well-differentiated pNETs that are unresectable. NETs, like other normal and neoplastic cells, frequently possess multiple types of the 20 different tyrosine kinase (TK) receptors that are known and mediate the action of different growth factors. Numerous studies demonstrate that TK receptors in normal and neoplastic tissues as well as NETs are especially important in mediating cell growth, angiogenesis, differentiation, and apoptosis. Whereas a number of TK inhibitors show antiproliferative activity in NETs only sunitinib has undergone a phase III controlled trial. Sunitinib is an orally active small-molecule inhibitor of TK receptors (PDGFRs, VEGFR-1, VEGFR-2, c-KIT, FLT-3). In a phase III study in which 171 patients with progressive, metastatic, nonresectable pNETs were treated with sunitinib (37.5 mg/d) or placebo, sunitinib treatment caused a doubling of progression-free survival (11.4 vs 4.5 months, $p < .001$), an increase in objective tumor response rate (9% vs 0%, $p = .007$), and an increase in overall survival. Sunitinib treatment was associated with an overall threefold increase in side effects, although most were grade 1 or 2. The most frequent grade 3 or 4 side effects were neutropenia (12%) and hypertension (9.6%), which were controlled by dose reduction or temporary interruption. There is no consensus regarding the order of sunitinib or everolimus use in patients with advanced, well-differentiated, progressive pNETs.

PRRT for NETs involves treatment with radiolabeled somatostatin analogues. The success of this approach is based on the finding that somatostatin receptors (sst) are overexpressed or ectopically expressed by 60–100% of all NETs, which allows the targeting of cytotoxic, radiolabeled somatostatin receptor ligands.

Three different radionuclides are being used. High doses of [^{111}In-DTPA-D-Phe^1]octreotide, which emits γ-rays, internal conversion, and Auger electrons; ^{90}yttrium, which emits high-energy β-particles coupled by a DOTA chelating group to octreotide or octreotate; and ^{177}lutetium-coupled analogues, which emit both, are all in clinical studies. At present, the ^{177}lutetium-coupled analogues are the most widely used. ^{111}Indium-, ^{90}yttrium-, and ^{177}lutetium-labeled compounds caused tumor stabilization in 41–81%, 44–88%, and 23–40%, respectively, and a decrease in tumor size in 8–30%, 6–37%, and 38%, respectively, of patients with advanced metastatic NETs. In one large study involving 504 patients with malignant NETs, ^{177}lutetium-labeled analogues produced a reduction of tumor size of >50% in 30% of patients (2% complete) and tumor stabilization in 51% of patients. An effect on survival has not been established. At present, PRRT is not approved for use in either the United States or Europe, but because of the above promising results, a large phase III study is now being conducted in both the United States and Europe. The ENETS 2012, NANETS 2010, Nordic 2010, and European Society for Medical Oncology (ESMO) guidelines list PRRT as an experimental or investigational treatment at present.

The use of liver transplantation has been abandoned for treatment of most metastatic tumors to the liver. However, for metastatic NETs, it is still a consideration. Among 213 European patients with NETs (50% functional NETs) who had liver transplantation from 1982 to 2009, the overall 5-year survival was 52% and disease free-survival was 30%. In various studies, the postoperative mortality rate is 10–14%. These results are similar to the United Network for Organ Sharing data in the United States in which 150 NET patients had liver transplants and the 5-year survival was 49%. In various studies, important prognostic factors for a poor outcome include a major resection performed in addition at the time of the liver transplant; poor tumor differentiation; hepatomegaly; age >45 years; a primary NET in the duodenum or pancreas; the presence of extrahepatic metastatic disease or extensive liver involvement (>50%); Ki-67 proliferative index >10%; and abnormal E-cadherin staining. The ENETS 2012 guidelines conclude that liver transplantation should be viewed as providing palliative care, with cure an exception, and recommend it be reserved for patients with life-threatening hormonal disturbances refractory to other treatments or for selected patients with a nonfunctional tumor with diffuse liver metastatic disease refractory to all other treatments.

114 Bladder and Renal Cell Carcinomas

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BLADDER CANCER

Transitional cell epithelium lines the urinary tract from the renal pelvis to the ureter, urinary bladder, and the proximal two-thirds of the urethra. Cancers can occur at any point: 90% of malignancies develop in the bladder, 8% in the renal pelvis, and 2% in the ureter or urethra. Bladder cancer is the fourth most common cancer in men and the thirteenth in women, with an estimated 72,570 new cases and 15,210 deaths in the United States predicted for the year 2013. The almost 5:1 ratio of incidence to mortality reflects the higher frequency of the less lethal superficial variants compared to the more lethal invasive and metastatic variants. The incidence is roughly four times higher in men than in women and twofold higher in white men than in black men, with a median age of 65 years.

Once diagnosed, urothelial tumors exhibit polychronotropism, which is the tendency to recur over time in new locations in the urothelial tract. As long as urothelium is present, continuous monitoring is required.

EPIDEMIOLOGY

Cigarette smoking is believed to contribute to up to 50% of urothelial cancers in men and nearly 40% in women. The risk of developing a urothelial cancer in male smokers is increased two- to fourfold relative to nonsmokers and continues for 10 years or longer after cessation. Other implicated agents include aniline dyes, the drugs phenacetin and chlornaphazine, and external beam radiation. Chronic cyclophosphamide exposure also increases risk, whereas vitamin A supplements appear to be protective. Exposure to *Schistosoma haematobium*, a parasite found in many developing countries, is associated with an increase in both squamous and transitional cell carcinomas of the bladder.

PATHOLOGY

Clinical subtypes are grouped into three categories: 75% are superficial, 20% invade muscle, and 5% are metastatic at presentation. Staging of the tumor within the bladder is based on the pattern of growth and depth of invasion. The revised tumor, node, metastasis (TNM) staging system is illustrated in Fig. 114-1. About half of invasive tumors presented originally as superficial lesions that later progressed. Tumors are also rated by grade. Low-grade (highly differentiated) tumors rarely progress to a higher stage, whereas high-grade tumors do.

More than 95% of urothelial tumors in the United States are transitional cell in origin. Pure squamous cancers with keratinization constitute 3%, adenocarcinomas 2%, and small cell tumors (often with paraneoplastic syndromes) <1%. Adenocarcinomas develop primarily in the urachal remnant in the dome of the bladder or in the periurethral tissues. Paragangliomas, lymphomas, and melanomas are rare. Of the transitional cell tumors, low-grade papillary lesions that grow on a central stalk are most common. These tumors are very friable, have a tendency to bleed, and have a high risk for recurrence, yet they rarely progress to the more lethal invasive variety. In contrast, carcinoma in situ (CIS) is a high-grade tumor that is considered a precursor of the more lethal muscle-invasive disease.

PATHOGENESIS

The multicentric nature of the disease and high recurrence suggests a field effect in the urothelium that results in a predisposition to develop cancer. Molecular genetic analyses suggest that the superficial and invasive lesions develop along distinct molecular pathways. Low-grade noninvasive papillary tumors harbor constitutive activation of the receptor tyrosine kinase-Ras signal transduction pathway and high frequencies of fibroblast growth factor receptor 3 and phosphoinositide-3