Chapter 11
Onconephrology

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Introduction

The National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program reported that approximately 15.3 million people in the United States had cancer of any site in 2016 [1]. Also, approximately 1.7 million new cases of cancer were diagnosed in 2019. The number of people living with cancer has been increasing during the past few years in part due to improved patient survival with more modern approaches to cancer therapy. The 5-year survival of cancer patients was around 69% in 2011 compared to 49–55% in the 1970s–1980s with traditional chemotherapy [1]. The unintended consequence of improved cancer survival is that more patients will likely experience the short- and long-term side effects of cancer treatment. More patients with cancer will also develop chronic conditions like chronic kidney disease (CKD) which carry their own impact on morbidity and mortality.

Caring for patients with both cancer and kidney disease poses a significant challenge to the medical team. Cancer populations are often vulnerable and have a multitude of risk factors for acute kidney injury including treatment-related nephrotoxicity. CKD, on other hand, may be a consequence of a specific cancer itself or due to comorbidities like hypertension and diabetes similar to the general population. As cancer survival improves, more patients with cancer will live long enough to reach end-stage renal disease (ESRD) requiring renal replacement therapy. Although the approach to the diagnosis and treatment of most kidney diseases

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is similar among cancer patients and the general population, we will discuss below conditions and issues unique to cancer patients which highlights the growing need for onconephrology training.

Assessment of Kidney Function in Cancer Patients

Kidney function is commonly expressed in terms of creatinine clearance or glomerular filtration rate (GFR). Accurate measurement of kidney function among cancer patients is important as it is considered in the choice and dosing of chemotherapeutic drugs and because kidney injury can complicate the clinical course of cancer patients. However, reliable measurement of kidney function in this population is often challenging due to the limitations in the tools available to the clinician. Serum creatinine-based formulas like the Cockroft and Gault (CG), the Modification of Diet in Renal Disease (MDRD), and the CKD Epidemiology Collaboration (CKD-EPI) are easy to use and estimate the glomerular filtration rate (eGFR). The Kidney Disease: Improving Global Outcomes (KDIGO) recommends the use of CKD-EPI in the general population [2]. Cancer patients, however, often suffer from sarcopenia resulting in decreased creatinine generation. Serum creatinine-based formulas tend to overestimate kidney function in this setting and may lead to unwanted drug toxicity. The underestimation of kidney function is equally worrisome as it may lead to sub-therapeutic dosing and treatment failure. Despite losing favor in clinical practice, the CG formula developed back in 1976 is still the basis of most drug-dosing recommendations for adjustment for kidney function. The CG formula predates the standardization of Cr assays, is seldomly reported by standard laboratories, and is less accurate in the elderly, the age group in which the majority of cancer patients fall into [3, 4]. The largest study that validated eGFR formulas among cancer patients was by Janowitz and colleagues in 2017 [5]. Among 2582 cancer patients, the CKD-EPI formula when adjusted to body surface area was the most accurate published formula compared against chromium-51 (51Cr) EDTA excretion as the gold standard. More accurate measures of kidney function include inulin and iothalamate clearance, but they are expensive and mostly used in research settings. 24-hour urine creatinine clearance measurement can be utilized but may be cumbersome particularly in non-hospitalized patients. Cystatin C is not affected by differences in muscle mass or diet and is relatively inexpensive. This can be used to estimate GFR either alone or in conjunction with serum creatinine using CKD-EPI cystatin C equations. However, cystatin C can increase in states of high cell turnover and non-Hodgkin's B-cell lymphoma limiting its use in certain cancers [6]. There are no clear recommendations on the best method to determine kidney function among cancer patients.

Tubular function is an important aspect of kidney function that is often neglected. Among cancer patients, attention to tubular function is necessary as many chemotherapeutic drugs cause tubular toxicity that may lead to acid-base and electrolyte

abnormalities. Measuring urinary beta-2 microglobulin, a marker of proximal tubular injury, and calculating for the fractional excretion of urinary ions may be valuable tests as serum creatinine and blood urea nitrogen (BUN) may remain normal with tubular dysfunction [5, 7].

Acute Kidney Injury in Cancer Patients

Acute kidney injury (AKI) often complicates the clinical course of cancer patients. In a Danish study of 37,267 cancer patients, the 1-year risk of AKI after cancer diagnosis was 17%, and the 5-year risk was around 27% [8]. In a US cancer center, among 3558 patients admitted over 3 months, 12% had AKI based on the RIFLE (Risk, Injury, Failure, Loss, ESRD) criteria [9]. The risk of AKI may depend on the underlying malignancy with renal cancer, multiple myeloma, and liver cancer being associated with the highest risk [8]. Other risk factors include underlying diabetes, iodinated contrast exposure, chemotherapy, and antibiotic use [9]. Similar to the general population, AKI in cancer patients results in higher costs of hospitalization, longer hospital stay, and increased morbidity and mortality [10]. In a Brazilian cohort of 288 cancer patients in an intensive care unit, mortality rates were 49%, 62%, and 87% for patients with RIFLE criteria R, I, and F, respectively, compared to 13.6% in those without AKI [11].

Based on pathophysiology, the causes of AKI among cancer patients can be divided into prerenal, intrinsic, and postrenal similar to how we approach AKI in the general population (Table 11.1). AKI in cancer patients can also be classified as being cancer-related (caused by the cancer itself), therapy-related, or cancer-nonspecific. Cancer-nonspecific causes include volume depletion, iodinated contrast exposure, medications (e.g., non-steroidal anti-inflammatory drugs [NSAIDs], angiotensin-converting enzyme inhibitors [ACEIs], antibiotics, diuretics), ischemic acute tubular necrosis (ATN), sepsis, and renal vein or artery occlusion. In a cohort of 975 patients admitted in a medical-surgical intensive care unit, 32% had AKI with shock/ischemia and sepsis accounting for the majority of cases [12]. The management of cancer-nonspecific causes of AKI follow recommendations for the general population. Hypovolemia, shock, and sepsis should be approached aggressively as cancer patients can be frail and immunocompromised. Nephrotoxic medications and iodinated contrast should be avoided if possible, but their use should be weighed against their benefits if it can alter the course of treatment (e.g., cancer staging) and the goals of care (e.g., palliative vs curative). Despite the inaccuracy of estimates of GFR in AKI, appropriate dose adjustment of medications should still be attempted. Consultation with pharmacy should be considered to avoid over- or under-dosing chemotherapeutic drugs and life-saving antibiotics. Medical teams should also pay attention to medications commonly prescribed to cancer patients, like renally excreted analgesic medications. Morphine and other opioids have metabolites that may accumulate with reduced kidney function and can result in life-threatening neurologic and respiratory depression. Gabapentin and baclofen are also commonly

Table 11.1 Causes of acute kidney injury in cancer patients

Mechanism of AKI	Causes
Prerenal	Volume depletion Cardiorenal syndrome/heart failure Hepatorenal syndrome Drugs
Intrinsic	
Glomerular	Paraprotein-related diseases, thrombotic microangiopathy, atheroembolism, paraneoplastic glomerulonephritis
Vasculature	Renal vein/artery thrombosis
Interstitium	Medications, paraprotein-related disease, infections/sepsis
Tubular	Cast nephropathy Tumor lysis syndrome Ischemic acute tubular necrosis Nephrotoxins, iodinated contrast Rhabdomyolysis
Postrenal	Renal calculi Papillary necrosis Tumor invasion of the ureter/bladder Bladder or prostate malignancy Retroperitoneal fibrosis post-surgery/radiation

used analgesic medications that require dose adjustment for eGFR and can lead to neurotoxicity at high doses.

The incidence of AKI requiring dialysis among critically ill cancer patients ranges from 2% to 5% [8–10]. The indications for initiating dialysis among cancer patients are similar to those without cancer. These include acid-base and electrolyte abnormalities that are refractory to medical management, volume overload with oliguria, and uremia. Active cancer should not be a hindrance to offering dialysis to patients especially in the setting of a reversible process. However, it is important to recognize that dialysis is an invasive procedure and also carries its own risks (e.g., bleeding from dialysis access insertion, infection, arrhythmias, hemodynamic changes). Factors like cancer prognosis, previously set goals of care, advanced directives, and baseline physical function/frailty prior to the acute illness should all be part of the discussion before initiating dialysis. The cost of hospitalization increases by around 21% for patients with AKI who require dialysis [10]. Furthermore, 10–15% of those who required dialysis for AKI will progress to ESRD [8].

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) results from the rapid release of intracellular substances into the extracellular compartment due to destruction of cancer cells. It often occurs in response to therapy but can rarely occur spontaneously in certain

cancers. TLS is characterized by hyperuricemia, hyperkalemia, and hyperphosphatemia with secondary hypocalcemia due to calcium binding to phosphate. AKI results for uric acid and calcium phosphate precipitation in the tubule. Since the development of effective hypouricemic agents, calcium phosphate precipitation is now a more dominant process in AKI from TLS. The Cairo-Bishop definition is used for the laboratory and clinical diagnosis of TLS (Table 11.2) [13].

Acute lymphoblastic leukemia (ALL), non-Hodgkin's lymphoma, and acute myeloid leukemia (AML) are the most common malignancies associated with TLS [13, 14]. With the emergence of more effective anticancer drugs, TLS is being increasingly seen in cancers not historically associated with it like chronic lymphocytic leukemia. Tumor-related risk factors for developing TLS include high cell proliferation rate, increased chemosensitivity of the cancer, and a large tumor burden (organ infiltration, bone marrow involvement, elevated lactate dehydrogenase [LDH]) [15]. Certain parameters for different hematologic malignancies are used to identify which patients are at high, moderate, or low risk of developing TLS (e.g., AML with WBC count $\geq 100 \times 10^9$/L or lymphoblastic lymphoma with LDH $\geq 2 \times$ upper limit of normal are considered high risk) [16]. Other risk factors for TLS include pre-treatment hyperuricemia (>7.5 mg/dl), prior kidney disease/AKI, exposure to other nephrotoxins, acidic urine, oliguria, volume depletion, and a higher calcium phosphate product (>60mg^2/dl^2) [13, 17]. TLS with AKI is associated with a fivefold increased risk of death within 6 months compared to the absence of AKI [14].

Preventive strategies for TLS include aggressive intravenous or oral hydration with at least 3 L/m^2 per day to achieve a urine output of 80–100 ml/m^2/hour [13]. Loop diuretics should be used when oliguria with volume overload occurs. Allopurinol and/or rasburicase can be given prophylactically to patients who have an intermediate or high risk for developing TLS. Febuxostat can also be used instead of allopurinol but is more expensive. Urine alkalinization is no longer recommended as it can promote calcium phosphate deposition and may worsen AKI [13]. Close monitoring of electrolytes and LDH should be done during chemotherapy for early detection. When TLS occurs, aggressive medical management of electrolyte derangements should be done to avoid organ damage and life-threatening events like cardiac dysrhythmias. Hypouricemic medications should be administered

Table 11.2 The Cairo-Bishop definition of tumor lysis syndrome in adults

Laboratory[a]	Clinical[b]
Uric acid $\geq$ 8 mg/dL[c]	Increase in creatinine $\geq$ 1.5 ULN
Potassium $\geq$ 6 mEq/L[c]	Cardiac arrhythmia
Phosphorus > 4.5 mg/dL[c]	Seizure
Calcium $\leq$ 7 mg/dl[c]	

Abbreviations: *ULN* upper limit of normal

[a]$\geq$2 of the laboratory changes within 3 days before or 7 days after chemotherapy

[b]Clinical tumor lysis syndrome refers to laboratory tumor lysis syndrome and at least one clinical complication and can be graded based on severity of clinical complication

[c]or a 25% increase from baseline

promptly. With severe hyperkalemia, medications that shift potassium intracellularly should be given as a temporizing measure, but eventual excretion from the body should be the goal. Exogenous sources of potassium and phosphate (intravenous or dietary) should be limited, and binders can be administered. Calcium replacement is only indicated for severe or symptomatic hypocalcemia (electrocardiogram changes, dysrhythmias, tetany) as excessive repletion will promote calcium phosphate binding and precipitation. Indications for renal replacement include oliguria or anuria, volume overload not responding to diuretics, refractory hyperkalemia, symptomatic hypocalcemia, and a calcium phosphate product >70mg^2/dl^2 [13, 17, 18]. The efficiency of intermittent hemodialysis varies depending on the size of dialyzer used and the duration of treatment. Uric acid and potassium are rapidly lowered by intermittent hemodialysis treatments lasting 4–6 hours. In severe hyperkalemia, intermittent hemodialysis may be done first to rapidly lower potassium levels followed by continuous renal replacement therapy (CRRT) to avoid a rebound effect [14]. Phosphate clearance is slower and time dependent due to its large volume of distribution. It may require more frequent treatments if intermittent hemodialysis is planned, and continuous renal replacement therapy is a better option in cases of severe hyperphosphatemia. Peritoneal dialysis is less efficient and is not commonly done for TLS. TLS complicated by AKI is associated with higher in-hospital and 6-month mortality, even after adjusting for severity of illness [19].

Therapy-Related Acute Kidney Injury

Cancer therapy has greatly evolved in the past century. In the first half of the twentieth century, therapy options for cancer were limited to radiotherapy and traditional chemotherapeutic drugs. As the effects of these treatments were not specific to cancer cells, patients suffered from numerous side effects. The 1980s harbored in the era of targeted therapy. Tyrosine kinase inhibitors and monoclonal antibodies were developed to act against specific molecular targets like altered oncogenes or tumor suppressor genes that were responsible for tumor growth and progression. Targeted therapy is efficacious against cancer cells and has limited effects on normal cells improving the tolerability of chemotherapy. In 2010, immunotherapy started taking center stage by targeting immune tolerance that allows certain cancers to proliferate.

The kidneys are particularly susceptible to drug toxicity due to its role in drug metabolism and excretion. Certain anticancer drugs are toxic to certain segments of the nephron or the interstitium resulting in varied renal manifestations depending on which segment is affected. Electrolyte abnormalities are common in proximal tubulopathies, proteinuria occurs in glomerular involvement or podocytopathies, and thrombotic microangiopathy (TMA) can develop with insult to the vasculature and causes hypertension and proteinuria. As newer anticancer drugs come into play, it is important for the clinician to be familiar with their associated toxicities. As the indications for immunotherapy grow, clinicians may start encountering

immune-mediated nephrotoxicity more frequently than the typical tubular toxicities that are observed with traditional chemotherapeutic drugs.

Traditional Chemotherapeutic Agents

Platinum Salts

Cisplatin and its analogues carboplatin and oxaliplatin exert their anticancer effect by cross-linking with purine bases resulting in interference with DNA replication and repair. These agents are commonly used in head and neck, gynecologic, testicular, and lung cancer. Several mechanisms have been described in the literature including direct proximal and distal tubular epithelial cell toxicity, renal vasoconstriction, and pro-inflammatory effects [20]. Cisplatin-induced nephrotoxicity can therefore present with a Fanconi-like syndrome (phosphate and potassium wasting, glucosuria in the setting of normoglycemia, hypouricemia, aminoaciduria, and tubular acidosis), TMA, and AKI. In a recent study of 821 adults treated with cisplatin for various cancers, AKI occurred in 31.5% with a median decline in eGFR by ~10 ml/min per 1.73 m^2 [21]. Risk factors for developing AKI with platinum salts include older age, higher peak plasma concentrations, previous cisplatin therapy, pre-existing kidney disease, and concomitant use of other nephrotoxic agents like amphotericin or aminoglycoside [22–24]. AKI is usually non-oliguric as urine output is preserved due to the kidney's decreased ability to concentrate urine. Preventive measures include using lower doses or alternative agents, maintaining adequate hydration with normal saline infusion, and correction of hypomagnesemia. Other "nephroprotective" strategies like the use of amifostine, sodium thiosulfate, N-acetylcysteine, or theophylline are more controversial. Cisplatin-induced AKI is generally reversible with dose reduction, but the drug should be discontinued when severe and progressive kidney dysfunction occurs with a ≥50% increase in serum creatinine from baseline or presence of oliguria. When cisplatin therapy is associated with TMA or hemolytic uremic syndrome (HUS), it should also be discontinued. Carboplatin and oxaliplatin are thought to be less nephrotoxic and may be considered as alternatives to cisplatin.

Methotrexate and Pemetrexed

Methotrexate (MTX) inhibits the dihydrofolate reductase enzyme resulting in a shortage of thymidylate and purines required for nucleic acid synthesis. MTX is used in acute lymphoblastic leukemia, lymphomas, osteosarcoma, and gestational trophoblastic disease. Around 90% of MTX is excreted in the urine unchanged. Drugs that inhibit renal excretion of MTX like NSAIDs, phenytoin, proton pump inhibitors (PPIs), and sulfamethoxazole/trimethoprim can lead to toxicity. The incidence of AKI with MTX has historically been reported to be as high as 30–50% [4]. A more recent study reported a much lower incidence of just 1.8% in 3887 patients

with osteosarcoma [25]. Lower doses of MTX do not commonly result in nephrotoxicity. At doses ≥500 mg/m^2, MTX can precipitate in the tubules causing obstruction and direct tubular injury. Acidic urine, volume depletion, elevated plasma concentration, and mutations in the multidrug resistance protein 2 (MRP2) transporter in the proximal tubule all promote MTX precipitation [4, 26]. MTX has also been associated with a transient decline in eGFR occurring within a week of initiation and is thought to be due to arteriolar and mesangial constriction [27].

Intravenous hydration and urine alkalinization (targeting a urine pH of 7.0–8.0) can be used to decrease tubular precipitation of MTX. Leucovorin and thymidine can restore DNA synthesis in normal hematopoietic and enteric cells and are used as rescue therapy. Urgent hemodialysis has been used to decrease MTX levels when it is markedly elevated in the serum with signs of organ damage such as elevated hepatic enzymes, AKI, myelosuppression, or neurologic dysfunction. Depending on the modality and duration of treatment, around 50–80% of MTX can be removed with hemodialysis. The use of high-flux hemodialysis appears to result in the greatest decrease in MTX levels with a single treatment [25]. After discontinuation of hemodialysis, a rebound increase in serum MTX levels is expected and may necessitate additional treatment sessions. Peritoneal dialysis is generally ineffective in reducing MTX levels. The recombinant enzyme carboxypeptidase G2 (glucarpidase) cleaves MTX into inactive metabolites. It can rapidly decrease MTX levels by 97–99% within 30 minutes of administration and can be used instead of hemodialysis when available [28, 29].

Pemetrexed is a derivative of MTX and is used in the treatment of advanced non-small cell lung cancer (NSCLC) and pleural mesotheliomas. Similar to MTX, 70–90% of the drug is excreted in the urine unchanged. It has been associated with acute tubular necrosis (ATN), acute tubulointerstitial nephritis (ATIN), renal tubular acidosis (RTA), and diabetes insipidus based on case reports [30–32].

Ifosfamide and Cyclophosphamide

Ifosfamide and cyclophosphamide are alkylating agents that inhibit DNA synthesis by causing DNA strand breaking. Ifosfamide is used in the treatment of patients with lymphomas, sarcomas, and testicular and ovarian cancers. Cyclophosphamide is commonly used in lymphomas, leukemias, and breast cancer. Nephrotoxicity can present as AKI from ATN, proximal tubular dysfunction with Fanconi syndrome, RTA types 1 and 2, and nephrogenic diabetes insipidus (DI). Risk factors for nephrotoxicity include the concomitant use of platinum salts, pre-existing kidney disease, nephrectomy, and renal irradiation. Nephrotoxicity is commonly dose dependent, but there have been reports of it being sporadic [4, 33]. Both syndrome of inappropriate antidiuretic hormone (SIADH) and nephrogenic DI have been reported with cyclophosphamide. Nephrotoxicity resulting from these alkylating agents can be managed with drug discontinuation, adequate hydration, and electrolyte repletion. Lastly, ifosfamide and cyclophosphamide can cause hemorrhagic cystitis from accumulation of the toxic metabolite acrolein that triggers an intense inflammatory reaction. Mesna inactivates acrolein and has been used in the

prevention of hemorrhagic cystitis in conjunction with aggressive hydration and forced diuresis in patients receiving high-dose cyclophosphamide or ifosfamide.

Nitrosoureas

Nitrosoureas are alkylating agents that deactivate a variety of reductases leading to inhibition of DNA synthesis [34]. Carmustine (BiCNU), streptozotocin, and lomustine (CCNU) belong to this group and are used for treatment of gliomas, central nervous system tumors, lymphomas, and melanoma. It is also administered prior to bone marrow stem cell transplant. These agents result in nephrotoxicity by causing direct proximal tubular cell injury, chronic interstitial nephritis, and AKI. Hypotension also occurs during carmustine infusion and can lead to renal hypoperfusion. Nephrotoxicity usually manifests 2–3 weeks after drug administration but can also be delayed presenting months to years after the drug has been discontinued. Forced diuresis during infusion can prevent nephrotoxicity [35]. Infusion-related hypotension can be addressed with slower infusion rates, administration of vasopressors, and holding antihypertensive medications prior to infusion [4].

Gemcitabine and Mitomycin C

Gemcitabine is a pyrimidine antimetabolite that inhibits the ribonucleotide reductase and DNA polymerase. It is used for pancreatic cancer, bladder cancer, and NSCLC. Mitomycin C (MMC) is an antibiotic that acts as an alkylating agent and is used in some gastrointestinal cancers. Nephrotoxicity for these agents is in the form of TMA with hemolytic anemia, thrombocytopenia, and AKI. Gemcitabine-induced TMA is rare, with a reported incidence of 0.015–0.4% [36–38]. Immune and non-immune mechanisms are proposed but are not well understood. The development of TMA seems to be dependent on the cumulative dose received. It can have a delayed presentation occurring 3–18 months after drug discontinuation [37]. Clinical presentation can be similar to HUS or thrombotic thrombocytopenic purpura (TTP) with more prominent neurologic symptoms. New-onset or worsening hypertension was found to precede the diagnosis of TMA [36]. Discontinuation of the medication is recommended when TMA develops. Plasmapheresis has been used in some case reports [39].

Targeted Therapy

Vascular Endothelial Growth Factor (VEGF) Inhibitors

VEGF functions as the main growth factor that controls angiogenesis by binding to VEGF receptors with tyrosine kinase activity on the vascular endothelium. The US Food and Drug Association (FDA) has approved several VEGF inhibitors including

monoclonal antibodies against VEGF (bevacizumab) or its receptor (ramucirumab). Tyrosine kinase inhibitors (TKI) are small molecules that block the intracellular domain of the VEGF receptor. Compared to the monoclonal antibodies, TKIs (sunitinib, sorafenib, pazopanib) have the advantage of oral bioavailability but are less specific and may inhibit other tyrosine kinase receptors. Aflibercept is another VEGF inhibitor that works by acting as a decoy receptor trapping VEGF before it binds to its endothelial receptor. VEGF inhibitors are used in renal cell cancer and a variety of other solid tumors. The monoclonal antibodies are used in cervical, ovarian, breast, and colorectal cancer. TKIs have been used in hepatocellular, thyroid, and small cell lung cancer (SCLC).

In the kidney, VEGF is important to maintain podocyte and endothelial function which explain the nephrotoxicity associated with VEGF inhibitors. Proteinuria has been reported in 21–64% of patients receiving VEGF inhibitors, and nephrotic syndrome can occur in 1–2% of patients [4, 40]. Minimal change disease (MCD), focal segmental sclerosis (FSGS), and even proliferative glomerulonephritis have been reported in kidney biopsies of patients treated with VEGF inhibitors [40–44]. TMA is a feared complication of VEGF inhibitors and results from endothelial injury. The incidence of TMA with VEGF inhibitor therapy is unknown, and the development of TMA warrants drug discontinuation. TKIs have also been associated with acute and chronic interstitial nephritis, hypophosphatemia, and nephrogenic DI [20, 45]. Renal effects of VEGF inhibitors manifest around 6 months after initiating therapy [44]. AKI is often reversible with drug discontinuation, while proteinuria often decreases but may be persistent [45].

Hypertension (HTN) develops in around 13–40% of patients treated with VEGF inhibitors and is dose dependent [41, 43]. It is thought to develop due to the downregulation of nitric oxide production and impaired natriuresis. The development of HTN actually correlates with better response to anticancer treatment and does not warrant drug discontinuation [26, 41]. ACEIs or angiotensin receptor blockers (ARBs) are reasonable choices for blood pressure control, especially in the setting of concomitant proteinuria [45]. However, there are no recommendations on the preferred antihypertensive agent for patients with VEGF inhibitor-induced HTN.

BRAF Inhibitors

B-raf proteins are involved in signal transmission for cell growth via the MAPK pathway [20]. BRAF inhibitors like vemurafenib and dabrafenib have been approved for the treatment of advanced melanoma with BRAF mutations. Various renal toxicities have been reported in patients treated with BRAF inhibitors, ranging from AKI, metabolic derangements (hypokalemia, hyponatremia, hypophosphatemia) [41], acute tubulointerstitial nephritis (AIN), podocytopaties, and granulomatous formation in the glomeruli. A decline in eGFR can occur within 2 months of initiation of therapy [20].

Anaplastic Lymphoma Kinase (ALK) Inhibitors

Anaplastic lymphoma kinase (ALK) is found in various tumors like Hodgkin's lymphoma, NSCLC, and rhabdomyosarcoma and is the target of ALK inhibitors like crizotinib. In a study of 38 patients with NSCLC treated with crizotinib, Brosnan et al. reported a decline in eGFR by 24% from baseline around 2 weeks after treatment [46]. It is unclear whether the decline in eGFR is due to true AKI or is a result of decreased creatinine secretion by the proximal tubule, as both have been described in the literature. A small decline in eGFR does not usually warrant discontinuation of therapy, but careful monitoring of renal function is recommended when this happens. Renal cyst progression has also been documented with crizotinib therapy, but malignant transformation has not been reported [41].

Proteasome Inhibitors

Proteasome inhibitors exert their antitumor effect by impairing proteasome function leading to accumulation of abnormal proteins within cancer cells. Bortezomib and carfilzomib are used in multiple myeloma and have both been associated rarely with TMA, AIN, and AKI [41]. Carfilzomib has also been associated with podocytopathy and a tumor lysis-like syndrome.

Immunotherapy

Immune Checkpoint Inhibitors (ICPI)

T cells have specific surface receptors that when bound to ligands on antigen-presenting cells result in a downregulation of the immune response [47]. These "checkpoints" promote tolerance and survival of certain cancers. Immune checkpoint inhibitors (ICPI) are monoclonal antibodies that bind to these receptors or their ligands, allowing the immune system to go "unchecked" to start attacking cancer cells. Two receptors have been identified, cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) and programmed cell death protein 1 (PD1). Ipilimumab is a monoclonal antibody against CTLA4 and has been approved for the treatment of metastatic melanoma and renal cell cancer [48]. Nivolumab and pembrolizumab are antibodies against PD1 and have been approved in many types of cancer, although they are mainly used for melanoma, NSCLC, head and neck cancer, colon cancer with microsatellite instability, triple negative breast cancer, and renal cell cancer. Cemiplimab is another PD1 inhibitor that has been approved for cutaneous squamous cell cancer. Atezolizumab, durvalumab, and avelumab inhibit the ligand of PD1 (PD-L1) and are now the first line for urothelial cell cancer due to prolonged overall and progression-free survival [48]. The former two are also approved for

NSCLC. Since ICPIs exert its anticancer effect through a form of "autoimmunity," immune-related adverse events (irAE) have been described with ICPIs involving the skin, gastrointestinal tract, endocrine system, and, less commonly, kidneys.

AKI has been reported to occur in 3–17% of patients treated with an ICPI [48, 49]. ICPI-associated AKI (ICPI-AKI) is not clearly defined in literature. It is suspected in the setting of an increase in serum creatinine (usually ≥50% from baseline) with ICPI therapy and in the absence of an alternative etiology. ICPI-AKI is more probable if it occurs concomitantly or following an irAE, sterile pyuria, and/or eosinophilia. In a study of 138 patients with ICPI-AKI, AKI occurred with an irAE in 43% of cases. Rash was the most common irAE associated with ICPI-AKI [50]. Development of AKI occurs around 3.5 months after initiation of ICPI, but has been reported to occur even after a year of an extrarenal irAE [51].

The pathophysiology of ICPI-AKI is still unknown. One hypothesis is that the tubules act as a target of self-reactive T cells, resulting in AIN which is commonly seen on renal biopsies of patients with ICPI-AKI. Another hypothesis is that exposure to certain drugs (acting as direct triggers or as haptens) result in T-cell priming and subsequent ATIN. Prior or concomitant use of proton pump inhibitors (PPIs) has been documented in the majority of patients with ICPI-AKI [49, 50]. Some hypothesize that PPI exposure results in sensitization, although PPIs by itself are known to cause ATIN in the general population. Other risk factors for developing ICPI-AKI include combination therapy with an anti-CTLA4 and an anti-PD-1/PD-L1 agent and a lower baseline eGFR. There is no defining feature that characterizes ICPI-AKI. As mentioned, it can present with sterile pyuria, eosinophilia, and sub-nephrotic range proteinuria similar to ATIN from other etiologies [50].

The National Comprehensive Cancer Network recommends considering a kidney biopsy only for those with a threefold rise in serum creatinine [51]. Some authors advocate for a more lenient approach to performing biopsies even in milder forms of AKI and prior to empiric treatment with corticosteroids if ATIN is suspected, especially in the absence of contraindications to doing a biopsy [48]. Kidney biopsies should also be performed when alternative diagnoses like glomerulonephritis are being considered. Retrospective studies reported the efficacy of steroids in reversing ICPI-AKI. In a study of 138 patients with ICPI-AKI, 85% achieved either complete or partial renal recovery with corticosteroid therapy [50]. Although there are no controlled trials supporting a particular steroid regimen, a dose of 1 mg/kg of prednisone can be considered as a starting dose. Pulse methylprednisolone can be considered for more severe AKI. The use of other immunosuppressive agents like mycophenolic acid and cyclophosphamide has been reported, but data is too sparse to draw any conclusions on their efficacy [48].

Since ICPIs have resulted in improved overall survival for certain cancers, the decision to re-challenge patients who have developed ICPI-AKI is important. The American Society of Clinical Oncology recommends against restarting ICPI in patients who developed severe AKI described as a serum creatinine >3× or >4.0 mg/dL of baseline or a need for dialysis [52]. However, the risk of kidney injury should be carefully weighed against the benefit of a potentially life-saving therapy, and the decision should be individualized. About a quarter of patients who are re-challenged will have a recurrence of AKI [50].

Another unique issue arising from ICPIs is among solid organ transplant (SOT) recipients, including kidney recipients. SOT recipients have a higher risk of cancer compared to the general population due to immunosuppression. Among recipients who develop cancers sensitive to ICPIs, the use of these agents raises the possibility of triggering an episode of rejection as it boosts the immune response. Case reports of rejection after ICPIs have been published, but due to the absence of larger series, it has been difficult to establish a strong association due to confounding factors [53]. For instance, a diagnosis of cancer in a transplant recipient would likely entail a reduction in immunosuppression, which by itself can account for episodes of rejection.

Chimeric Antigen Receptor T-Cell (CAR-T) Therapy

CAR-T therapy is a form of adoptive cell transfer and has been approved by the US FDA for certain cancers in 2017. It involves harvesting a patient's own T cells and bioengineering them to produce surface receptors (chimeric antigen receptors) which attach to a specific tumor antigen (e.g., CD19 on B cells). These CAR-T cells are expanded ex vivo and then infused back into the patient resulting in antitumor activity. CAR-T therapy is approved for children and adults with relapsed and refractory acute lymphoblastic leukemia (tisagenlecleucel) and more recently for large B-cell lymphoma (axicabtagene ciloleucel and tisagenlecleucel). CAR-T is also being studied for a variety of solid tumors.

Immune-mediated nephrotoxicity has been reported with CAR-T therapy. Cytokine release syndrome results in a systemic inflammatory response from a surge in cytokines produced by the CAR-T cells themselves or activated native immune cells. Cytokine release syndrome was observed in >40% of patients receiving CAR-T therapy and may present with fever, shock, cardiac, neurologic symptoms, and AKI [54]. The mechanism of AKI is prerenal due to systemic vasodilation and/or acute tubular injury from renal hypoperfusion. Cardiorenal syndrome can also occur in the setting of cardiovascular compromise. A rise in serum creatinine can be observed 7–10 days after CAR-T infusion. The management of cytokine release syndrome is mainly supportive, but anti-cytokine therapies such as IL6 receptor antagonist tocilizumab and steroids have also been used [55]. Hemophagocytic lymphohistiocytosis and tumor lysis syndrome have also been documented with CAR-T therapy and are also associated with AKI. CAR-T therapy is also associated with electrolyte abnormalities like hypokalemia, hyponatremia, and hypophosphatemia.

Radiation Nephropathy

Radiation is part of the definitive therapy for certain cancers like testicular cancer, lymphomas, or sarcoma. Total body irradiation (TBI) is also performed as part of conditioning prior to hematopoietic stem cell transplantation (TBI-HSCT). Ionizing

radiation results in disruption of chemical bonds and production of oxygen radical species that cause injury to DNA and killing cancer cells. During radiation for abdominal, pelvic, or retroperitoneal tumors or during TBI, the kidneys are commonly exposed to ionizing radiation due to their location. A total dose of 23 Gy of photon irradiation to both kidneys is considered the threshold dose that can result to radiation nephropathy [56]. For patients who undergo radiation prior to HSCT, a single dose of 10 Gy can cause kidney injury. Some proposed mechanisms for radiation nephropathy include oxidative stress, increased production of fibrosis transforming growth factor B, vascular injury, and activation of the renin-angiotensin system (RAS) [57]. "Acute" radiation nephropathy actually presents around 6–12 months after irradiation with various symptoms like headaches, dyspnea, fatigue, edema, and malignant hypertension. It can also present with hemolytic uremic syndrome (HUS) or TMA. Proteinuria may be present but is commonly in the non-nephrotic range. Chronic radiation nephropathy can be primary, with the initial presentation occurring ≥18 months after irradiation, or secondary, resulting from an episode of acute radiation nephropathy progressing to CKD. The management of radiation nephropathy is mostly supportive. RAS blockers are a reasonable option for hypertensive patients with proteinuria, although there are no controlled trials proving their benefit. Prevention of radiation injury includes the use of protective shields to limit the volume of the kidneys exposed and fractionated dosing allowing for recovery between treatments.

Hematopoietic Stem Cell Transplantation (HSCT)

The number of patients who undergo hematopoietic stem cell transplantation (HSCT) has continued to increase, and long-term follow-up is available. Most data on outcomes of HSCT are obtained from pediatric populations. AKI and CKD are common complications of HSCT and affect anywhere from 10% to 70% of recipients [57]. AKI is more common in patients who undergo allogenic HSCT compared to autologous transplant (50% vs 10%) [58]. Mechanisms of kidney injury unique to HSCT include graft-versus-host disease (GVHD), hepatic sinusoidal obstruction from veno-occlusive disease/sinusoidal obstruction syndrome (SOS), and calcineurin inhibitor (CNI)-associated nephrotoxicity. GVHD causes injury to the skin, gastrointestinal tract, liver, and kidneys due to an inflammatory cascade leading to activation of cytotoxic T cells. SOS results from injury to the sinusoidal endothelial cells due to conditioning therapy. This results in acute portal hypertension leading to AKI due to decreased renal perfusion and tubular injury. Meanwhile, CNI nephrotoxicity is caused by renal arteriolar vasoconstriction and ischemic injury. TMA can also occur in the setting of both GVHD and CNI use. The use of TBI as conditioning therapy also contributes to the AKI observed after HSCT. AKI develops in up to 70% of patients who undergo myeloablative therapy prior to allogenic HSCT [57]. GVHD can present with nephrotic-range proteinuria, but other glomerulopathies should still be considered. MCD, membranous nephropathy,

membranoproliferative glomerulonephritis (MPGN), FSGS, and IgA nephropathy have all been describe after HSCT and can only be diagnosed by kidney biopsy. Among those who require dialysis for AKI, mortality rates range from 55% to 100% [59, 60].

Around 15% of patients who undergo HSCT will develop CKD [57]. The presence of pre-existing CKD has previously excluded patients from receiving an HSCT. However, this has changed over the years with more patients with CKD undergoing HSCT, especially in the setting of multiple myeloma. It is therefore expected that the prevalence of CKD after HSCT will only increase further in the future. The management of CKD after HSCT should be similar to any patient with CKD and proteinuria. Blood pressure control with a RAS blocker is preferred. Consideration should be given to stopping or switching from CNIs to an alternative immunosuppressive agent to prevent further kidney injury. The true incidence of ESRD after HSCT is unknown but is associated with poor outcomes as compared to ESRD from other causes [61].

Cancer-Related Kidney Disease

Paraprotein-Related Kidney Disease

Classification of Paraprotein-Related Diseases

Monoclonal plasma cell disorders result from an abnormal proliferation of a clone of plasma cells producing excessive amounts of paraproteins which may be immunoglobulins (IgG, IgA, IgD, IgE, and IgM) and/or its components (κ or λ light chains). The range of monoclonal disorders includes premalignant diseases such as monoclonal gammopathy of undetermined significance (MGUS), monoclonal gammopathy of renal significance (MGRS), and smoldering multiple myeloma to defined malignancies such as multiple myeloma (MM), Waldenström macroglobulinemia, or chronic lymphocytic leukemia (CLL). MGUS represents a plasma cell monoclonal gammopathy with a small amount of the paraprotein, specifically a serum monoclonal immunoglobulin <30 g/l and <10% monoclonal bone marrow plasma cells with no end organ damage. Multiple myeloma has a higher burden of either paraprotein or end organ damage, and this damage will prompt treatment. For example, active MM is defined after the paraprotein causes end organ damage mainly represented by hypercalcemia, anemia, renal disease characterized by cast nephropathy, and/or bone disease with lytic lesions. Smoldering MM requires a serum monoclonal immunoglobulin levels >30 g/l or >10% monoclonal bone marrow plasma cells without evidence of end organ damage. In 2012, the International Kidney and Monoclonal Gammopathy Research Group (IKMG) introduced the term MGRS after increased recognition of renal disease in patients with a low burden monoclonal gammopathy. Despite the small amount of circulating protein and the fact that there are no other organs involved, the monoclonal gammopathy is

associated with monoclonal renal deposits demonstrated by immunofluorescence, and the presentation is different than myeloma kidney or cast nephropathy. Currently, MGRS is defined by a B-cell or plasma cell lymphoproliferative disease with a kidney lesion related to the monoclonal gammopathy but does not cause any other organ damage and does not otherwise meet hematological criteria for specific therapy [62]. Most of the renal diseases associated with monoclonal immunoglobulins will present as deposits of monoclonal immunoglobulin in a specific part of the glomeruli with the exception of C3 glomerulopathy and TMA that do not present with deposits.

Clinical and Histological Manifestations of Renal Involvement in Plasma Cell Dyscrasias

A wide range of renal manifestations can occur with plasma cell disorders. As previously mentioned, renal manifestations of plasma cell dyscrasias can be classified according to paraprotein-dependent and paraprotein-independent mechanisms. Sepsis, hypercalcemia, volume depletion, contrast-induced nephropathy, tumor lysis, and medication toxicity (e.g., bisphosphonates) can occur, and they are independent of the monoclonal protein burden. The most common paraprotein-related kidney diseases are cast nephropathy, monoclonal immunoglobulin deposition disease (MIDD), and light chain amyloidosis (AL) and account for 75% of paraprotein-related kidney disease [63]. Other renal presentations include different glomerulonephritis (membranoproliferative, diffuse proliferative, crescentic, cryoglobulinemia, IgA, minimal change, or membranous glomerulopathy), tubulointerstitial nephritis, immunotactoid and fibrillary glomerulopathy, and TMA.

Renal injury in MGRS results from deposition of paraproteins in the tubular and glomerular basement membranes. The IKMG group generally divides MGRS into diseases with organized or non-organized deposits on histology. The organized deposits can also be classified as fibrillary (immunoglobulin-related amyloidosis and monoclonal and fibrillary glomerulonephritis), microtubular (immunotactoid and cryoglobulinemic glomerulonephritis), or inclusion or crystalline deposits. The non-organized deposits include MIDD (including light chain deposition disease [LCDD] or heavy chain deposition disease [HCDD] or a combination of both) and proliferative glomerulonephritis with monoclonal immunoglobulin deposits. As mentioned, MGRS can also present without monoclonal immunoglobulin deposits as C3 glomerulopathy with monoclonal gammopathy and thrombotic microangiopathy [62].

Patients with active multiple myeloma and renal involvement frequently have acute kidney injury, but other clinical presentations such as different degrees of proteinuria including nephrotic syndrome, nephritic syndrome, rapidly progressive glomerulonephritis, and progressive CKD can also be seen. In contrast, renal involvement in MGRS tends to be more subtle, presenting as urinary abnormalities and mild CKD [64].

Multiple Myeloma

Of all the monoclonal gammopathies, multiple myeloma (MM) requires a specific mention due to its frequency and its common association with kidney disease. MM accounts for 10% of all hematologic malignancies [65]. It is incurable and is characterized by treatment-responsive disease followed by relapsed and refractory disease in its treatment course. MM accounts for 20% of deaths from hematologic malignancies. Renal dysfunction from cast nephropathy is considered the only renal myeloma-defining event and can be used to make the diagnosis of MM in addition to the hematologic criteria. Around 50% of the patients with MM present with renal dysfunction at time of diagnosis with about 25% presenting with a serum creatinine greater than 2 mg/dl and 2–10% even requiring dialysis at presentation [66, 67]. Renal failure in the context of MM is one of the strongest predictors of poor outcomes [68]. As a myeloma-defining event, renal dysfunction is defined as an eGFR <40 ml/min per 1.73 m^2 and a definitive or presumptive diagnosis of cast nephropathy [69]. Cast nephropathy, historically known as myeloma kidney, results from tubular injury from the excessive amounts of filtered free light chains (FLC). In the distal tubules, FLCs bind with Tamm-Horsfall protein resulting in cast formation and intratubular obstruction. This can occur abruptly with rapid development of oliguria. In the proximal tubule, filtered FLCs are reabsorbed via endocytosis and can cause direct proximal tubular injury from the accumulation and degradation of FLCs. Tubulointerstitial fibrosis can result from distal tubule rupture and the release of pro-inflammatory substances with proximal tubular injury [70]. Different paraproteins have different affinity to Tamm-Horsfall proteins resulting in varying degrees in their ability to cause nephrotoxicity. Light chain myeloma accounts for 40–50% of severe cast nephropathy. Volume depletion and markedly elevated levels of serum and urinary FLC are associated with increased risk of renal dysfunction. The proteinuria in MM is composed of Bence-Jones proteins and is not detected by urine dipstick, which detects urinary albumin. Spot or 24-hour urine protein collection can be sent to measure proteinuria in MM. When significant albuminuria is present, paraprotein-related glomerular involvement from MIDD or AL amyloidosis should be considered.

Evaluation of Suspected Monoclonal Gammopathy

Serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP) are used to identify monoclonal proteins. They are inexpensive tests but have poor sensitivity in detecting serum FLC and may not always differentiate between polyclonal from monoclonal proteins. Urine electrophoresis provides differentiation between the urine albumin and urine paraprotein excretion which helps with diagnosing, prognosticating, and monitoring of response to therapy. Immunofixation (IF) is now routinely done and has better sensitivity in identifying the monoclonal protein involved. Since it is a qualitative test, it cannot be used to monitor

progression or partial response to treatment. The FLC immunoassay has recently been made available and has better precision in detecting FLC. It is used to determine the amount of serum free or unbound λ and κ chains. It is also used to determine the κ:λ free light chain ratio. In kidney dysfunction from other etiologies or in systemic inflammatory conditions, serum FLCs may be elevated, but the κ:λ is mainly preserved. The reference range of κ:λ is normally 0.2–1.65. The range can increase to 0.34–3.10 in patients with significant renal disease such as CKD stage 5 or in hemodialysis patients. In paraprotein diseases, κ:λ will be abnormal, and the absolute value of the involved light chain will be markedly elevated to around 100–200× of the reference range, usually >1000 mg/l. In the clinics, FLC immunoassays should be used to complement but not replace SPEP with IF. Due to the ease of performing serum assays and the rapid results of the newer FLC immunoassays, it may be reasonable to forgo performing a kidney biopsy to diagnose paraprotein-related kidney disease in certain clinical settings. The risk of under-diagnosis of a condition that can be treated versus the risk of the kidney biopsy procedure should be balanced in every patient. Kidney biopsy should, however, be pursued if an alternative diagnosis is being entertained, especially if it may alter treatment in a patient with preserved eGFR. A kidney biopsy would also be the only way to definitively diagnose or differentiate the different kinds of MGRS. It is important to note that these patients may have relatively large kidneys in the setting of paraprotein deposition, and kidney size on ultrasound may not always be a reliable indicator of the chronicity of renal dysfunction. To determine monoclonality on the kidney deposits, immunofluorescence staining for κ, λ light chains, as well as IgG subclasses should be performed.

Treatment of Monoclonal Gammopathies with Renal Involvement

Treatment of patients with paraprotein-related kidney disease is composed of supportive care and treatment directed against the underlying malignancy or clonal cell involved. For cast nephropathy, volume expansion with intravenous crystalloids will decrease the concentration of FLC in the tubules and result in increased tubular flow to flush them out. Forced diuresis with loop diuretics may increase precipitation and is not recommended. Initiation of dexamethasone with chemotherapy should be done immediately to rapidly reduce the burden of FLC in MM. Plasmapheresis does not provide benefit due to the large volume of distribution of light chains, and hemodialysis using high cutoff dialyzers remains controversial. Definitive treatment of MM includes chemotherapy with regimens that include bortezomib and daratumumab and autologous stem cell transplant for those who are eligible for it. These can be performed even for patients with renal failure. Definitive treatment for MGRS will depend on the type of clonal cell identified producing the immunoglobulin. In general, patients with a lesser degree of renal dysfunction at presentation, lower urinary light chain excretion, and hypercalcemia are more likely to have reversible renal dysfunction. With the discovery of effective chemotherapeutic agents, up to 80% of patients with MM will have renal recovery

when early reduction in FLC levels is achieved [70]. Response to treatment and improvement in renal function are associated with better overall clinical outcomes in MM.

Leukemia and Lymphoma

Kidney infiltration by leukemia and lymphoma cells is typically asymptomatic and may be suspected when enlarged kidneys are seen on imagining in conjunction with a diagnosis of leukemia and lymphoma. In a review of autopsy findings of several case series, the incidence of infiltrative renal disease with lymphoma ranged from 18% to 61% [71]. Renal injury results from a variety of mechanisms, including tubular compression from infiltrating cells, lysozyme overproduction, ATN, and intrarenal leukostasis. Treatment is directed against the underlying malignancy.

Paraneoplastic Glomerular Disease

A variety of glomerular diseases have been associated with different cancers and are hypothesized to result from a paraneoplastic process. Substances like growth factors, cytokines, or hormones are secreted by cancer cells resulting in an impaired immune response and glomerulonephritis (GN). Paraneoplastic GN thus occurs in the absence of direct tumor invasion. The diagnosis of paraneoplastic GN is difficult to establish, especially since renal manifestations can predate or present years after the diagnosis of cancer. The diagnosis is only truly established if renal manifestations resolve with control of the cancer and recur with cancer recurrence. Detection of tumor antigens or antitumor antibodies in immune deposits on renal biopsy will also support the diagnosis of paraneoplastic GN. Many patients are asymptomatic from their cancer at the time of renal diagnosis, and this frequently predates their cancer diagnosis, emphasizing the need for a high index of suspicion and a thorough cancer workup in the appropriate context.

Membranous nephropathy (MN) is the most common glomerular pathology associated with cancer. In a series of 240 biopsy-proven MN, the largest to date, around 10% of patients had a diagnosis of cancer [72]. MN has been reported in a wide range of cancers including solid tumors like lung, colon, prostate, gastric, breast, and renal cancer as well as hematologic malignancies like AML and CML. Proteinuria can predate the diagnosis of cancer, commonly by a year, but can be delayed by up to 10 years after renal biopsy. The likelihood of MN being secondary to cancer increases with age >65 years and >20 pack per day smoking history. Unlike primary MN, antibodies against PLA_2R are usually absent in paraneoplastic MN, and IgG1 and IgG2 immune deposits are more prominent. MCD is commonly associated with Hodgkin's lymphoma and has also been described in lung, colon, and renal cancer. VEGF is hypothesized to be one factor that may be contributing to

the development of MCD with certain cancers due to its ability to increase renal glomerular permeability [73]. MPGN, IgA nephropathy, FSGS, and rapidly progressive GN have all been described associated with cancer. Treatment of paraneoplastic GN is focused on treating the underlying malignancy. It is important, however, to remember that primary and other secondary GNs may coexist with paraneoplastic GNs which may require separate therapy.

Urinary Tract Obstruction

Urinary obstruction can occur from urologic (bladder or prostate) or non-urologic cancers that cause compression or invasion of the urinary tract. Hydronephrosis is usually seen on renal ultrasound, although patients with retroperitoneal tumors or fibrosis causing ureteral obstruction may need more invasive testing. Malignant dissemination to three or more sites, severe hydronephrosis, and a low serum albumin (<3 mg/dl) were factors associated with lower survival among patients requiring urinary diversion. The predicted 6-month survival of patients with 2–3 of these risk factors was only 2% compared to 70% in patients with none [74]. The reported median survival after urinary diversion was around 3–6 months, and around 40–50% will experience complications related to the diversion [75]. In general, overall survival of patients with malignant ureteral obstruction is poor, without even accounting for the severity of post-renal AKI. Close communication between the medical team and urology is necessary.

Renal Cell Carcinoma

The incidence of renal cell carcinoma (RCC) has been increasing through the years and accounts for around 4% of new cases of cancer and 2% of all cancer deaths [1]. The increase may be due to improved detection as half of the cases are diagnosed as incidental findings on imaging. The majority of patients with RCC are asymptomatic with less than 10% of patients reporting the classic triad of hematuria, flank pain, and a palpable abdominal mass. RCC can be associated with production of erythropoietin and parathyroid-related protein and can result in erythrocytosis and hypercalcemia, respectively. Contrast-enhanced CT scan (CECT) and MRI have better sensitivity to detecting malignant lesions as compared to regular ultrasound. Contrast-enhanced ultrasound (CEUS) has the advantage of not using iodinated contrast, which may benefit patients with moderate to severe CKD. A recent meta-analysis reported that CEUS was at the least equally sensitive to CECT in the diagnosis of renal masses [76]. The Bosniak classification categorizes renal cystic masses according to their likelihood of being malignant. Features suggestive of malignancy include heterogeneity, thick and irregular septations and borders, and contrast-enhancing nodules. Larger tumors have a higher chance of being malignant

especially if >7 cm [77]. Those that are indeterminate (Class III) or presumed to be malignant (Class IV) require surgical exploration. Historically, clinicians have shied away from pursuing biopsy of renal masses due to fear of percutaneous seeding and bleeding complications. More recently, biopsy has been increasingly performed especially in cases that with inconclusive imaging findings or in high-risk surgical candidates.

The 5-year survival of patients with localized RCC is around 80–90% [78]. Trends in surgical management have changed through the years. Nephron-sparing surgery or partial nephrectomy is now preferred for masses <7 cm and result in a slower decline in eGFR during long-term monitoring. Radical nephrectomy is reserved for masses >7 cm and/or with signs of local invasion. Radiofrequency ablation and cryosurgery are options for small localized masses less than 4 cm and for those who are high-risk surgical candidates. Around 20% of patients present with metastasis, and the 5-year survival for those with distant metastasis is around 12%. ICPI and VEGF inhibitors are now the preferred agents for adjunctive therapy for those with advanced or metastatic RCC.

CKD, ESRD, and Cancer

The epidemiological interaction of CKD, ESRD, and cancer is complex. CKD and ESRD carry a higher risk of developing cancer [79]. CKD and ESRD on dialysis are associated with a higher incidence of lip, thyroid, renal cell, and urinary tract cancers. ESRD patients who received a transplant are at a higher risk of immune-mediated or infection-associated cancers like lymphomas. Even more interesting, incident dialysis by itself carries a worse 5-year survival than common cancers like breast, prostate, and colorectal cancer. Meanwhile, for patients with existing cancer, cancer-related mortality is higher in patients with ESRD [78]. Despite this, there is a paucity of data on safety and efficacy of anticancer therapy in patients with reduced renal function as up to 75% of ongoing clinical trials in cancer exclude patients with reduced renal function [4]. This conundrum poses a challenge to the clinician in terms of the cost-effectiveness of cancer surveillance, diagnosis, and treatment of cancers in advanced CKD or ESRD.

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