CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will recognize features from the patient's presentation that help earlier detection of the most common cancers, as well as uncommon but highly curable tumor types

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Detecting cancer: Pearls for the primary care physician

ABSTRACT

Five-year survival rates have improved over the past 40 years for nearly all types of cancer, partially thanks to early detection and prevention. Since patients typically present to their primary care physician with initial symptoms, it is vital for primary care physicians to accurately diagnose common cancers and to recognize unusual presentations of highly curable cancers such as Hodgkin lymphoma and testicular cancers, for which the 5-year overall survival rates are greater than 85%. This paper reviews these cancers and provides clinically relevant pearls from an oncologic perspective for physicians who are the first point of contact.

KEY POINTS

By detecting breast cancer lesions 2 years before they are discovered by clinical breast examination, mammography has been found to reduce the mortality rate from breast cancer.

In the United States, 20% of colorectal cancer patients have distant metastases at the time of diagnosis. The most common sites are the lymph nodes, liver, lungs, and peritoneum.

The patient should fully understand the risks and benefits of prostate-specific antigen (PSA) screening and that it is controversial because, since the advent of PSA testing, the lifetime risk of being diagnosed with prostate cancer has increased, but the lifetime risk of dying from it has remained the same.

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According to the Surveillance, Epidemiology, and End Results database, 5-year overall survival rates have improved for nearly all tumor types during the past 40 years.[1] This has been accomplished with better treatment and earlier detection of the most common cancers, as well as the uncommon but highly curable tumor types.

Primary care physicians play a vital role in detecting cancers at earlier stages and synthesizing information from a patient's presentation, vital signs, physical examination, and results of laboratory and radiographic testing. Yet cancers can be easily overlooked, and highly curable cancers such as Hodgkin lymphoma and testicular cancer, with 5-year survival rates above 85%, can have unusual presentations. Aside from the obvious health consequences, missed cancer diagnoses are often the subject of malpractice suits.

This paper reviews cancers that are easily missed and provides clinically relevant pearls from an oncologic perspective for primary care physicians, who are generally the first point of contact for patients.

BREAST CANCER DETECTION AND SCREENING

Breast cancer is the second most common cause of cancer death in US women and the most common cause of death in US women ages 20 to 59 (**Table 1**).[2–4]

Screening mammography has had a significant impact on early detection rates, and this has translated into a 20% to 30% decrease in the breast cancer mortality rate.[5,6] But despite national screening guidelines, up to 15% of cases are diagnosed on the basis of a palpable breast mass not detected on mammography, and 30%

TABLE 1

New cases and deaths from cancer

Cancer type	Estimated new cases			Estimated deaths		
	Both sexes	Male	Female	Both sexes	Male	Female
Breast	234,190	2,350	231,840	40,730	440	40,290
Colorectal	132,700	69,090	63,610	49,700	26,100	23,600
Prostate	220,800	220,800	0	27,540	27,540	0
Lung	221,200	115,610	105,590	158,040	86,380	71,660
Hodgkin lymphoma	9,050	5,100	3,950	1,150	660	490
Testicular	8,430	8,430	0	380	380	0

Based on information from the American Cancer Society, reference 2.

are diagnosed with a breast mass during the interval between mammograms.[5,6] Moreover, delay in breast cancer diagnosis is one of the most common reasons for malpractice suits.[7,8]

Warning signs

Breast cancer can present clinically as a single, dominant, indurated mass with irregular borders. The mass can have associated ecchymosis, erythema, nipple discharge, nipple retraction, and nipple eczema.[9,10] Pay close attention to any history of breast trauma, pain, signs or symptoms suggestive of local infection, and the lesion's relationship to the patient's menstrual cycle. Locally advanced disease typically presents with axillary adenopathy, as well as skin findings such as erythema, thickening, and dimpling.

Starting breast cancer screening earlier can lead to overdiagnosis and to unnecessary tests and procedures

Initial imaging workup for a breast mass

Women presenting with a breast mass should undergo breast imaging, followed by core needle biopsy of any suspicious abnormality. Depending on the clinical breast examination and the interpretation of the mammogram, as reported as a Breast Imaging Reporting and Data System (BIRADS) score, ultrasonography, magnetic resonance imaging, or biopsy may be the next course of action. Ultrasonography is recommended in evaluating masses in women who are under age 30 (who are more likely to have dense breasts that make standard mammography difficult to interpret) or who are pregnant (because it does not involve radiation).

For patients with a borderline or indeterminate clinical examination (eg, asymmetric skin-thickening or discoloration, nipple discharge or inversion, nodularity, finding on imaging [ie, BIRADS 3 lesion]), closer follow-up with repeat or additional imaging or biopsy, or both, is strongly recommended.

Screening recommendations vary

The age at which to start breast cancer screening has been a matter of debate in recent years, and different organizations have different recommendations (**Table 2**).[11–13] According to the American Cancer Society (ACS), women should begin screening mammography at age 45 and should continue it indefinitely as long as they are in good health.[11] This guideline is in line with those of the National Comprehensive Cancer Network (NCCN)[12] but differs from those of the US Preventive Services Task Force (USPSTF).[13]

One reason for the controversy is that although starting screening at a younger age may allow for earlier detection, it also leads to overdiagnosis and to unnecessary tests and procedures. However, the NCCN noted limitations in studies looking at the overdiagnosis of breast cancer, including their use of incidence data from the 1970s, which not only underestimated the annual incidence of breast cancer in the United States, but also neglected to differentiate invasive cancer from ductal carcinoma in situ.[12] Additionally, by detecting breast cancer lesions 2 years before they are discovered by clinical breast examination, mammography has been found to reduce the mortality rate from breast cancer.[14]

TABLE 2

US guidelines for breast cancer screening

American Cancer Society[11]	US Preventive Services Task Force[13]	National Comprehensive Cancer Network[12]
Women ages 40 to 44 should have the choice to start annual breast cancer screening with mammography. The risks of screening and the potential benefits should be considered. Women ages 45 to 54 should undergo mammography every year. Women age 55 and older should switch to mammography every 2 years, or have the choice to continue yearly screening.	The decision to start regular biennial screening mammography (ie, every 2 years) before age 50 should be an individual one and should take patient context into account, including the patient's values regarding specific benefits and harms. Biennial screening mammography for women ages 50 to 74.	Women age 40 and older should have an annual breast examination, annual screening mammography, and education about breast cancer awareness. Women should be counseled on the potential benefits, risks, and limitations of breast cancer screening.

The frequency of mammography should be individualized and should involve not only an assessment of the patient's risk factors (eg, age, family history, genetic predisposition, history of precancerous lesions, history of radiation exposure) but also a discussion of the benefits, limitations, and potential harms of screening. Both the ACS and the NCCN recommend yearly mammography for women ages 45 to 54. For those age 55 and older, the ACS recommends screening mammography every 2 years until the patient's life expectancy is less than 10 years, whereas the NCCN recommends yearly screening mammography indefinitely. Meanwhile, the USPSTF recommends mammograms every 2 years for women ages 50 to 74.

Pearls

- Pay close attention to a history of breast trauma, pain, and signs of infection.
- Consider ultrasonography for women under age 30, who are more likely to have dense breasts.

COLORECTAL CANCER

With an estimated annual incidence of 132,700 cases diagnosed in the United States in 2015, colorectal cancer is the third most common cancer.

National guidelines that recommend colonoscopy (starting at age 50 for people at standard risk) have had a significant impact on early detection rates and have translated into a significant decrease in mortality rates.[2,15,16] However, a missed diagnosis of colorectal cancer is one of the most common reasons for malpractice suits, typically because the patient was not referred for colonoscopy according to national guidelines.[17–19]

Symptoms depend on tumor location

In symptomatic cases, clinical manifestations differ depending on tumor location.

Left-sided tumors can present with hematochezia, colicky abdominal pain, and a change in bowel habits. And because the descending (left) colon has a smaller lumen than the right and tumors typically are annular in shape, left-sided cancers may present with abdominal distention with or without bowel obstruction or nausea and vomiting.

Right-sided tumors typically present with iron deficiency anemia from unrecognized blood loss.

Tumors near the rectum can cause tenesmus, rectal pain, and diminished caliber of stools.

In the United States, 20% of colorectal cancer patients have distant metastases at the time of diagnosis, and the most common sites are the lymph nodes, liver, lungs, and peritoneum.[17]

Uncommon presentations of colorectal cancer include pneumaturia, fecaluria or recurrent urinary tract infection from a fistula, bacteremia with *Streptococcus bovis* or *Clostridium septicum*, and intra-abdominal abscess from a localized bowel perforation.[20,21]

Missed diagnosis of colorectal or breast cancer is a common reason for malpractice suits

TABLE 3

US guidelines for colorectal cancer screening

American Cancer Society[23]	US Preventive Services Task Force[24]	National Comprehensive Cancer Network[12]
Beginning at age 50, men and women should use one of the screening tests below: **Tests that find polyps and cancer** (preferred): Flexible sigmoidoscopy every 5 years Colonoscopy every 10 years Double-contrast barium enema every 5 years Computed tomographic colonography every 5 years **Tests that find cancer only:** Guaiac-based fecal occult blood test every year Fecal immunochemical test every year Stool DNA test every 3 years	Screen for colorectal cancer using fecal occult blood testing, sigmoidoscopy, or colonoscopy in adults beginning at age 50 and continuing until age 75. The risks and benefits of these screening methods vary. The evidence is insufficient to assess the benefits and harms of computed tomographic colonography and fecal DNA testing as screening modalities for colorectal cancer.	Patients age 50 and older should be screened for colorectal cancer with colonoscopy, high-sensitivity guaiac-based or immunochemical testing, or flexible sigmoidoscopy, plus or minus interval stool-based testing at year 3.

Initial workup

Once cancer is suspected, colonoscopy is the most accurate and versatile diagnostic test. It not only permits localization and biopsy of lesions throughout the large bowel, but also detects synchronous neoplasms and permits removal of polyps. Computed tomographic (CT) colonography is an alternative if colonoscopy is contraindicated, but it can only detect larger (ie, > 6-mm) tumors.[22]

According to the ACS,[23] men and women at average risk should undergo colorectal cancer screening beginning at age 50. ACS screening recommendations for polyps and colorectal cancer include flexible sigmoidoscopy every 5 years, colonoscopy every 10 years, double-contrast barium enema every 5 years, or CT colonography every 5 years. Tests that detect cancer but not polyps include guaiac-based fecal occult blood test (every year), fecal immunochemical test (every year), stool DNA test (every 3 years). These recommendations are fairly consistent with those of the NCCN[12] and USPSTF[24] (**Table 3**).[12,23,24]

Pearls

- Uncommon presentations include urinary tract problems and intra-abdominal abscess.
- CT colonography can only detect larger tumors.

PROSTATE CANCER

With an estimated 220,800 cases and 27,540 deaths in 2015, prostate cancer is the most common cancer and the second most common cause of cancer-related death in US men.[2] Widespread use of serum prostate-specific antigen (PSA) testing has increased the rate of detection of prostate cancer.

Signs and symptoms

Most men with early-stage prostate cancer have no symptoms attributable to the disease

Most men with early-stage prostate cancer have no symptoms directly attributable to the disease.

Obstructive symptoms such as hesitancy, decreased stream, retention, and nocturia are common but are usually related to concomitant benign prostatic hypertrophy. As in prostatitis, patients with prostate cancer may present with irritative symptoms such as urinary frequency, dysuria, and urgency.

Patients who present with locally advanced prostate cancer may have symptoms secondary to local invasion, such as hematuria, hematospermia, and new-onset erectile dysfunction.

Prostate cancer usually metastasizes to bone, most commonly to the vertebrae and sternum, and the associated pain can be acute or insidious.

Diagnosis

Prostate cancer is most often diagnosed after biopsy prompted by an elevated PSA

TABLE 4

US guidelines for prostate cancer screening

American Cancer Society[26]	US Preventive Services Task Force[27]	National Comprehensive Cancer Network[12]
Men should make an informed decision with their physician about whether to be screened based on an understanding of the uncertainties, risks, and benefits of screening. The discussion about screening should take place at: **Age 50** for men at average risk of prostate cancer with a life expectancy of at least 10 years **Age 45** for men at high risk of prostate cancer (blacks, men with a first-degree relative diagnosed with prostate cancer before age 65) **Age 40** for men at even higher risk (more than one first-degree relative diagnosed with prostate cancer at an early age).	Recommends against screening with prostate-specific antigen testing.	Based on family history, race, and a history of prostate disease and screening, men ages 45 to 75 should have a discussion with their physician about the risks and benefits of prostate cancer screening, including prostate-specific antigen testing and digital rectal examination.

level or an abnormal digital rectal examination. The most common abnormal laboratory findings in patients with metastatic prostate cancer are an elevated serum PSA level (typically > 10 ng/mL), an elevated serum alkaline phosphatase level, and anemia, which are all proportional to the extent of bone involvement.

Screening is still controversial

There has been considerable controversy in recent years with regard to PSA screening because of the lack of significant benefit and the potential for harm to the patient, with an overdiagnosis rate ranging from 23% to 42%.[25]

According to the ACS,[26] certain groups of men should make an informed decision with their physician about whether to undergo screening: men over age 50 at average risk of prostate cancer and with at least a 10-year life expectancy, men over age 45 at high risk, and men over age 40 at an even higher risk. These ACS guidelines are consistent with those of the NCCN[12] but differ from those of the USPSTF[27] (**Table 4**).[12,26,27]

The patient should fully understand the risks and benefits of prostate cancer screening, as well as why it is controversial: ie, while the lifetime risk of being diagnosed with prostate cancer has increased, the lifetime risk of dying from it has remained the same after the advent of PSA testing.

Adverse effects of biopsy and treatment

Prostate biopsy is associated with infectious and bleeding complications, in addition to anxiety and physical discomfort.[28] Treatment-related adverse effects include urinary incontinence, sexual dysfunction, and bowel problems.

Could these potential harms be overstated and the benefit be greater than currently thought? The NCCN[12] noted that some of the landmark prostate cancer screening studies found a potential benefit in screening high-risk patients such as black men. Moreover, the studies used the sextant prostate biopsy technique, whereas now the extended core biopsy technique is the standard of care. And the studies may have underestimated the benefit of screening because the trial patients were relatively old (age 60) when their first PSA measurement was done, they were screened at long intervals (every 4 years), and the treatment options available at the time were not as good as those available today.[12]

Patients should fully understand the risks and benefits of prostate cancer screening, and why it is controversial

Pearls

- Laboratory findings in metastatic prostate cancer are proportional to the extent of bone involvement.
- Most men with early-stage prostate cancer have no symptoms attributable to the disease.

LUNG CANCER

Lung cancer is the second most common type of cancer in men and women but has the highest mortality rate. In the United States, in 2015, an estimated 221,200 new cases of lung cancer and 158,040 deaths were expected.[2] Lung cancer deaths have begun to decline in both men and women, and this is due to the decline in smoking. The impact of lung cancer screening may not be seen for another 5 to 10 years.[29]

A wide range of symptoms, presentations

Many patients with squamous cell carcinoma and small-cell lung carcinoma present with symptoms related to tumor involvement of the central airways,[30] including cough, hemoptysis, and postobstructive pneumonia. Partial obstruction of a bronchus may cause localized wheezing, heard by the patient or by the clinician on auscultation, whereas obstruction of larger airways can cause stridor.

Lung cancer deaths are declining due to less smoking, but screening should also start to have an impact

Patients with advanced disease present with dull, aching, persistent chest pain from mediastinal, pleural, or chest wall extension, dyspnea from lymphangitic tumor spread, tumor emboli, pneumothorax, pleural effusion, or pericardial effusion with tamponade. Less commonly, patients may present with unilateral paralysis of the diaphragm from phrenic nerve damage or with hoarseness from recurrent laryngeal nerve compression.[31]

Bronchorrhea—production of large volumes of thin, mucoid secretions resulting in cough—may be a feature of bronchoalveolar cell carcinoma, a rare subtype of non-small-cell lung carcinoma.

Patients uncommonly present with superior vena cava syndrome, an oncologic emergency that most often causes facial and arm swelling, dyspnea, cough, and headache.

Non-small-cell lung carcinoma arising in the superior sulcus may in rare cases cause Pancoast syndrome (manifested by shoulder pain and atrophy of the hand muscles from brachial plexus involvement), Horner syndrome (manifested by ptosis, miosis, and anhidrosis), or rib destruction.

If metastasis occurs, lung cancer commonly metastasizes to the liver and adrenal glands. At the time of diagnosis, 20% to 30% of patients with small-cell lung carcinoma have symptoms of central nervous system metastasis.

The screening controversy

Lung cancer screening is controversial because previous large studies have failed to show a clinical benefit (ie, improved survival rates) of CT screening in smokers. However, based on the results of a later large randomized trial,[32] the ACS[33] now recommends that patients ages 55 to 74 who are in fairly good health, have at least a 30-pack-year smoking history, and are currently smoking or have quit smoking within the last 15 years should discuss with their physician the benefits, limitations, and potential harms of lung cancer screening. These recommendations are similar to those of the NCCN[12,34] and USPSTF[35] (**Table 5**).[12,33–35] The ACS guidelines also emphasize that screening should be done only at facilities with extensive experience with low-dose CT.

Follow-up evaluation

If imaging detects a lung nodule, its size and consistency are crucial in determining the course of action.[33] If an endobronchial growth or solid nodule larger than 8 mm is discovered, the primary care physician should consider ordering either a repeat low-dose CT scan after 1 month or a positron-emission tomography CT scan.[34] The diagnosis should be confirmed by biopsy or by surgical removal of the nodule if localized and accessible, with sites of metastasis typically taking priority.

Pearl

- At diagnosis, 20% to 30% of patients with small-cell lung cancer have symptoms of central nervous system metastasis.

HIGHLY CURABLE CANCERS WITH UNUSUAL PRESENTATIONS

Hodgkin lymphoma

With 9,190 new cases in the United States annually and a 5-year overall survival rate over

TABLE 5

US guidelines for lung cancer screening

American Cancer Society[33]	US Preventive Services Task Force[35]	National Comprehensive Cancer Network[12,34]
Patients who meet all of the following criteria may be candidates for lung cancer screening: 1) Age 55 to 74 2) In fairly good health 3) Smoking history > 30 pack-years 4) Currently smoking or having quit smoking within the last 15 years.	Annual screening for lung cancer with low-dose computed tomography in adults ages 55 to 80 who have a 30-pack-year smoking history and who currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery.	For patients at high risk (ages 55 to 74 with a 30-pack-year or greater smoking history, smoking cessation less than 15 years ago) OR Age 55, with a 20-pack-year smoking history, and one additional risk factor other than second-hand smoke.

85%, Hodgkin lymphoma is one of the least common but most curable cancers.[1,2] In the United States, there are two diagnostic peaks, one around age 20 and one around age 65.[36] In patients with human immunodeficiency virus infection, the rate is 15 to 30 times higher than in the general population, regardless of disease status or compliance with highly active retroviral therapy.[37]

Hodgkin lymphoma typically presents as a nontender painless mass with rubbery consistency. The involved lymph node is typically cervical or supraclavicular. Although not detectable on physical examination, enlarged mediastinal nodes and retroperitoneal nodes are often present. Less commonly, patients may present with enlarged axillary and inguinal nodes.[38]

A second common presentation is the discovery of a mediastinal mass on routine chest radiography. A large percentage of patients present with at least one systemic symptom, which may include fever, night sweats, and unintentional weight loss. Generalized pruritus occurs early in the disease course in 10% to 15% of patients and is occasionally severe enough to cause intense scratching and excoriations.

A more unusual presentation of Hodgkin lymphoma is severe pain at areas of involvement after alcohol ingestion.

Most patients present with overt disease, but the presenting symptoms and signs may be relatively nonspecific and subtle and more consistent with an infectious process.

Hodgkin disease has a variable tempo, but overt symptoms typically occur after several months rather than years. As a general rule, it starts at a single site within the lymphatic system, usually a lymph node, and then spreads to adjacent nodes via lymphatic channels before disseminating to distant nonadjacent sites and organs. With this in mind, it is unusual to have bilateral axillary involvement without disease in the lower neck, and extremely unusual to have hepatic or bone marrow infiltration without disease in the spleen.

The diagnosis is established by whole lymph node tissue biopsy. Due to the high rate of inflammation in the area, inguinal nodes should not be biopsied if other equally suspicious peripheral nodes are present elsewhere. When the diagnosis of Hodgkin lymphoma is made from biopsy of an extranodal site, such as the stomach, spleen, Waldeyer ring, central nervous system, lung, bone, or skin, lymph node biopsy is also desirable for diagnostic confirmation.

Testicular cancer

Although accounting for only about 1% of all cancers in men, testicular cancer is the most common solid tumor affecting males between ages 15 and 35.[1,2] With a 5-year survival rate of over 95%, testicular cancer is also one of the most curable cancers.

Testicular tumors usually present as a painless nodule or swelling of one testicle. Uncommonly, patients have metastatic disease at diagnosis, with the most common sites being

Any testicular mass, even a painful scrotal lesion, should be evaluated as if it is testicular cancer until it is proven otherwise

lymph nodes, lung, bone, and the brain. Gynecomastia, associated with the production of human chorionic gonadotropin, occurs in about 5% of men with testicular germ cell tumors and 20% to 30% of men with Leydig cell tumors.[39] Rarely, patients may present with paraneoplastic hyperthyroidism, which is secondary to thyroid-stimulating hormone and human chorionic gonadotropin sharing a common homologous alpha and beta subunit.[40]

Prompt diagnosis and treatment of testicular cancer provides the best opportunity for cure. Therefore, any testicular mass, even a painful scrotal lesion, should be evaluated as if it is testicular cancer until it is proven otherwise. The diagnostic evaluation of suspected testicular cancer includes scrotal ultrasonography. Radiographic testing, as deemed clinically necessary by the consulting urologist and medical oncologist, may include chest radiography, CT (chest, abdomen, pelvis), brain magnetic resonance imaging, or bone scan.

The primary care laboratory evaluation should include a complete metabolic profile and measurements of lactate dehydrogenase and serum tumor markers such as alpha fetoprotein and human chorionic gonadotropin. In nonseminomatous germ cell tumors, alpha fetoprotein or human chorionic gonadotropin, or both, can be elevated in 80% to 85% of patients. However, in seminoma, alpha fetoprotein is never elevated, and the serum human chorionic gonadotropin is elevated in only 20% to 25% of patients.[41]

Patients with a suspicious testicular mass should be referred promptly to a urologist for consideration of radical inguinal orchiectomy and, in some cases, retroperitoneal lymph node dissection. Testicular biopsy is not part of the evaluation as it may result in tumor seeding into the scrotal sac or metastatic spread of tumor to the inguinal nodes. Inguinal biopsy of the contralateral testis is considered if ultrasonography raises suspicion of an intratesticular abnormality, cryptorchid testis, or marked testicular atrophy. Discussing sperm banking with the patient is part of the diagnostic workup, as cumulative cisplatin doses greater than 400 mg/m^2 can result in permanent infertility in 50% of men.[42]

Pearls

- In Hodgkin lymphoma, bilateral axillary involvement without disease in the lower neck is unusual.
- Discussing sperm banking is part of the diagnostic workup for testicular cancer.

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