KEY POINTS

- Favorable factors of recurrent head and neck cancer include small, localized disease; longer time to recurrence; and site of recurrence in the larynx or nasopharynx.
- Patients with good performance status and advanced disease not amenable to surgery or radiation should first receive a combination of a platinum agent (cisplatin or carboplatin) with 5-fluorouracil and cetuximab.

Genitourinary Cancer

Prostate Cancer

Epidemiology and Risk Factors

Adenocarcinoma of the prostate remains one of the most commonly diagnosed types of cancer among men in the United States, with an estimated lifetime risk of one in seven. Age is a very important risk factor; prostate cancer is rarely diagnosed before age 40 years, but after that point, the incidence increases significantly. Ethnicity is also an important risk factor, with the incidence significantly greater for black men than for white or Hispanic men. Further, black men are more likely to be diagnosed at a younger age with higher-risk disease. Genetics and family history also play an important role in risk. Men with a first-degree relative diagnosed with prostate cancer are twice as likely to be diagnosed. Prostate cancer is also linked with germline mutations in different genes, such as *BRCA2*, *HOXB13*, and the Lynch syndrome genes.

Diagnosis and Staging

Prostate cancer is most commonly diagnosed after identification of an elevated serum prostate-specific antigen (PSA) level during screening and in the absence of symptoms. See MKSAP 18 General Internal Medicine for a discussion of current issues relating to prostate cancer screening.

Although urinary symptoms might be present in patients with prostate cancer, they are usually related to benign prostatic hyperplasia and not to the cancer. In some men diagnosed with metastatic disease at the time of initial presentation, bone pain or back pain can be the presenting symptom. If the diagnosis is suspected on the basis of an elevated serum PSA level, the elevation should first be confirmed by a second measurement at least 1 month later. Persistent serum PSA elevation should prompt urology referral, as should a palpable abnormal finding in the prostate on digital rectal examination.

Prostate biopsy is performed using transrectal ultrasonography for guidance, and several cores should be taken from different regions of the gland. Studies have found that increasing the number of cores improves diagnostic accuracy without causing a significant increase in complications. Most commonly, at least five to seven cores are taken per side to provide a sufficient diagnostic yield. Atypical small acinar proliferation and multifocal high-grade prostatic intraepithelial neoplasia are both associated with a high risk of underlying cancer and should prompt rebiopsy.

Risk stratification using serum PSA, Gleason score, and TNM cancer staging based on biopsy results and digital rectal examination is essential for determining prognosis and treatment options (**Table 47**). Imaging studies need not be done in patients whose risk is very low or low but should be obtained in others to evaluate regional lymph node involvement and metastatic disease.

KEY POINT

- Prostate cancer is most commonly diagnosed after identification of an elevated serum prostate-specific antigen level during screening and in the absence of symptoms.

Treatment

Treatment options for men with newly diagnosed localized prostate cancer include active surveillance, radiation, and radical prostatectomy. For men with limited life expectancy or significant medical comorbidities, observation is most appropriate.

Active surveillance is deferral of curative-intent therapy in lieu of regular monitoring for evidence of disease progression. It is an option for men with very-low-risk or low-risk prostate cancer who have a life expectancy of at least 10 years. Active surveillance should consist of digital rectal examination (not more than every 12 months), serial measurement of

TABLE 47. Prostate Cancer Risk Stratification

Risk Category	Definition[a]
Very low	Stage T1c, serum PSA <10 ng/mL (10 µg/L), Gleason score ≤6, fewer than 3 biopsy cores positive, ≤50% cancer in each core, PSA density <0.15 ng/mL/g
Low	T1-T2a, Gleason score ≤6, PSA <10 ng/mL (10 µg/L)
Intermediate	T2b-T2c OR Gleason score 7 OR PSA 10-20 ng/mL (10-20 µg/L)
High	T3a OR Gleason score 8-10 OR PSA >20 ng/mL (20 µg/L)
Very high	T3b-T4, primary Gleason pattern 5, >4 cores with Gleason score 8-10

PSA = prostate-specific antigen.

[a]T1 = tumors that are not palpable or seen on imaging; T1a (<5% of specimen) and T1b (>5% of specimen) are discovered incidentally in a pathologic specimen resected for benign disease; T1c discovered in prostate biopsy for elevated serum PSA.

T2 = palpable tumors; T2a involves <50% of one lobe; T2b involves >50% of one lobe; T2c are in both lobes of the prostate.

T3a extends through the prostate capsule; T3b involves the seminal vesicles.

T4 tumors are fixed to adjacent structures.

Data from NCCN Clinical Guidelines in Oncology. Prostate Cancer. Version 2.2017. NCCN.org. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed February 17, 2018.

serum PSA (assessing level changes and calculating PSA doubling time), and repeat biopsy. A PSA doubling time of less than 3 years is considered an indication for treatment. Repeat biopsy is typically done at 1 year, and if no high-grade disease is identified, it can be done less often after that. Fifteen-year metastasis-free survival is as high as 97% in appropriately selected patients.

Active treatment of low-risk localized prostate cancer is typically a choice between external beam radiation and radical prostatectomy. Brachytherapy, in which radioactive implants are inserted into the prostate, is also an option for men with low-risk cancer or selected men with low-volume intermediate-risk cancer.

Radiation is associated with short-term risks of enteritis (approximately 20% of men) and cystitis (approximately 50% of men). These conditions become long-term complications in a very small percentage of men. Erectile dysfunction typically increases over time after radiation, such that by 2 years, approximately 60% to 70% of men have at least moderate erectile dysfunction.

With radical prostatectomy, the main risks are urinary incontinence and erectile dysfunction. Urinary incontinence is relatively common immediately after surgery. The rate of chronic moderate to severe incontinence is approximately 5% to 10%. Erectile dysfunction is relatively common after surgery and can persist for several years. Approximately 40% of men reported erectile dysfunction 2 years after surgery.

A recent study showed no difference in survival after 10 years for patients with localized prostate cancer detected through serum PSA screening who were randomized to receive active surveillance, surgery, or radiation therapy. There was a trend toward improved survival for patients older than 65 years of age who received either of the active interventions. Patients receiving surgery or radiation had decreased disease progression and decreased metastatic disease.

For men with intermediate-risk or higher-risk localized disease who are treated with radiation therapy, the addition of a gonadotropin-releasing hormone (GnRH) agonist will delay disease progression. It has also been shown to improve overall survival in men with high-risk and very-high-risk prostate cancer. For those men with high-risk or very-high-risk localized prostate cancer, six cycles of adjuvant docetaxel given after radiation therapy in addition to androgen deprivation therapy improves disease-free survival and overall survival.

After definitive local treatment, men are monitored for evidence of recurrence with serial serum PSA measurements every 3 to 4 months and digital rectal examination yearly unless PSA is undetectable. After radical prostatectomy, the PSA should rapidly become undetectable, but after radiation treatment, the PSA will fall gradually, will reach a nadir, and will not necessarily become undetectable. PSA recurrence after surgery is defined as a detectable PSA level that increases on at least two measurements; after radiation, PSA recurrence is defined as an increase in the PSA level by at least 2 ng/mL (2 µg/L) above the nadir PSA.

For men with PSA-only recurrence, an evaluation to look for evidence of clinical local or metastatic disease with imaging studies is indicated. If men were treated with initial surgery and metastatic disease has not been identified, salvage radiation with or without androgen deprivation therapy (ADT) can be offered. Likewise, if men were treated initially with radiation, salvage surgery can be offered, but it is only indicated if a transrectal ultrasound-guided biopsy specimen is positive and no metastatic disease is identified; if the specimen is negative, then ADT can be considered.

It is important to note that for men with PSA-only recurrence, with or without clinical metastatic disease, observation is a reasonable consideration depending on patient and disease-specific factors, such as symptoms and PSA doubling time. This is especially true for men with PSA-only recurrence, as it can take several years for clinical metastatic disease to develop in that setting.

KEY POINTS

- Active surveillance, including serial serum prostate-specific antigen (PSA) and repeat biopsy, is appropriate for men with very-low-risk or low-risk prostate cancer.
- Treatment of localized low-risk prostate cancer is typically either external beam radiation or radical prostatectomy, in which both have equal efficacy; brachytherapy is also an option.
- Gonadotropin deprivation is typically administered after radiation therapy for localized intermediate-risk or high-risk prostate cancer.
- Patients with PSA-only recurrence may be treated with androgen deprivation therapy, although observation is a reasonable choice because it may take several years for overt metastatic disease to develop.

HVC

Metastatic Prostate Cancer

Once distant metastatic disease is diagnosed, the mainstay of therapy is ADT. Options for providing ADT include orchiectomy, GnRH-agonist therapy (with or without antiandrogen) and GnRH-antagonist therapy (**Table 48**). Psychological aversion to orchiectomy by both patients and physicians has limited its use in the United States, although it is a rapidly acting and cost-effective way to achieve androgen depletion and remains the mainstay of ADT in other parts of the world.

At present, there is no clear advantage to combined androgen blockade using a GnRH agonist or antagonist plus an antiandrogen. In patients who have clinical metastatic disease, antiandrogen therapy should precede or be started at the same time as a GnRH agonist, and the combination should be continued for at least 7 days because of the risk of a transient worsening of disease-related symptoms, termed a flare reaction. Continuation is not necessary if a GnRH antagonist is used. Intermittent ADT is not typically recommended in men with clinical metastatic disease, although it can be offered to

TABLE 48. Treatments for Metastatic Prostate Cancer

Class	Agents	Mechanism of Action	Indications
GnRH agonist	Leuprolide, goserelin, triptorelin, buserelin, histrelin	Binds to GnRH receptor, causes initial release of FSH/LH (and also testosterone) followed by suppression	Metastatic prostate cancer; neoadjuvant/adjuvant ADT in combination with radiation
GnRH antagonist	Degarelix	Binds to GnRH receptor and suppresses activity without initial increase in activity seen with GnRH agonists	Metastatic prostate cancer; neoadjuvant/adjuvant ADT in combination with radiation
Antiandrogen	Bicalutamide, flutamide	Binds to androgen receptor with competitive inhibition of testosterone binding	Metastatic castrate-sensitive prostate cancer (not indicated as monotherapy, only in combination with GnRH agonist or antagonist)
CYP17 inhibitor	Abiraterone plus prednisone	Blocks androgen synthesis in tumor tissue, testes, and adrenal glands	Metastatic castrate-resistant prostate cancer; used in combination with prednisone as it can cause adrenal insufficiency
Androgen receptor blockade	Enzalutamide	Binds to the androgen binding site of the androgen receptor in a non-competitive fashion	Metastatic castrate-resistant prostate cancer
Tumor vaccine	Sipuleucel-T	Autologous dendritic cell therapeutic vaccine Aims to increase T cell response to prostatic acid phosphatase	Asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer with no visceral metastatic disease Not indicated for PSA-only relapse; does not result in PSA response
Bone-seeking isotope	Radium-223	Alpha particle–emitting isotope that concentrates in bone	Metastatic castrate-resistant prostate cancer with symptomatic bone metastases and no known visceral metastatic disease
Chemotherapeutic	Docetaxel plus prednisone	Antimicrotubule agent	Metastatic castrate-resistant prostate cancer with clinical metastatic disease Metastatic castrate-sensitive prostate cancer in combination with ADT in men with clinical metastatic disease Adjuvant therapy after radiation in men with high-risk or very-high-risk prostate cancer, in combination with ADT
Chemotherapeutic	Cabazitaxel plus prednisone	Antimicrotubule agent	Metastatic castrate-resistant prostate cancer following disease progression after docetaxel treatment

ADT = androgen-deprivation therapy; CYP17 = 17α-hydroxy/17,20-lyase; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; PSA = prostate-specific antigen.

mitigate side effects. Response can be assessed most easily by serial serum PSA measurement, but imaging also plays a role. The serum testosterone level should be less than 50 ng/dL (1.7 nmol/L) in men treated with ADT.

Men with clinical metastatic disease who respond to ADT are considered to have castrate-sensitive prostate cancer. In this population, evidence from two recently reported phase III randomized clinical trials indicates that treatment with docetaxel for six cycles with ADT results in improved disease-free survival and overall survival.

ADT results in many short-term and long-term side effects. Short-term effects include loss of lean body mass, fatigue, gynecomastia, hair loss, decreased libido, erectile dysfunction, and vasomotor symptoms. Long-term risks include a possible increase in cardiovascular disease, increased risk of venous thromboembolism, and reduction in bone density. Osteoporosis is a prevalent and underappreciated complication of ADT. All men being treated with ADT should take supplemental calcium and vitamin D, and baseline fracture risk should be assessed using a dual-energy x-ray absorptiometry (or "DEXA") scan. Osteoclast inhibitors will reduce bone pain and lower fracture risk in men with ADT-resistant, metastatic prostate cancer.

After identification of progressive disease in men being treated with ADT (castrate-resistant prostate cancer), many treatment options exist (see Table 48). There is no optimal sequence of therapies. Initial treatment options for castrate-resistant prostate cancer include docetaxel with prednisone, abiraterone with prednisone, enzalutamide, radium-223 (for symptomatic bone metastases), and secondary hormone

therapy. Secondary hormone therapies are older treatments that are generally not as effective as newer treatments. Secondary hormone therapies include the addition of an antiandrogen in men not previously exposed to one, addition of ketoconazole (with or without hydrocortisone), antiandrogen withdrawal and use of diethylstilbestrol, or another form of estrogen. For patients who develop progressive disease after treatment with docetaxel, cabazitaxel with prednisone can be used.

KEY POINTS

- Continuous androgen deprivation therapy (ADT), including orchiectomy, gonadotropin-releasing hormone-agonist therapy, and gonadotropin-releasing hormone-antagonist therapy is most appropriate for metastatic prostate cancer.
- Men who respond to ADT and then receive docetaxel chemotherapy will have prolonged survival without disease progression and prolonged overall survival.
- All men who are treated with ADT should take supplemental calcium and vitamin D and have measurement of baseline bone mineral density because osteoporosis is a prevalent and underappreciated complication of ADT.

Testicular Cancer

Testicular cancer is the most common solid tumor diagnosed in men aged 15 to 35 years, although it accounts for only about 1% of all cancers diagnosed in the United States. It is also one of the most curable forms of cancer, due in large part to its sensitivity to chemotherapy. It most commonly presents as a unilateral testicular swelling or mass. However, other presentations are also possible in men with more advanced disease at diagnosis.

Patients with localized symptoms should have a scrotal ultrasound to rule out benign cystic or infectious causes of scrotal enlargement and baseline tumor markers, including α-fetoprotein and β-human chorionic gonadotropin. Diagnosis is made most commonly through inguinal orchiectomy. Needle biopsy of a testicular mass is contraindicated because of concern regarding tumor seeding to the scrotum and inguinal nodes. When the diagnosis is confirmed, evaluation with chest radiography, CT of the abdomen and pelvis, and tumor marker levels after orchiectomy are used for staging. It is important to realize that marker levels fall at predictable rates after surgery, with serum α-fetoprotein the slowest to fall because of its longer serum half-life. Therefore, sufficient time is needed before concluding that markers remain elevated after orchiectomy.

The most common site of spread is to retroperitoneal nodes. Histologically, testicular cancers are either pure seminomas or nonseminomatous germ cell tumors. Management depends on histology, the results of staging studies, and the presence or absence of serum tumor marker elevation after orchiectomy. It is essential to discuss and offer cryopreservation of sperm before initiating additional treatment.

For pure seminoma, active surveillance can be offered after surgery for early-stage disease; adjuvant radiation or chemotherapy with one to two cycles of carboplatin is also appropriate options. Stage II seminoma is defined by retroperitoneal lymph node metastases. For patients with low-volume lymph node metastatic disease, either adjuvant radiation or cisplatin-based combination chemotherapy can be used. In general, as the size of the largest lymph node metastasis increases to more than 2 cm, chemotherapy is preferred over radiation. For stage III seminoma disease, which signifies distant metastatic disease, cisplatin-based chemotherapy is used. PET-CT can be used to determine whether residual masses after chemotherapy require resection. Residual masses that show negative results on PET scan may be benign and can be followed, with resection based on any further increase in size. Residual masses that show positive results on PET scan should be promptly resected, as cure remains possible.

Patients with early-stage nonseminomatous germ cell tumors can be managed with active surveillance (in selected patients), retroperitoneal lymph node dissection (RPLND), or limited chemotherapy. Adjuvant chemotherapy can be considered in patients with positive findings on RPLND. Persistence of tumor marker elevation after orchiectomy without abnormal imaging findings is an indication for chemotherapy. Patients with clinically metastatic retroperitoneal nodes can be managed with RPLND or primary chemotherapy if markers are negative and nodal metastases are limited and small. For patients with several positive nodes, large nodes (>5 cm), or elevated markers, chemotherapy is recommended. Any residual masses after chemotherapy should be resected.

For the first year after treatment, patients should be seen for interview and examination every 2 to 3 months and should have tumor marker measurement and imaging studies periodically, with specific intervals determined by histology, stage, and previous treatment. After the first year, evaluations can be performed less often.

Patients with recurrent disease are treated with combination chemotherapy and can also be treated with high-dose chemotherapy and autologous hematopoietic stem cell transplantation.

Men treated with chemotherapy for testicular cancer are at risk for many different long-term complications, including cardiovascular disease, metabolic syndrome, pulmonary toxicity, hypogonadism, infertility, chronic kidney disease, and neurotoxicity. Further, there is a well-described risk of a second malignancy among men treated for testicular cancer. The risk of a second solid tumor is approximately twofold higher than in men without a history of testicular cancer.

KEY POINTS

- Measurement of serum tumor markers (α-fetoprotein, lactate dehydrogenase, β-human chorionic gonadotropin) are important before and after inguinal orchiectomy for staging and prognosis of testicular cancer.
- Patients with stage II seminoma, defined by retroperitoneal lymph node metastasis, can be treated with adjuvant radiation or cisplatin-based chemotherapy, although chemotherapy is preferred if the largest metastasis increases above 2 cm.
- Patients with seminoma and residual masses after chemotherapy should receive PET-CT; masses with negative findings on PET-CT can be observed with follow-up imaging to assess progression, and masses with positive findings should be resected.
- Patients with nonseminoma and clinically metastatic nodes can be treated with retroperitoneal lymph node dissection or primary chemotherapy; chemotherapy is preferred if there are several positive nodes, large nodes (>5 cm), or elevated serum tumor markers.

Renal Cell Carcinoma

Renal cancers typically arise in the cortex of the kidney. The most common histology is clear cell carcinoma, which is also the most responsive to medical treatment. In the past, the most common presenting symptoms of renal cell carcinoma were hematuria, abdominal mass, and weight loss, but most patients are currently diagnosed incidentally based on imaging studies done for other reasons. Ultrasonography can be used to differentiate benign cysts from complex cysts or solid masses. If a lesion is not clearly a benign cyst, CT is indicated for further evaluation. Biopsy is only indicated if CT does not clearly indicate renal cell carcinoma.

Many different paraneoplastic syndromes can be seen in patients with renal cell carcinoma, including anemia, hepatic dysfunction in the absence of liver metastases (known as Stauffer syndrome), fever, hypercalcemia, erythrocytosis, AA amyloidosis, thrombocytosis, and polymyalgia rheumatica. Many of these conditions can improve with resection of the primary tumor, metastatic sites, or both.

For localized disease, surgery is indicated. This consists of either radical nephrectomy or partial nephrectomy, depending on the size and location of the primary tumor. In most patients no adjuvant therapy is indicated. Sunitinib has recently been approved by the US Food and Drug Administration (FDA) for use as adjuvant treatment in patients with high risk clear cell carcinoma of the kidney following definitive surgery. In a phase III trial it improved disease free survival by 1.2 years compared with no treatment. Postoperative surveillance to identify recurrent disease is indicated, with the frequency of interventions depending on the extent of local disease. This typically consists of a history and physical examination, basic laboratory studies, and imaging of the chest and abdomen. Cryoablation, radiofrequency ablation, or even active surveillance may be indicated for managing small tumors in frail patients who have a high risk of postoperative complications.

Resection of the primary renal cell cancer improves survival for select patients with metastatic disease. Debulking nephrectomy can be considered because there is evidence indicating that this procedure is associated with improved survival. Surgery also has a possible role in the treatment of isolated or several easily resected areas of metastatic disease.

No specific front-line therapy has been shown superior for patients who present with metastatic clear cell or non-clear cell histology. Various novel agents, including the programmed death 1 (PD-1) receptor antibody nivolumab and the vascular endothelial growth factor (VEGF) inhibitors lenvatinib and axitinib, have shown activity for patients with disease recurrence.

KEY POINTS

- Many different paraneoplastic syndromes can be seen in patients with renal cell carcinoma, including anemia, hepatic dysfunction in the absence of liver metastases, fever, hypercalcemia, erythrocytosis, AA amyloidosis, thrombocytosis, and polymyalgia rheumatica. Resecting a primary renal cell cancer may improve the response to chemotherapy in patients with metastatic disease.

Bladder Cancer

Bladder cancer is the most common cancer of the genitourinary tract. Most patients have transitional cell carcinoma, which is the focus of this section. The most common presenting symptom is hematuria, which is often gross hematuria and may be intermittent. It is typically painless, although irritative urinary symptoms can be present with or without hematuria. It is important to assess for gross hematuria in review of systems questioning for all patients and confirm with a urinalysis if a patient does note hematuria. Any patient with gross hematuria should be referred for urologic evaluation, as should any patient confirmed to have persistent microscopic hematuria after evaluating benign causes, such as urinary tract infection, nephrolithiasis, or underlying kidney disease with a glomerular source of erythrocytes. Notably, use of anticoagulants does not alter these recommendations.

The primary modality of initial evaluation is cystoscopy combined with urine cytology, with biopsy of any visible tumor or mucosal abnormality. Random biopsy is performed if no abnormality is seen. If cancer is confirmed, then transurethral resection of the bladder tumor (TURBT) and examination under anesthesia is performed to determine histology and also depth of invasion.

Most patients are found to have non-muscle invasive disease. This can include exophytic lesion (Ta, which can be low grade or high grade), carcinoma in situ (Tis, always high grade), or early-stage invasive cancer (T1). Small low-grade Ta tumors are treated with TURBT followed by a single dose of

intravesical chemotherapy. All other noninvasive disease (including recurrent low-grade Ta disease) is treated with TURBT followed by six treatments of intravesical chemotherapy, most commonly bacillus Calmette-Guérin or mitomycin, although other compounds are used. After primary treatment, cystoscopic surveillance is indicated because of the risk for recurrent disease. There is a higher risk for muscle invasive recurrence for patients with larger tumors, less differentiated tumors, tumors that invade into the lamina propria, and tumors with multifocal or noninvasive recurrence. Most patients require cystoscopy 3 months after initial therapy, with subsequent cystoscopy at 3-month to 1-year intervals based on risk of recurrence. Cystectomy can be considered for patients at high risk for developing muscle-invasive disease.

If muscle-invasive disease is diagnosed, cystectomy is indicated, with or without neoadjuvant cisplatin-based chemotherapy. Partial cystectomy can be considered in very carefully selected patients. If bladder preservation is desired, maximal TURBT can be combined with concurrent chemoradiotherapy. Adjuvant chemotherapy after surgical resection is appropriate to consider in patients with poor-risk features, such as positive nodes and extension beyond the bladder.

Treatment of metastatic disease requires systemic therapy, and treatment outcomes remain poor. Cisplatin-based combination chemotherapy remains the evidence-based choice in patients eligible to receive cisplatin. After further progression, single-agent therapy is recommended. Immunotherapy plays a role here with the recent FDA approval of atezolizumab, a monoclonal antibody directed against the programmed death ligand 1 (PD-L1) receptor.

KEY POINTS

- Any patient with gross hematuria should be referred for urologic evaluation, as should any patient confirmed to have microscopic hematuria in the absence of an apparent benign cause; use of anticoagulants does not alter these recommendations.
- Bladder cancer typically does not invade the muscle, and treatment includes transurethral resection of the bladder tumor (TURBT) plus intravesical chemotherapy, usually bacillus Calmette-Guérin or mitomycin.
- Muscle-invasive bladder cancer is treated with cystectomy with or without neoadjuvant cisplatin-based chemotherapy; partial cystectomy with bladder preservation through maximal TURBT and concurrent chemoradiotherapy can be performed in select patients.

Lymphoid Malignancies

Epidemiology and Risk Factors

The American Cancer Society estimates that in 2018 83,180 new cases of lymphoma will be diagnosed in the United States. The lifetime risk of developing non-Hodgkin lymphoma is 2.1%, whereas the lifetime risk of developing Hodgkin lymphoma is considerably less. Although incidence has only slightly declined recently, death rates have decreased significantly owing to improvements in treatment. The incidence of non-Hodgkin lymphoma rises with increased age, whereas the incidence of Hodgkin lymphoma shows a bimodal age distribution, with an early peak in the second and third decades of life, then a decline, followed by a sustained increase with older age.

Although most of these cases seem sporadic, familial clustering can be seen, with an increased relative risk in first-degree relatives. Patients with both congenital and acquired immunosuppression (such as HIV infection, organ transplantation, or an inherited immunodeficiency) are at greater risk.

Various viral infections are also associated with increased risk. Epstein-Barr virus is associated with Burkitt lymphoma, seen in African pediatric patients, as well as some cases of Hodgkin lymphoma. Human T-cell lymphotropic virus type 1 (HTLV-1) is associated with T-cell leukemias and lymphomas, endemic in Japan, West Africa, Central America, the southeastern United States, and the Caribbean. Hepatitis C virus is associated with an increased risk of lymphoma, particularly splenic marginal zone lymphoma. HIV infection is associated with an increased risk of principally B-cell lymphomas, typically with aggressive histology, more advanced stage, more B symptoms, and a higher risk of extranodal and central nervous system involvement. Kaposi sarcoma herpesvirus (human herpesvirus 8) is associated not only with Kaposi sarcoma but also with primary effusion lymphoma.

Patients with autoimmune rheumatic disorders, such as Sjögren syndrome, systemic lupus erythematosus, and rheumatoid arthritis, have an increased risk of non-Hodgkin lymphoma. The strongest association is with Sjögren syndrome and extranodal marginal zone lymphomas.

Evaluation and Diagnosis

Enlarged lymph nodes are the most common sign of lymphoma. There are many causes of lymphadenopathy, and in most patients, it is of benign origin (infectious or inflammatory). Palpable small and modest-sized cervical and inguinal lymph nodes may be noted in otherwise healthy adults and need not be evaluated further. This finding in young adults and of brief (less than 3 to 4 weeks) duration is likely to be benign. CT scan of the chest, abdomen, and pelvis can assess palpable lymph nodes not amenable to physical examination but generally should not be done in asymptomatic patients. When the size, distribution, or persistence of enlarged lymph nodes or systemic symptoms raises concern for lymphoma, a diagnosis is generally established based on lymph node biopsy. An excisional biopsy is often preferable to a core needle biopsy as it may better determine nodal architecture. Fine-needle aspiration cytology is generally inadequate to make a specific diagnosis, but it may show features suspicious for lymphoma, requiring a more definitive excisional biopsy or, conversely,