Kidney and Neoplastic Disease: Overview with a Particular Interest to Interpretation of Cancer Biomarkers

12

Giuseppe Coppolino, Mariadelina Simeoni, Laura Rivoli, Chiara Summaria, and Davide Bolignano

Contents

Key Facts of Renal Disease Subsequent to Neoplasia 250
Key Facts of Neoplasia Risk in Renal Patients 251
Key Facts of Neoplasia Risk in Renal Patients 251
Definitions 251
Introduction 252
Renal Disease Associated with Malignancies 252
Malignancy Associated with Renal Disease 254
Breast Cancer 255
Colorectal Cancer 256
Women-Specific Tumoral Diseases: Cervical Cancer and Ovary Cancer 256
Lung Cancer 257
Liver Cancer 257
Prostate Cancer 258
Tumors of the Urinary Tract: Kidney, Ureters, and Bladder 259
Markers of Cancer and Renal Function 259
Conclusions 262
Summary Points 264
References 265

G. Coppolino (✉)
Nephrology and Dialysis Unit, University Hospital of Catanzaro, Catanzaro, Italy
e-mail: gcoppolino@hotmail.it

M. Simeoni • L. Rivoli • C. Summaria
Nephrology and Dialysis Unit, University Hospital of Catanzaro, Catanzaro, Italy
e-mail: adelina_simeoni@yahoo.it; rivoli.laura@gmail.com; chiara.summaria@hotmail.com

D. Bolignano
CNR – Institute of Clinical Physiology, Reggio Calabria, Italy
e-mail: davide.bolignano@gmail.com

V.B. Patel, V.R. Preedy (eds.), *Biomarkers in Kidney Disease*, Biomarkers in Disease: Methods, Discoveries and Applications, DOI 10.1007/978-94-007-7699-9_13

Abstract

Tumor markers represent useful tools in diagnosis and clinical management of patients with cancer, because they are easy to use, minimally invasive, and easily measured either by blood or urine. Unfortunately, such an ideal marker, as yet, does not exist. Different pathological states may increase the level of a tumor marker in the absence of any neoplasia, or alternatively during these conditions, not every subject with cancer has abnormally high levels of the tumor marker usually associated with that neoplasia. We aimed at reviewing study literature examining the association between tumor markers and different renal impairment conditions. Each tumor marker was found to be differently influenced by these criteria; additionally, we revealed in many cases a lacking of available published data.

Keywords

Tumor markers • Chronic renal failure • Renal impairment • Hemodialysis • Transplant

Abbreviations

ADPKD	Autosomal dominant polycystic kidney disease
AFP	Alpha-fetoprotein
ARF	Acute renal failure
Beta-hCG	Beta-human chorionic gonadotropin
CAPD	Continuous ambulatory peritoneal dialysis
CEA	Carcinoembryonic antigen
CKD	Chronic kidney disease
CRF	Chronic renal failure
ESRD	End-stage renal disease
NSAIDs	Nonsteroidal anti-inflammatory drugs
NSE	Neuron-specific enolase
PSA	Prostate-specific antigen
PTH	Parathyroid hormone

Key Facts of Renal Disease Subsequent to Neoplasia

- Renal impairment of different origin and severity occurs in patients affected by a neoplasia.
- It could be caused by a prerenal volume depletion, for example, due to the vomiting and diarrhea associated with chemotherapy.
- It may be originated by a postrenal compression to excretory system but also by multiple intrarenal causes of kidney function impairment, including glomerular, tubulointerstitial, and vascular diseases.

Key Facts of Neoplasia Risk in Renal Patients

- Patients in different stages of chronic kidney disease, but in particular in renal failure requiring substitutive therapy with hemodialysis or peritoneal dialysis, have an increased risk.
- Probably as a result of the accumulation of uremic toxins, patients in chronic renal failure are in immunosuppressed state and more prone to translate into an increased incidence of cancer.
- In renal transplant patients, the risk is furtherly increased by immunosuppression therapy.

Key Facts of Neoplasia Risk in Renal Patients

- Elevated levels of several tumor markers can be frequently detected in patients with impaired kidney function because their renal elimination is retarded.
- In other cases, neoplasia is really present, given the higher risk of developing malignancies in these patients.
- During renal replacement therapy by hemodialysis or peritoneal dialysis, tumor markers could result even lower because of removal by the dialysis procedure.
- Consequently, while cancer screening and surveillance are important in this population, the possibility of false-positive results notably reduces the diagnostic value of those markers that are mainly eliminated by renal excretion.

Definitions

Chronic kidney disease (CKD) A pathological condition characterized by a reduced renal function with consequent alterations in fluid regulation, blood pressure control, waste product elimination, and metabolic alterations. CKD may progress, more or less rapidly, to end stages.

End-stage renal disease (ESRD) The final stage of CKD, also known as terminal uremia. Residual renal function is not anymore sufficient to control the body homeostasis so that patients need to start in due course chronic hemodialysis treatment or be transplanted.

Hemodialysis (HD) Chronic or acute therapy for replacing renal function. ESKD patients usually undergo chronic hemodialysis thrice a week. Each HD session lasts 3.5–4 h. During the HD session, fluid and electrolyte excess and waste products are removed from the blood circulation.

Peritoneal dialysis (PD) Alternative technique to hemodialysis consisting in using the patient's own peritoneal membrane as an exchange surface for balancing fluid, electrolyte, and waste homeostasis. The peritoneal cavity is accessed via a

permanent catheter placed in the patient's abdomen that is linked to an external machine. Exchanges are induced and regulated according to diffusion and convection principles by fluid bags with established content.

Introduction

Cancer biomarkers are useful tools for cancer diagnosis and clinical management of neoplastic patients. Additionally, their determination involves mini-invasivity for the patient and simple lab procedures. Although reference ranges have been developed for the correct interpretation of cancer biomarkers, kidney function often represent a confounder, due to several different aspects influencing renal load and clearance in the course of neoplasia. In fact, renal involvement is a frequent event associated with cancer. By contrast, a preexisting renal impairment represents an independent-risk factor for cancer development. Finally, in the presence of all cause of renal function decline, cancer markers raise without a clinical meaning (Coppolino et al. 2014). In the following paragraphs discussed in detail are all these issues, with particular attention to the interpretation of cancer markers as diagnostic and prognostic lab parameters influenced by the renal function.

Renal Disease Associated with Malignancies

The occurrence of renal failure is an additional morbidity and mortality risk factor in the course of neoplasia (Lameire et al. 2005). Renal involvement occurs as consequence of the neoplasia or due to the nephrotoxicity of antitumoral drugs (Table 1). Acute renal failure (ARF) is the most frequent renal complication induced by chemotherapeutic treatment occurring in 12–49 % of terminal cancer patients. Although a preexisting renal impairment might influence the outcome, it is estimated that 9–32 % of ARF cancer patients need hemodialysis showing a high mortality rate (72–85 %) (Darmon et al. 2006). Chronic renal failure (CRF) accompanied with clinical appearance of nephrotic syndrome or isolated proteinuria or tubulopathy is another frequent renal complication associated with cancer and its treatment (Humphreys et al. 2005). More often than in noncancer-associated CRF, electrolyte disorders occur. Hypercalcemia is mainly due to local osteolysis but can also depend on the ectopic production of PTH-like peptides and/or calcitriol (Stewart 2005). Sodium homeostasis is often altered for several reasons such as paraneoplastic antidiuretic hormone inappropriate secretion, gastrointestinal losses, and/or diabetes insipidus. Kalemia and magnesemia abnormalities might occur due to associated ARF or to electrolyte loss in the renal tubule or in the gastrointestinal tract. A milder presentation of renal involvement is common in oncohematologic diseases, showing trend to reversibility after treatment suspension and/or disease remission (Manning et al. 1996).

The tumor lysis syndrome is another remarkable cause of renal impairment. The syndrome is determined by metabolic abnormalities such as hyperuricemia,

Table 1 Causes of renal failure in cancer patients

Prerenal
Extracellular fluid depletion (vomiting, diarrhea, and hyperkalemia)
Hepatorenal syndrome (VOD and hepatic resection)
Drugs (calcineurin inhibitors and NSAIDs)
Renal
Glomerular membranous nephropathy amyloidosis (MM)
Pamidronate-associated glomerulopathy (incidence unknown) LCDD
Acute tubulointerstitial necrosis (toxic/ischemic)
Lymphomatous renal infiltration
LCDD
Drug (cisplatin and ifosfamide) endovenous contrast media
Cast nephropathy (MM)
Vascular thrombotic thrombocytopenic purpura/hemolytic uremic syndrome
Tumor infiltration (renal cell carcinoma with renal vein thrombosis)
Postrenal
Intratubular obstruction uric acid nephropathy Methotrexate
Cast nephropathy (MM) extrarenal obstruction
Ureteral diseases (primary diseases and retroperitoneal lymphadenopathies)
Retroperitoneal fibrosis

LCDD light-chain deposition disease, *MM* multiple myeloma

hyperkalemia, hypocalcemia, hyperphosphatemia, and renal failure related to rapid tumoral cell lysis due to apoptosis or chemotherapy.

With regard to pathophysiological mechanisms determining renal involvement in the course of neoplastic disease, it is practical and useful to look for obstructive, parenchymal, or prerenal *primum movens* for a correct diagnosis and treatment modulation. In more than half cases, vomiting or/and diarrhea related to antineoplastic treatment, especially if not balanced by appropriate liquid intake due to ureteral obstruction or to renal hypoperfusion, induce renal damage. The evidence of acute postrenal failure due to bilateral obstruction in patients not diagnosed for cancer and in the absence of lithiasis has to be highly suspected for a neoplastic obstructive cause (Rosad et al. 2014). The obstruction can affect any urinary segment, even in the absence of hydronephrosis, and can depend on extrinsic mechanical obstructive causes (retroperitoneal lymphadenopathy, metastases of urogynecological cancers) (Wong et al. 2007) or on *ab intrinseco* blockage to urinary flow. As for intrinsic obstruction, regardless of the cause (tubular deposit of urate or calcium phosphate crystals in high-turnover cancers; direct crystallization of methotrexate), the general indication is to maintain an adequate urine output, evaluating the administration of urate-lowering therapy and urinary alkalizing agents, aimed at implementing renal damage prophylaxis (Kjellstrand et al. 1974; Thomas and Chisholm 1973; Buemi et al. 2009).

Renal parenchymal damage occurs with a variable frequency (6–60 %) in cancer patients. Microangiopathy, disseminated intravascular coagulation, tumoral infiltration of the renal tissue, and tumor lysis are typical causes of parenchymal kidney

impairment strictly dependent on tumoral disease. Also, severe forms of acute leukemia or lymphoma induce parenchymal impairment when able to infiltrate both kidneys causing a nephromegaly without hydronephrosis, renal function loss, and/or urinary abnormalities (Simsek et al. 2003). Solid tumors infrequently infiltrate or metastasize the kidney. However, primary lung, breast, and stomach tumors are described for metastasizing the kidney (Wagle et al. 1975). Another interesting modality for renal damage classification in neoplastic patients is based on determining the nephron portion primarily affected. Glomerular paraneoplastic syndromes are generally due to the intraglomerular deposition of amyloid or neoplastic antigens. In most cases, a secondary membranous glomerulonephritis can be detected, representing 9 % of all biopsies diagnostic for glomerulonephritis. Therefore, the finding of a membranous glomerulonephritis could be a "spy" for occult malignancy in adults and should be followed by neoplastic screening, especially looking for lung and gastrointestinal cancer (Birkeland and Storm 2003; Burstein et al. 1993). Beside cancer-related parenchymal causes, the chemotherapeutic agents' nephrotoxicity is a major factor for renal involvement in the course of cancer. In fact, antitumoral drugs, such as bisphosphonates and mitomycin C, can induce a specific glomerular damage. Pamidronate at high-dose infusion commonly induces collapsing focal and segmental glomerulosclerosis (Perazella and Markowitz 2008), while treatment of solid tumors with mitomycin C significantly correlates with thrombotic microangiopathy occurrence (Antman et al. 1979). Tubulointerstitial nephropathy secondary to cancer is a common example of tubular involvement mainly depending on cisplatin and ifosfamide effects on proximal tubule and being potentially age dependent (Kintzel 2001). A well-established correlation between neoplasia and tubulointerstitial damage is also described for multiple myeloma with remarkable prevalence (20 %). Moreover, renal involvement in the course of multiple myeloma has to be considered as a marker of disease severity and predictor of mortality (Blade et al. 1998). Although multiple myeloma represents 1 % of all-type cancers, end-stage renal disease (ESRD) secondary to multiple myeloma has accounted for 58 % of all cases of cancer-related kidney damage between 1997 and 2001. The renal deposition of monoclonal light chains in the course of multiple myeloma induces three different mechanisms of renal damage, depending on amyloidosis, light-chain deposition disease, or cast nephropathy (2003; Tang et al. 1989).

Malignancy Associated with Renal Disease

Development of cardiovascular and infectious complications is the main contributor for high mortality in patients with renal failure. However, the occurrence of cancer remains a major concerning comorbidity factor increasing mortality rate in both ARF and CRF. Several data suggest a role for CRF as an independent-risk factor for cancer development, with high incidence rates (Vajdic et al. 2006; Wong et al. 2009). According to the Michigan Kidney Registry collected between 1973 and 1984, prostate cancer, renal cell carcinoma, and cervical carcinoma are the most common tumoral diseases occurring in CRF patients (Arican et al. 1999). Even neoplasms arising in other organs such as the liver, thyroid, and tongue resulted more frequently

in CRF patients than in the general population. Among oncohematologic diseases, multiple myeloma and non-Hodgkin lymphoma are the most commonly associated with CRF, especially in patients with glomerulonephritis. Bladder transitional cancer has also being found associated with nonsteroidal anti-inflammatory drug (NSAID) nephropathy (Maisonneuve et al. 1999). Not surprisingly, a different geographical distribution has been found for kidney and urinary tract tumors. Kidney cancers are more common in Europe, Australia, and New Zealand, while urinary tract cancers show prevalence peaks in Taiwan and in the Balkan nephropathy-endemic area, mostly affecting females and localizing in the upper urinary tract (Wang et al. 2014). ESRD patients undergoing renal replacement treatment are considered at high-risk population for developing cancer with an overall standardized cancer incidence of 1:18. Moreover, cancer incidence in ESRD patients appears age correlated showing prevalence three times higher in over 65-year-old patients compared to younger patients. Dialysis age is an additional risk factor for cancer-related mortality with highest incidence of neoplasm occurrence after 3 years of dialytic treatment (Collins et al. 2003). A specific tumoral disease associated with kidney transplant is Kaposi sarcoma. Kidney transplant together with glomerulonephritis treated with immunosuppressants is a condition at higher risk than renal insufficiency alone for cancer development. Latrogenic influence by immunosuppressant agents in fact adds the impairment of DNA repair mechanisms and alterations of immunosurveillance processes, to the accumulation of carcinogenic agents and the reduced antioxidant response due to the renal impairment (Kooman et al. 2014; Heidland et al. 2000; Wang et al. 2014). Another renal disease showing an increased risk for neoplastic transformation is the autosomal dominant polycystic kidney disease (ADPKD) due to the tendence to malignant evolution of renal cysts. An additional factor predisposing to cancer in ADPKD is represented by long-term abuse of NSAIDs as painkillers, which contributes to metaplasia occurrence in the bladder (Stewart et al. 2003).

Breast Cancer

Breast cancer is the most common cancer in the world, although females are prevalently affected. In 2008, more than one million of cases of breast cancer were diagnosed, with a higher incidence in industrialized areas (North America, Australia, New Zealand, Northwest Europe, South Asia, and sub-Saharan Africa), confirming the influence of environmental risk factors in cancer pathogenesis (Parkin et al. 2005; Kajbaf et al. 2002). The prevalence of breast cancer in women with CRF is comparable to the general population. However, life expectancy is reduced due to the comorbidity influence on death rate. It remains valid the recommendation for annual mammography screening after menopause with anticipation in women over 40 years old on hemodialysis treatment and waiting for kidney transplantation (Holley and Von Roenn 2010). However, mammography is more difficult to interpret in these patients because of the interference of vascular calcifications (Castellanos et al. 2006; Siegel et al. 2013). Breast cancer biomarkers, CA 15-3, CA 27.29, and CEA, cannot be used for diagnostic purpose in renal patients due to the tendence to

accumulation. However, they could find space as recurrence markers in the follow-up. Other tissutal markers, particularly estrogen and progesterone receptors, were identified as prognostic indices for predicting tumor aggressiveness and response to treatment.

Colorectal Cancer

Colorectal cancer is the second tumor most diagnosed in women and the third in men. However, men are more affected than women in absolute. In recent years, a trend to reduction of prevalence and incidence has been registered, probably due to screening programs and improved therapy efficacy. However, in 2008 over one million of incident cases and over 600,000 deaths for colorectal cancer were reported with variable geographical distribution (Jemal et al. 2011, 2013). According to general data, colorectal cancer has a higher incidence in kidney transplant recipients, overlapping that of 60-year-old subjects that are reported to have the highest risk for colorectal cancer. Hence, the current recommendation is for starting antineoplastic screening in all 40-year-old kidney transplant recipients or, regardless of anagraphic age, at 5-year after transplant (Park et al. 2010). Patients on chronic hemodialysis have also a greater risk for developing colorectal cancer. However, reliability of fecal occult blood for determining eventual indication for colonoscopy is limited in this population due to the high frequency of gastritis and gastrointestinal telangiectasias (Ajam et al. 1990). On the other hand, not even cancer markers are reliable tools for diagnosing colorectal cancer in both general population and patients with renal failure. CEA and CA 19-9, in fact, result altered in the advanced tumoral disease, limiting their usefulness to the follow-up. Moreover, CA 19-9 specificity is low, being shared as a marker also by pancreatic cancer.

Women-Specific Tumoral Diseases: Cervical Cancer and Ovary Cancer

The uterine cervical cancer is the third most common cancer in sexually active women, because it is closely related to HPV infection. Being considered a sexually transmitted disease, about 85 % of new cases occur in developing countries. The squamous cell variant has a higher prevalence compared to adenocarcinoma. In the United States, 12,360 new cases were reported in 2014, accounting for an estimation of 4,020 cancer-related deaths, the equivalent of about 1.5 % of cancer deaths in women (Siegel et al. 2014; Jemal et al. 2011). Screening for uterine cervical cancer is entrusted to cervical cytology and to the HPV DNA individuation. Controversial is the utility of the HPV vaccination aimed at protecting women from the high-risk viral genotypes responsible for 70 % of uterine cervical cancer (Ault 2006). In CKD patients and in hemodialysis patients waiting for a renal transplant, HPV vaccination has not yet a strong indication. However, in over 21-year-old renal transplant candidates, a strong recommendation applies to annual Pap test and HPV DNA assay (Kajbaf et al. 2002). The second most common gynecological neoplasia is

ovarian cancer, although it belongs to the group of rare cancers. In industrialized countries, it is estimated that ovarian cancer incidence is equivalent to 9,4 new cases per 100,000, and mortality rate reaches 5.1 related deaths per 100,000. Furthermore, it is consistent that the risk for ovarian cancer development increases with age. The epithelial variant of ovarian cancer is the most common accounting for 95 % of cases. The most specific marker for epithelial ovarian cancer is CA 125, although CA 72-4, CEA, and LASA-P are other less-specific but useful markers for such variant. The germ cell variant of ovarian cancer is more sporadic and correlates with the increase of human chorionic gonadotropin (hCG) and AFP. However, regardless of the variant, the diagnosis of ovarian cancer is often tardive due to its radiological escape, and not so rarely, the diagnosis is based on the exploratory surgery (Siegel et al. 2013). However, the use of the high-specific markers hCG and AFP appears useful not only in the follow-up but also in the diagnosis of the germ cell variant, while CA 125 is validated only for the follow-up of the epithelial variant of ovarian cancer.

Lung Cancer

The lung cancer is the leading cause of death for cancer in men and the second in women with a variable incidence not only by gender but also with respect to the geographical area and the smoking cigarette habit (Parsons et al. 2010). It is remarkable that most data on lung cancer come from industrialized countries, where industrial fumes and environmental pollution could play a major role. A previous renal impairment does not appear as a significant risk factor for lung cancer, while renal complications due to chemotherapy are very common. Apart from carcinoembryonic antigen (CEA) in ongoing non-small cell lung cancer and neuron-specific enolase (NSE) in small-cell lung cancer in patients with intact renal function, lab markers show low specificity and sensibility in early detecting lung cancer. On the contrary, tomography screening is recognized to be effective and reliable and, thus, is recommended in all cigarette smokers with more than 30 years of exposure (Boiselle 2013).

Liver Cancer

Liver cancer is another leading form of neoplastic disease with different incidence within men and women. Liver cancer is fifth neoplastic disease diagnosed in men and the second leading cause of death for cancer. Instead, in women, it represents the seventh carcinoma for prevalence and the sixth causing death for cancer. The estimated incidence in the United States in 2010 was six cases per 100,000 in adults and 0.05 cases per 100,000 in children (El-Serag and Kanwal 2014). Because of his aggressiveness, the incidence of liver cancer virtually coincides with the associated mortality rate. Chronic HBV or HCV infection is the major causal determinant of hepatocellular carcinoma (Perz et al. 2006; Allan et al. 2014). The cornerstone of

liver cancer screening and follow-up, especially in patients with cirrhosis and/or hepatitis, is alpha-fetoprotein (AFP). However, the routinary use of AFP as screening has been found more useful in Asia, where there is a greater spread of liver cancer.

Prostate Cancer

Prostate cancer is the most common neoplasm in men and in patients with CKD (Port et al. 1989). Overall, prostate cancer is the most diagnosed within visceral cancers with a report in the United States of 200,000 new cases and 30,000 related deaths in 2014. On this basis, all American men show an estimated risk for developing prostate cancer of 16 % and a risk for prostate cancer-related mortality of 2.9 % (Siegel et al. 2014). Consequently, prostate cancer is the leading cause of cancer-related death in men after nonmelanoma skin cancer and lung cancer. Furthermore, epidemiological data tend to underestimate the magnitude of the problem. In fact, slow-progressor patients can remain clinically silent, and prostate cancer is often found incidentally at autopsy (Dorr et al. 1993). The 5-year prognosis for prostate cancer is strongly influenced by the timing of the diagnosis, being very favorable in the case of local extension of the cancer and extremely poor for metastatic tumors. In the past, the obsolete prostatic acid phosphatase was the only available prostate cancer marker but showed very low sensitivity. Since 1990, prostate-specific antigen (PSA) has been validated as the cornerstone marker in the diagnosis and follow-up of prostate cancer. In 1992, in fact the ability of PSA in early detecting the tumor resulted in a peak of prostate cancer diagnosis mainly at a localized stage. However, PSA in rare variants of prostate cancer (e.g., small-cell neuroendocrine tumor) is not affected and could represent a confounder delaying the diagnosis. Instead, the most reliable cancer marker for these atypical prostate tumors is chromogranin A. These are tumors responsive to hormone therapy, which profit instead of chemotherapy. Their diagnosis may be delayed only by the observation of the PSA or, on the contrary, confirmed by an alteration in the levels of chromogranin A. PSA appears also as a very useful tool in the assessment of the response to treatment or relapse. An increase of PSA after prostatectomy is a sign of relapse of the disease. A different behavior is observed after radiotherapy. PSA values, in fact, undergo a drastic reduction after treatment with a gradual return to normal levels within a few years, and the recovery is identified only with a further PSA increase exceeding the standard range. Unfortunately, PSA levels are influenced by the renal function; therefore, its use as routinary screening is controversial in CKD patients. A cost-benefit balance should be assessed between the trend to overdiagnosis leading to improper prostate biopsies and the recognized advantage deriving from an early detection of prostate cancer (Smith et al. 2001; Khairullah et al. 2004). However, the utility of PSA as routinary screening is more consolidated in kidney transplant and in young patients undergoing dialysis, although in these patients cannot be considered as a marker of tumor aggressiveness and extension (Joseph et al. 2010).

Tumors of the Urinary Tract: Kidney, Ureters, and Bladder

Renal cell carcinoma affects preferentially male subjects in old age and has a high incidence in the Czech Republic and North America (Siegel et al. 2014). The kidney cancer tends to develop from a renal cyst especially in the context of a hereditary renal cystic disease with a risk about 30 times higher than the general population. In contrast, patients with acquired renal cysts seem to have a risk of neoplastic transformation approximately comparable to the general population (6 %) (Brennan et al. 1991; Truong et al. 1995). Also, in patients with a cystic hereditary disease, the tumor assumes clinical characteristics that differ from sporadic renal tumors, having a multicentric and bilateral localization multicentric with a sarcomatoid aspect (Keith et al. 1994). Upper urinary tract cancer and CKD appear bidirectionally related probably due to the action of some oncogenic nephrotoxins, such as aristolochic acids and analgesics. These cancerogenic agents not only increase the risk for cancer development but also are responsible for chronic interstitial nephritis, accounting for renal failure occurrence in 80 % of cases with progression to ESRD in 10 % of patients. Hematuria is the main clinical symptom of urinary tract cancer; however, its onset in patients on hemodialysis cannot be considered as highly significant due to additional causes of hematuria such as intradialytic heparinization. Furthermore, urinary cytology and cystoscopy, especially in anuric patients, show low sensitivity and require the integration with imaging for the diagnosis definition. In specific geographical areas in Asia (China and Taiwan), the prevalence of CKD in patients with upper urinary tract carcinoma exceeds 55 %, and a strong correlation has been reported with all age, aristolochic acid nephropathy and previous nephroureterectomy. Moreover, Hung et al. demonstrated a linear correlation between the prevalence of cancer and CKD severity, being prevalence increased up to 55 % and 71 % in CKD stages 4 and 5, respectively. Such correlation was found stronger in female patients being on chronic hemodialysis treatment or undergone renal transplantation (Wang et al. 2014). Bladder cancer is the fifth most common of cancer in the United States, and 13,000 related deaths are reported annually. Standard detection methods for bladder cancer diagnosis include urine cytology and cystoscopy. Only an early detection of bladder cancer leads to a favorable prognosis, while cytology and cystoscopy are generally performed at advanced stages of the disease. Specific urinary cancer markers such as bladder tumor antigen (BTA) and nuclear matrix protein-22 (NMP22) increase the accuracy of detection of bladder cancer when coupled with cystoscopy. In addition, BTA and NMP22, used alone, are useful for addressing instrumental control timing during the follow-up (Grossman et al. 2005).

Markers of Cancer and Renal Function

Among different hormones, metabolites, immunoglobulins, and antigens recognized as markers of neoplasia, the majority consists of relatively high molecular weight glycoproteins (3,400–5,000 kD) undergoing renal and/or liver metabolism. Their use

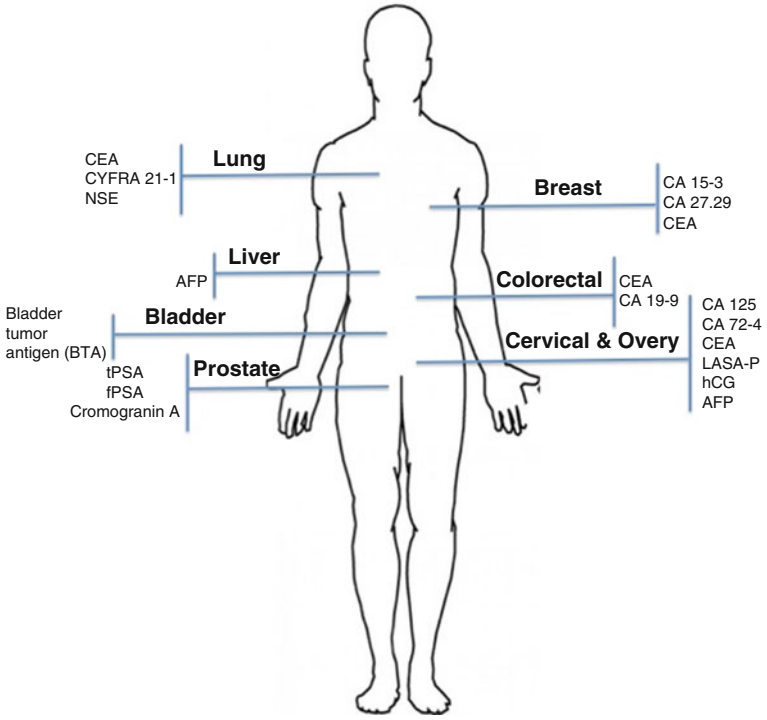

Fig. 1 Representation of main tumor markers on body

in screening for cancer the general population is progressively decreasing due to a poor sensitivity and specificity (Fig. 1). Furthermore, if a renal impairment is present at cancer biomarker determination, their predictive validity and specificity are even more limited due to kinetics alterations (Tzitzikos et al. 2010). Therefore, CRF should be considered as a nonneoplastic disease responsible for altering tumor marker blood concentration. Although the span of error in cancer biomarker determination according to various stages of renal failure has not been quantified, it is notorious that the specificity of some markers and renal failure stage are inversely correlated (Xiaofang et al. 2007). Consequently, cancer biomarker use could result in misleading the diagnostic process or the follow-up if a renal impairment coexists. As consequence, tumor markers should be classified as stable or unstable with respect to renal function. However, many unstable tumor markers tend to restabilize with dialysis, and a relative reduction of their concentration compared to pre-dialysis values should not be interpreted as an improvement of the neoplastic disease (Arik et al. 1996). Among the different variables influencing cancer, biomarker dosing should be considered the pro-inflammatory state associated with CRF, which could influence many biomarker levels. Furthermore, other than CFR, renal diseases can alter the interpretation of tumor markers: proteinuria affects metabolism and excretion of those protein structured; nephrolithiasis can trigger the production of certain

Table 2 Chemical structure and biological function of main tumor markers

Tumor marker	Chemical structure	Biological function
CEA	Glycoprotein	Membrane carcinoembryonic antigen
AFP	Glycoprotein	Alpha-fetoprotein
PSA	Protease	Prostate-specific antigen
CA125	Glycoprotein	Carbohydratic antigen (mucins)
CA19.9	Glycoprotein	Carbohydratic antigen (mucins)
CA15.3	Glycoprotein	Carbohydratic antigen (mucins)
CYFRA	Cytokeratin	Tissue polypeptide antigen
β- hCG	Glycoprotein	Hormonal function

ones already produced in small concentrations from normal tissues. Moreover, an analytical variability intrinsic to the dialysis process should be considered when determining cancer biomarkers. In fact, certain markers tend to accumulate or rapidly decrease based on several treatment parameters such as length, type of dialysis, and hemodialysis membrane characteristics (Lye et al. 1994). Cancer biomarkers have different molecular weights, and this represents an additional reason for the variable behavior of certain biomarkers in hemodialysis patients. In deep, cancer markers having a small molecular weight (<5–50 kD) easily undergo dialysis clearance, while those with a higher molecular weight are only partially removed by dialysis processes (Xiaofang et al. 2007; Table 2). The variability further increases with interindividual, demographic characteristics and comorbidity of the population undergoing treatment (Soletormos et al. 1993). It is particularly useful to evaluate for each patient on dialysis the different comorbidities able to cause an increased tumor marker concentration: inflammatory states of bowel or interesting coelomic epithelium tissues (pleura, pericardium, and peritoneum) and liver disease secondary to viral hepatitis B and C (Arican et al. 1999). This may result in false positive and false negative, with a significant reduction of the specificity of each marker. A remarkable example is CEA, a 180-kDa glycoprotein produced exclusively during fetal development, used as a marker of relapse in several malignancies. Because of its molecular weight, CEA is not removed by any dialysis modality (Arican et al. 1999). On the contrary, despite its hepatic metabolism, CEA level is affected by renal clearance (Lye et al. 1994). Moreover, smoking habit, chronic obstructive pulmonary disease, and chronic inflammatory bowel disease tend to increase CEA levels with high possibility of false-positive results. Biomarkers with independent metabolism are also available. AFP, a 65-kDa-oncofetal protein produced by the fetal liver, yolk sac, and adult liver, is considered as a "historical" marker, which is altered in 80 % of hepatomas and in 60 % of germ cell tumors. AFP is used for the management of hepatocarcinoma, liver metastasis, or non-seminoma testicular cancer. Nonetheless, as expressed by multiple tumors, it shows reduced specificity and can rise even in the course of ovarian cancer. A further example of stable cancer biomarker is PSA, a serine protease regulated by androgens and having a molecular weight of 33-kD. Differentiated cells of ductal and alveolar prostatic epithelium provide to PSA physiological secretion. However, PSA level increases at prostate cancer development resulting the main lab parameter useful for screening, diagnosis, risk

stratification, and follow-up of one of the most incident tumors, even in the dialysis population (Lindblom and Liljegren 2000). Unfortunately, several confounding variables can influence PSA, and recent prostatitis, digital prostatic examination, transrectal ultrasound, and colonoscopy should be excluded before PSA dosing for preserving specificity and lowering risk of false-positive results. A recent optimization in PSA lab determination has been introduced. Circulating PSA exists as free or complexed antigen, and both forms are detectable separately with specific laboratory techniques. This advancement allows to distinguish increases in PSA due to benign causes from prostate cancer. In the absence of the malignancy, an increase in total PSA due to diagnostic procedures or benign prostatic hypertrophy can be individualized in the isolated increase of free PSA (fPSA) levels (Robitaille et al. 2006). Thereby, current indication is for referring to fPSA in general population screening. However, in patients with reduced renal clearance, even fPSA has low specificity. Regardless of race and age, in fact, fPSA tends to accumulate with glomerular filtration rate (GFR) reduction. Similarly, in hemodialysis, patient fPSA accuracy is not optimal due to its low molecular weight and high permeability to dialysis filtration membranes (Joseph et al. 2010). A different class of cancer markers is that of carbohydratic antigens CA 19-9, CA 15.3, and CA 125, for which renal function influence on specificity is not clearly determined. CA19-9 belongs to Lewis blood type carbohydratic antigens and has low specificity (70 %) and high sensitivity (90 %) for malignancies of the gastrointestinal tract and pancreas. CA 15.3 is mainly useful in the surveillance of metastatic breast cancer. However, CA 15.3 specificity is affected by the coexistence of HCV infection and pregnancy, although with less interference from renal function (Han et al. 2012). CA 125 is a 90-kD membrane protein ubiquitary expressed in the eye, respiratory tract, and female reproductive epithelium. CA 125 is widely validated for ovarian cancer screening showing high sensitivity but limited specificity. CA 125 levels are in fact influenced by alterations in serous membranes, a condition frequently associated to both chronic hemodialysis and CRF. Although increased, CA 125 remains more stable during conservative phase of CRF and in hemodialysis, while in peritoneal dialysis, it has an oscillating trend. Finally, after renal transplantation, CA125 levels tend to normalization. This behavior, indeed, suggests a strict participation to CA125 metabolism and/or clearance. Moreover, CA 125 is gender specific and is higher in male CRF patients on conservative treatment (Sevinc et al. 2000). As for peritoneal dialysis, it is the particular case where a chronic stimulation on peritoneum induces a specific CA 125 production even in the absence of ovarian cancer. However, the CA 125 level increase stops when peritoneal sclerosis occurs in response to peritoneal dialysis age progression, and an underlying malignancy could be masked (Tables 3 and 4, and Fig. 2).

Conclusions

Among the wide availability of tumor markers, only a few are clinically relevant due to several reasons. Firstly, most cancer biomarkers are considered tumor associated rather than tumor specific. Their diagnostic power is often garbled, and further

Table 3 Summary of main variations of tumor markers levels in CKD, dialysis, and kidney transplantation (Coppolino et al. 2014)

	CKD	Hemodialysis	Peritoneal dialysis	Kidney transplantation
Alpha-fetoprotein (AFP)	=	=	=	=
Beta-2-microglobulin (B2M)	↑	↑	↑	↑
Beta-HCG	↑	↑	–	–
CA 15-3 and CA 27.29	↑	↑*; =*	–	=
CA 125	=	=	↑ In case of peritonitis or PD catheter placement	=
CA 19-9	=*; ↑*	–	–	–
Total tPSA	=	↓	=	–
Free fPSA	↑	↑	–	–
Chromogranin A	↑	↑	–	↑

Legend: = unvaried with respect to patients with normal renal function; ↑ increased;↓ decreased; – no sufficient data; * see text

Table 4 Hemodialysis removal of main tumor markers

Tumor marker	Molecular weight	Hemodialysis removal (cutoff: <5–50 kDa)
CEA	180 kDa	Not removed
AFP	65 kDa	Not removed
PSA	33 kDa	Removed
CA 125	90 kDa	Not removed
CA 19.9	360 kDa	Not removed
CA 15.3	300–400 kDa	Not removed
CYFRA	40 kDa	Removed
β- hCG	40 kDa (19 kDa for b subunit)	Removed

investigations are usually needed to confirm or countermand the diagnosis. Similarly, cancer biomarkers show a limited ability in monitoring the effectiveness of antineoplastic therapies or malignancy recurrence. Another important issue involves the appropriateness of antineoplastic screening in CRF. To correctly approach the problem, a distinction between CRF stages is mandatory. In young CFR patients on conservative treatment having a positive family history or clinical suspicion for malignancy, screening for cancer finds its rationale as in the general population. Conversely, patients on chronic dialysis should not be routinary screened for malignancy, unless they are a candidate for kidney transplantation. It is well established that patients undergoing chronic dialysis have a shortened life expectancy for different reasons, and the advantage in reducing neoplastic related mortality is not

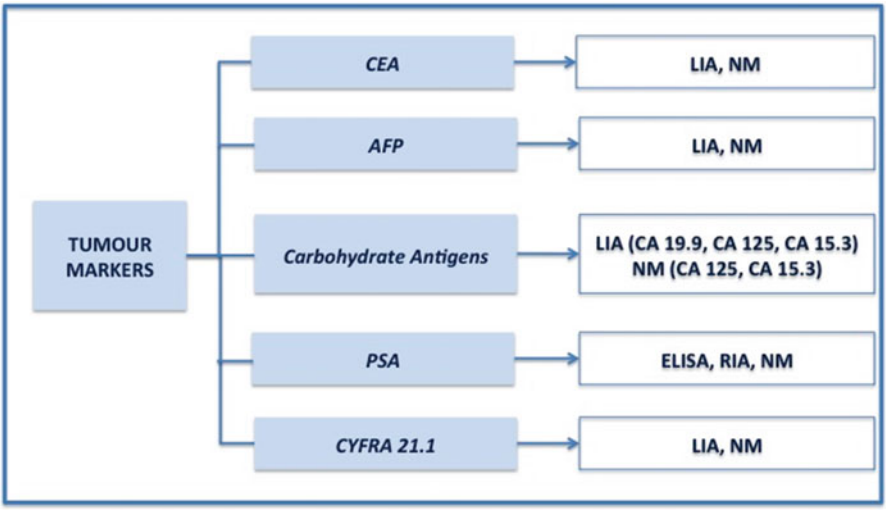

Fig. 2 Method of assay for tumor markers. *LIA* luminescence immunoenzymometric assay, *ELISA* enzyme-linked immunosorbent assay, *RIA* radioimmunoassay, *NM* microarray nanotechnology

relevant (0.2 %) compared to the costs (Kajbaf et al. 2002). Opposite is the case of dialysis patients on the waiting list for kidney transplant, in which, regardless of renal function, it is essential to discover any cancer or precancerous lesion before transplant, as the antirejection therapy may be precipitant. However, in all patients eligible for cancer biomarker screening, the following step consists in the correct interpretation of lab results in consideration of the residual renal function. Accordingly, the most reliable cancer markers are AFP, hCG, and PSA to a certain extent. In fact, compared to CEA and carbohydrates antigens, AFP, hCG, and PSA are not virtually affected by coexisting renal failure or liver infectious diseases or serous membrane diseases. An ideal cancer biomarker should be independent of renal function, stable, sensitive, and specific for achieving the goal of the reliability in the early diagnosis, staging, and monitoring of the neoplastic disease. So far, none of the available cancer biomarkers simultaneously has all these requirements. Hopefully, most advanced research in the future will allow the early detection of cancer and the management of antineoplastic therapy with a simple blood or urine test.

Summary Points

- There is a correlation between renal damage, in its various forms, and neoplastic disease.
- Chronic renal failure predisposes to a higher incidence of cancer than the general population.

- The tumor and/or its treatment can cause kidney damage, both acute and chronic.
- Tumor markers are affected in great part by renal metabolism and, therefore, by alterations of renal function whether preexisting or arisen ex novo.
- AFP is the only reliable tumor marker in case of renal damage.
- The antineoplastic screening in patients with impaired renal function should be individualized to expect life and concomitant risk factors for the development of neoplasia and then interpreted in a critical manner in relation to the behavior of each marker.

References

Ajam M, Ramanujam LS, Gandhi VC, Leehey DJ, Ing TS, Schnell TG, Daugirdas JT. Colon-cancer screening in dialysis patients. Artif Organs. 1990;14:95–7.

Allan BJ, Wang B, Davis JS, Parikh PP, Perez EA, Neville HL, Sola JE. A review of 218 pediatric cases of hepatocellular carcinoma. J Pediatr Surg. 2014;49:166–71. discussion 171.

Antman KH, Skarin AT, Mayer RJ, Hargreaves HK, Canellos GP. Microangiopathic hemolytic anemia and cancer: a review. Medicine (Baltimore). 1979;58:377–84.

Arican A, Ozdemir N, Sezer S, Erten Y, Guz G, Turan M, Inanoglu I, Haberal M. Tumor markers in hemodialysis patients. Transplant Proc. 1999;31:3367–8.

Arik N, Adam B, Akpolat T, Hasil K, Tabak S. Serum tumour markers in renal failure. Int Urol Nephrol. 1996;28:601–4.

Ault KA. Vaccines for the prevention of human papillomavirus and associated gynecologic diseases: a review. Obstet Gynecol Surv. 2006;61:S26–31.

Birkeland SA, Storm HH. Glomerulonephritis and malignancy: a population-based analysis. Kidney Int. 2003;63:716–21.

Blade J, Fernandez-Llama P, Bosch F, Montoliu J, Lens XM, Montoto S, Cases A, Darnell A, Rozman C, Montserrat E. Renal failure in multiple myeloma: presenting features and predictors of outcome in 94 patients from a single institution. Arch Intern Med. 1998;158:1889–93.

Boiselle PM. Computed tomography screening for lung cancer. JAMA. 2013;309:1163–70.

Brennan JF, Stilmant MM, Babayan RK, Siroky MB. Acquired renal cystic disease: implications for the urologist. Br J Urol. 1991;67:342–8.

Buemi M, Fazio MR, Bolignano D, Coppolino G, Donato V, Lacquaniti A, Mondello S, Buemi A, Allegra A. Renal complications in oncohematologic patients. J Invest Med. 2009;57:892–901.

Burstein DM, Korbet SM, Schwartz MM. Membranous glomerulonephritis and malignancy. Am J Kidney Dis. 1993;22:5–10.

Castellanos M, Varma S, Ahern K, Grosso SJ, Buchbinder S, D'Angelo D, Raia C, Kleiner M, Elsayegh S. Increased breast calcifications in women with ESRD on dialysis: implications for breast cancer screening. Am J Kidney Dis. 2006;48:301–6.

Collins AJ, Kasiske B, Herzog C, Chen SC, Everson S, Constantini E, Grimm R, McBean M, Xue J, Chavers B, Matas A, Manning W, Louis T, Pan W, Liu J, Li S, Roberts T, Dalleska F, Snyder J, Ebben J, Frazier E, Sheets D, Johnson R, Li S, Dunning S, Berrini D, Guo H, Solid C, Arko C, Daniels F, Wang X, Forrest B, Gilbertson D, St Peter W, Eggers P, Agodoa L. Excerpts from the United States Renal Data System 2003 Annual Data Report: atlas of end-stage renal disease in the United States. Am J Kidney Dis. 2003;42(A5-7):S1–230.

Coppolino G, Bolignano D, Rivoli L, Mazza G, Presta P, Fuiano G. Tumour markers and kidney function: a systematic review. Biomed Res Int. 2014;2014:647541.

Darmon M, Ciroldi M, Thiery G, Schlemmer B, Azoulay E. Clinical review: specific aspects of acute renal failure in cancer patients. Crit Care. 2006;10:211.

Dorr VJ, Williamson SK, Stephens RL. An evaluation of prostate-specific antigen as a screening test for prostate cancer. Arch Intern Med. 1993;153:2529–37.
El-Serag HB, Kanwal F. Epidemiology of hepatocellular carcinoma in the United States: where are we? Where do we go? Hepatology. 2014;60:1767–75.
Grossman HB, Messing E, Soloway M, Tomera K, Katz G, Berger Y, Shen Y. Detection of bladder cancer using a point-of-care proteomic assay. JAMA. 2005;293:810–6.
Han SN, Lotgerink A, Gziri MM, VAN Calsteren K, Hanssens M, Amant F. Physiologic variations of serum tumor markers in gynecological malignancies during pregnancy: a systematic review. BMC Med. 2012;10:86.
Heidland A, Bahner U, Vamvakas S. Incidence and spectrum of dialysis-associated cancer in three continents. Am J Kidney Dis. 2000;35:347–51. discussion 352–3.
Holley JL, Von Roenn J. Screening for breast cancer in women with CKD stages 4 to 5. Am J Kidney Dis. 2010;56:820–2.
Humphreys BD, Soiffer RJ, Magee CC. Renal failure associated with cancer and its treatment: an update. J Am Soc Nephrol. 2005;16:151–61.
Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61:69–90.
Jemal A, Simard EP, Dorell C, Noone AM, Markowitz LE, Kohler B, Eheman C, Saraiya M, Bandi P, Saslow D, Cronin KA, Watson M, Schiffman M, Henley SJ, Schymura MJ, Anderson RN, Yankey D, Edwards BK. Annual Report to the Nation on the Status of Cancer, 1975–2009, featuring the burden and trends in human papillomavirus(HPV)-associated cancers and HPV vaccination coverage levels. J Natl Cancer Inst. 2013;105:175–201.
Joseph DA, Thompson T, Saraiya M, Werny DM. Association between glomerular filtration rate, free, total, and percent free prostate-specific antigen. Urology. 2010;76:1042–6.
Kajbaf S, Nichol G, Zimmerman D. Cancer screening and life expectancy of Canadian patients with kidney failure. Nephrol Dial Transplant. 2002;17:1786–9.
Keith DS, Torres VE, King BF, Zincki H, Farrow GM. Renal cell carcinoma in autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 1994;4:1661–9.
Khairullah QT, Pamatmat SD, Chatha M, Provenzano R, Telang D, Temple M. Early detection of prostate cancer in the ESRD population. Clin Nephrol. 2004;61:308–15.
Kintzel PE. Anticancer drug-induced kidney disorders. Drug Saf. 2001;24:19–38.
Kjellstrand CM, Cambell 2nd DC, Von Hartitzsch B, Buselmeier TJ. Hyperuricemic acute renal failure. Arch Intern Med. 1974;133:349–59.
Kooman JP, Kotanko P, Schols AM, Shiels PG, Stenvinkel P. Chronic kidney disease and premature ageing. Nat Rev Nephrol. 2014;10:732–42.
Lameire NH, Flombaum CD, Moreau D, Ronco C. Acute renal failure in cancer patients. Ann Med. 2005;37:13–25.
Lindblom A, Liljegren A. Regular review: tumour markers in malignancies. BMJ. 2000;320:424–7.
Lye WC, Tambyah P, Leong SO, Lee EJ. Serum tumor markers in patients on dialysis and kidney transplantation. Adv Perit Dial. 1994;10:109–11.
Maisonneuve P, Agodoa L, Gellert R, Stewart JH, Buccianti G, Lowenfels AB, Wolfe RA, Jones E, Disney AP, Briggs D, Mccredie M, Boyle P. Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. Lancet. 1999;354:93–9.
Manning EC, Belenko MI, Frauenhoffer EE, Ahsan N. Acute renal failure secondary to solid tumor renal metastases: case report and review of the literature. Am J Kidney Dis. 1996;27:284–91.
Park JM, Choi MG, Kim SW, Chung IS, Yang CW, Kim YS, Jung CK, Lee KY, Kang JH. Increased incidence of colorectal malignancies in renal transplant recipients: a case control study. Am J Transplant. 2010;10:2043–50.
Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55:74–108.

Parsons A, Daley A, Begh R, Aveyard P. Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: systematic review of observational studies with meta-analysis. BMJ. 2010;340:b5569.

Perazella MA, Markowitz GS. Bisphosphonate nephrotoxicity. Kidney Int. 2008;74:1385–93.

Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol. 2006;45:529–38.

Port FK, Ragheb NE, Schwartz AG, Hawthorne VM. Neoplasms in dialysis patients: a population-based study. Am J Kidney Dis. 1989;14:119–23.

Robitaille R, Lafrance JP, Leblanc M. Altered laboratory findings associated with end-stage renal disease. Semin Dial. 2006;19:373–80.

Rosad J, Sydor A, Sulowicz W. Outcome of patients with acute kidney injury in the course of neoplastic diseases. Przegl Lek. 2014;71:72–7.

Sevinc A, Buyukberber S, Sari R, Kiroglu Y, Turk HM, Ates M. Elevated serum CA-125 levels in hemodialysis patients with peritoneal, pleural, or pericardial fluids. Gynecol Oncol. 2000;77:254–7.

Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013;63:11–30.

Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014;64:9–29.

Simsek S, Oen AL, Comans EF, V D Hoeven JJ, Zijlstra J. Acute renal failure due to non-Hodgkin lymphoma infiltration of the kidneys detected by ultrasonography and confirmed by positron emission tomography. Clin Nephrol. 2003;59:383–7.

Smith RA, Von Eschenbach AC, Wender R, Levin B, Byers T, Rothenberger D, Brooks D, Creasman W, Cohen C, Runowicz C, Saslow D, Cokkinides V, Eyre H, ACS PROSTATE CANCER ADVISORY COMMITTEE, A. C. S. C. C. A. C. A. C. S. E. C. A. C. American Cancer Society guidelines for the early detection of cancer: update of early detection guidelines for prostate, colorectal, and endometrial cancers. Also: update 2001 – testing for early lung cancer detection. CA Cancer J Clin. 2001;51:38–75. quiz 77–80.

Soletormos G, Schioler V, Nielsen D, Skovsgaard T, Dombernowsky P. Interpretation of results for tumor markers on the basis of analytical imprecision and biological variation. Clin Chem. 1993;39:2077–83.

Stewart AF. Clinical practice. Hypercalcemia associated with cancer. N Engl J Med. 2005;352:373–9.

Stewart JH, Buccianti G, Agodoa L, Gellert R, Mccredie MR, Lowenfels AB, Disney AP, Wolfe RA, Boyle P, Maisonneuve P. Cancers of the kidney and urinary tract in patients on dialysis for end-stage renal disease: analysis of data from the United States, Europe, and Australia and New Zealand. J Am Soc Nephrol. 2003;14:197–207.

Tang AL, Davies DR, Wing AJ. Remission of nephrotic syndrome in amyloidosis associated with a hypernephroma. Clin Nephrol. 1989;32:225–8.

Thomas MH, Chisholm GD. Retroperitoneal fibrosis associated with malignant disease. Br J Cancer. 1973;28:453–8.

Truong LD, Krishnan B, Cao JT, Barrios R, Suki WN. Renal neoplasm in acquired cystic kidney disease. Am J Kidney Dis. 1995;26:1–12.

Tzitzikos G, Saridi M, Filippopoulou T, Makri A, Goulioti A, Stavropoulos T, Stamatiou K. Measurement of tumor markers in chronic hemodialysis patients. Saudi J Kidney Dis Transpl. 2010;21:50–3.

USRDS: the United States Renal Data System. Am J Kidney Dis. 2003;42:1–230.

Vajdic CM, McDonald SP, Mccredie MR, VAN Leeuwen MT, Stewart JH, Law M, Chapman JR, Webster AC, Kaldor JM, Grulich AE. Cancer incidence before and after kidney transplantation. JAMA. 2006;296:2823–31.

Wagle DG, Moore RH, Murphy GP. Secondary carcinomas of the kidney. J Urol. 1975;114:30–2.

Wang LJ, Lee SY, Teh BT, Chuang CK, Nortier J. Upper tract urothelial carcinomas in patients with chronic kidney disease: relationship with diagnostic challenge. Biomed Res Int. 2014;2014:989458.

Wong LM, Cleeve LK, Milner AD, Pitman AG. Malignant ureteral obstruction: outcomes after intervention. Have things changed? J Urol. 2007;178:178–83. discussion 183.

Wong G, Hayen A, Chapman JR, Webster AC, Wang JJ, Mitchell P, Craig JC. Association of CKD and cancer risk in older people. J Am Soc Nephrol. 2009;20:1341–50.

Xiaofang Y, Yue Z, Xialian X, Zhibin Y. Serum tumour markers in patients with chronic kidney disease. Scand J Clin Lab Invest. 2007;67:661–7.