symptoms that typically occurs early in the course of treatment with GnRH agonists. The most commonly used antiandrogens are flutamide and bicalutamide. Enzalutamide is a newer antiandrogen that inhibits nuclear translocation of the androgen receptor, DNA binding, and coactivator recruitment. Compared with currently available antiandrogens, it has a greater affinity for the androgen receptor [60]. Enzalutamide has been found effective in metastatic castration-resistant prostate cancer and was FDA approved in 2012. The adverse effects of enzalutamide are mild. As many as 20% of patients receiving enzalutamide experience diarrhea, which can be seen as enterocolitis on restaging images [61].

## Imaging Approach in Hormonal Therapy

As it does in conventional chemotherapy and molecular targeted therapy, imaging plays an important role in the care of patients undergoing hormonal therapy, being used for assess-



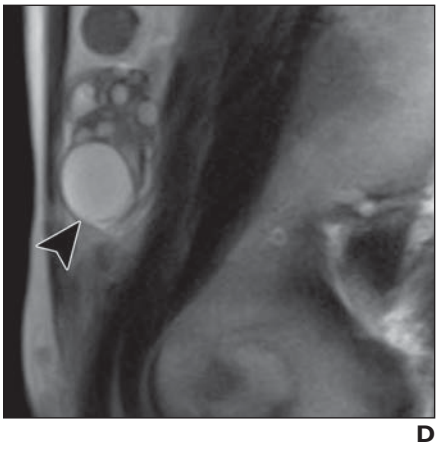




**Fig. 11**—42-year-old woman undergoing tamoxifen therapy.
**A,** Transabdominal ultrasound image of pelvis confirms thickening of endometrium (*calipers*).
**B–D,** Sagittal T2-weighted MR images show endometrial polyp with foci of cystic change (*arrow*, **B**), focal adenomyosis (*arrowhead*, **C**) in uterine fundus, small fibroid (*arrow*, **C**) in anterior myometrium, and ovarian cyst (*arrowhead*, **D**) consistent with tamoxifen effect.

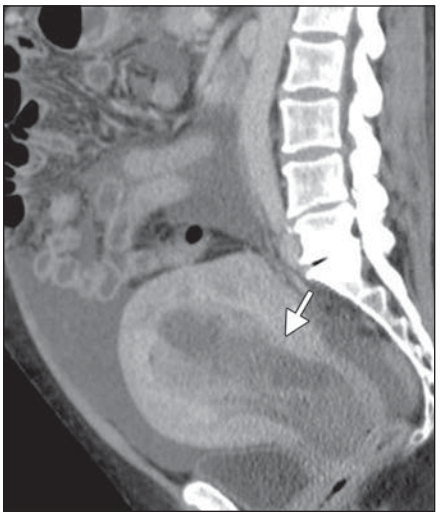


**Fig. 12**—53-year-old woman with history of tamoxifen therapy. Sagittal reformatted contrast-enhanced CT image of abdomen and pelvis shows large solid and cystic endometrial mass (*arrow*) invading right ovary (not shown) and associated with peritoneal carcinomatosis. Surgical histopathologic examination confirmed uterine adenosarcoma with sarcomatoid differentiation.

ment of response and detection of toxicities. The size changes occurring in response to hormonal therapy can be evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST). The decision to continue therapy is guided partly by the type of response found at imaging (complete response, partial response, stable disease, progressive disease) [28, 62]. Response assessment in bone metastasis, bone being the most common site of metastasis of breast and prostate cancer, can be challenging and may require the use of alternative criteria because RECIST considers bone metastasis nonmeasurable [63]. When the type of response is ambiguous at imaging, correlation with tumor markers and the clinical status of the patient can guide radiologists to make the appropriate decision.

## Conclusion

A wide range of hormones are used in oncologic practice. Corticosteroids are widely used in lymphoid malignancy and to treat cancer therapy–related side effects but can be associated with complications such as pneumatosis, osteoporosis, and osteonecrosis. Somatostatin analogues are used to manage neuroendocrine tumors and can be associated with gallstones and injection hematomas. Progestins are used to manage endometrial and breast cancer and are associated with thromboembolic complications. GnRH agonists and antagonists are used in ADT for prostate cancer and are associated with a risk of osteoporosis. Aromatase inhibitors are the first-line agents for postmenopausal breast cancer and are also associated with a risk of osteoporosis. Selective estrogen receptor modulators, such as tamoxifen, are frontrunners in breast cancer management but are associated with increased risk of endometrial abnormalities—including endometrial polyps, hyperplasia, carcinoma, and sarcomas—and thromboembolic phenomena. Familiarity with hormonal therapy can help radiologists stay vigilant for the common side effects and complications of these agents.

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