Renal Complications in Solid Tumor Patients Referred to an Onconephrology Clinic: A Three-Year Italian Experience

Articoli originali

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ABSTRACT

Onconephrology represents a burgeoning subspecialty within nephrology, dedicated to ensuring optimal oncological management for cancer patients with pre-existing or cancer-therapy-induced renal impairment. Epidemiological data regarding the early impact of renal function alterations in Italian oncology patients are currently lacking. This study presents a three-year single-center experience from an onconephrology clinic, evaluating patients with solid tumors and renal abnormalities, specifically acute kidney injury (AKI) or proteinuria. A total of 254 patients with solid malignancies were included. Among these, 153 (60.2%) were referred due to AKI, predominantly AKIN stages I-II, with 71 cases (46.4%) attributed to oncological treatment. Notably, antineoplastic therapy was permanently discontinued in only 27 patients (13.1%). The most frequent tumor types were pulmonary (17.5%) and gynecological (17.9%) cancers. Checkpoint inhibitors were the therapies most commonly associated with AKI. During the follow-up period, 83 of the 254 patients (34.5%) died, with 46 (55%) of these having experienced concurrent AKI, suggesting a potential risk for chronic kidney disease development. Among the surviving patients, 71% exhibited a decline in estimated glomerular filtration rate of <30 ml/min. This experience underscores the intricate relationship between cancer therapies and renal function, highlighting the critical need for early and continuous onconephrological assessment in this patient population.

KEYWORDS: onconephrology, AKI, CKD, outcome

Introduction

The increasing average life expectancy in the general population, and particularly the improved survival rates among cancer patients, has led to a greater prevalence of chronic diseases, including kidney disease. This convergence creates a phenotype of multi-morbid and highly vulnerable individuals. Multidisciplinary team care, including the essential role of the onconephrologist in managing renal aspects, is therefore necessitated [1].

The interplay between cancer and the kidney is bidirectional: neoplasms and antineoplastic agents can induce kidney damage, while conversely, patients with chronic kidney disease (CKD) face an elevated risk of developing malignancies and require therapeutic adjustments based on their glomerular filtration rate (GFR) [2].

Cancer patients exhibit an increased susceptibility to acute kidney injury (AKI) [3]. The reported incidence of AKI is 18% at one-year post-diagnosis, rising to 27% at four years. Certain malignancies, especially kidney cancer, liver and metastatic cancer are associated with an even higher AKI risk, reaching 44% within the first year [4]. On average, up to 40% of critically ill patients require renal replacement therapy [5].

Consistent with observations in the general population, a single episode of AKI in oncological patients, even if mild and with apparent renal function recovery, elevates mortality and the risk of developing CKD progressing to end-stage kidney disease (ESKD). This risk is particularly amplified in the presence of pre-existing CKD, age over 65 years, and higher AKI stages [6, 7].

Similar to neoplastic diseases, CKD poses a significant global public health concern, contributing to increased morbidity and mortality, with substantial human, social, and economic burdens [8]. We retrospectively analyzed a three-year experience from our single tertiary onconephrology outpatient service to investigate the impact of cancer-related renal complications.

Material and Methods

This retrospective, single-center, observational cohort study included patients with solid cancers who presented for their first nephrology consultation at the onconephrology outpatient clinic of the Nephrology, Dialysis, and Transplantation Department at the IRCCS Policlinico Sant'Orsola in Bologna between January 2021 and December 2023. Patients with hematological malignancies, those already undergoing renal replacement therapy, and pregnant women were excluded. Follow-up data were collected until June 30, 2024, ensuring a minimum follow-up period of six months for all participants. The primary objectives were:

1. To determine the prevalence and spectrum of renal complications in patients with solid oncological diseases.
2. To identify renal outcomes (AKI, CKD, ESKD) in patients with solid oncological diseases who develop renal complications.
3. To estimate the overall survival of cancer patients who develop renal complications.

The secondary objectives were:

1. To assess the distribution of oncological diseases in patients with secondary renal damage.
2. To evaluate the distribution of oncological therapies in patients with secondary renal damage.
3. To evaluate eGFR decline >30%, and ESKD in cancer patients with renal issues.

AKI was defined according to the AKIN criteria [9].

Clinical and laboratory data were collected at baseline, defined as the period before the initiation of any potential last-line oncological therapy or, for patients not undergoing specific therapy at the time of the first visit, the values preceding the oncological diagnosis. These data were retrieved from the hospital's electronic health record system.

Data were also collected at the time of the first onconephrology visit. The parameters acquired included clinical, demographic, and laboratory characteristics routinely documented in clinical practice. Demographic data included age and sex. Clinical data encompassed major comorbidities recognized as risk factors for kidney disease (diabetes mellitus, hypertension, ischemic cardiovascular disease, urological issues such as previous nephrectomy, presence of nephrostomy, ureteral stents, or neobladder), type of neoplasm, current and prior oncological therapies (chemotherapy, targeted therapy, and/or immunotherapy), use of other medications (RAAS inhibitors, SGLT2 inhibitors, bisphosphonates, NSAIDs, PPIs), ongoing or past radiotherapy, presence of other side effects attributed to oncological therapy, the reason for the first visit (categorized as AKI, proteinuria, nephrotic syndrome, nephrological dispensation, electrolyte disturbances, request for nephrological management, other), and the time in months from the start of the last oncological therapy line (if ongoing at the first visit) or from the oncological diagnosis in untreated patients. Available laboratory data included serum creatinine, spot urine test, 24-hour proteinuria, serum electrolytes, liver enzymes, complement levels and serum cystatin C. For patients with both creatinine and cystatin C values, eGFR calculated using creatinine (eGFRcr), cystatin C (eGFRcys), and a combination of both (eGFRcr-cys) were also obtained using the National Kidney Foundation's automatic calculation, which incorporates age and sex.

Finally, therapeutic decisions made by the oncologist or nephrologist following the onconephrology consultation were recorded, including modifications to oncological therapy (continuation, definitive or temporary discontinuation, dose reduction or frequency adjustment, therapeutic switch, clearance when required), adjunctive steroid therapy, hydration, discontinuation of drugs affecting GFR (RAAS inhibitors or SGLT2 inhibitors), and indication for renal biopsy.

Follow-up data were obtained using the same electronic systems, with the first re-evaluation point at 90 days from the initial referral. At this stage, histological findings from any renal biopsy performed, mortality data, ongoing therapy, the date of the last nephrology follow-up (in months), and the total number of visits were also integrated.

Statistical Analysis

Data analysis was performed using R software (version 4.4.2, R Foundation for Statistical Computing). Continuous variables are presented as mean ± standard deviation (SD) or median and interquartile range (IQR), depending on their distribution. Categorical variables are reported as percentages (%). Univariate logistic regression models were used to estimate the odds of developing the outcome.

Results

From January 2021 to December 2023, 489 patients were evaluated for a first nephrology consultation at the Onconephrology outpatient clinic of Policlinico Sant'Orsola, of whom 254 had a solid tumor. The baseline characteristics of these patients, defined as the characteristics before the initiation of the last oncological therapy line, are presented in Table I.

The mean age at the first visit was 68 ± 13 years, with 134 male participants. Baseline laboratory values showed a mean serum creatinine of 1.18 ± 0.36 mg/dl and a mean eGFR of 62 ± 21.33 ml/min/1.73m². Baseline 24-hour proteinuria data were available for only 26 patients (10.2%), with a median of 237 mg/day (IQR 162-423.75 mg/day). Baseline urine chemical-physical exam data were unavailable for 157 patients. The most prevalent comorbidities were arterial hypertension (66.1%), urological issues (26.1%), cardiovascular disease (23.6%), and diabetes mellitus (20.9%). Regarding pharmacological history, 45.7% of patients were taking RAAS inhibitors, 2% SGLT2 inhibitors, 39% PPIs, and 6.3% bisphosphonates.

	N = 254 patients
Average age, years	68 (±13.16)
Male gender, n (%)	134
Hypertension, n (%)	168 (66.1)
Diabetes mellitus, n (%)	53 (20.9)
Cardiovascular disease, n (%)	60 (23.6)
Previous nephrectomy, n (%)	36 (14.2)
RAASi treatment, n (%)	116 (45.7%)
SGLT2i treatment, n (%)	5 (1.9%)
sCreat, mg/dl	1.18 (±0.36)
GFR, ml/min/1.73 m²	62 (± 21.33)
Uprot, g/day	0.237 (0.162-0.423), N = 26 pts

Table I. Baseline characteristics. Abbreviations: RAASi, Renin Angiotensin Aldosterone System inhibitors; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitors; Creat, serum Creatinine; GFR, Glomerular Filtration Rate; Uprot, Urine protein.

Distribution of neoplasms

The most common solid tumors among the evaluated patients were gynecological (uterus and ovary, n = 45, 17.9%), followed by lung cancer (n = 44, 17.5%), breast cancer (n = 33, 13.1%), gastrointestinal tumors (stomach and colorectal, n = 25, 10%), and urinary tract tumors excluding kidney (n = 21, 8.4%). Kidney cancer and melanoma were both present in 17 patients (6.8%), and bone neoplasms in 15 (6%). Other tumor types were observed in 38 patients (13.5%) (Figure 1).

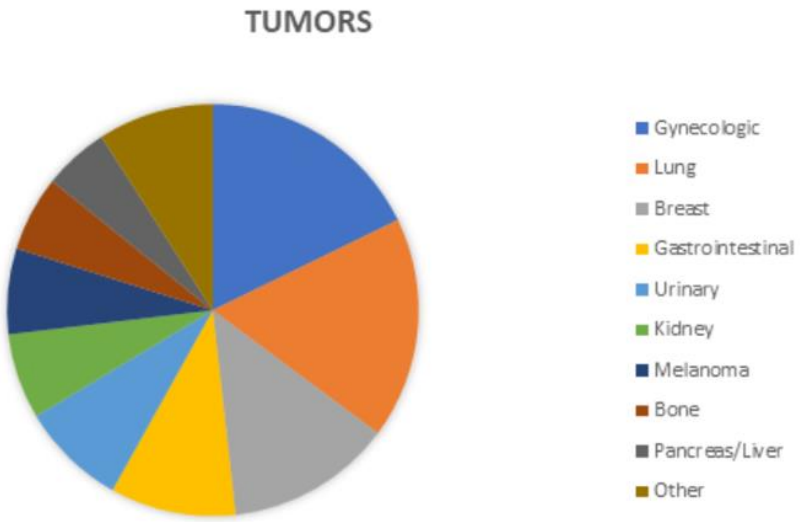

Figure 1. Distribution of neoplasms among patients referred to onconephrology consultation.

Distribution of oncological therapies

Forty-eight patients were not receiving specific oncological treatments. Among the remaining 206 patients, 105 (51%) were on monotherapy, and 101 (49%) were on combination therapy (81 patients on two drugs [39.3%] and 20 patients on three drugs [9]) (Figure 2). One hundred forty-three patients (69.4%) were receiving at least one conventional chemotherapy agent, 70 (33.9%) an immunotherapy drug, 62 (30.1%) a molecularly targeted agent (40 [19] TKIs and 22 [10] anti-VEGF), and 29 (14.1%) hormone therapy. Twenty patients (7.9%) were concurrently undergoing radiation therapy. Among conventional chemotherapy drugs, antimetabolites were used in 61 patients, and alkylating agents in 55 patients, with carboplatin being the most frequent (n = 27, 49.1% of alkylating agents). In the immunotherapy group, pembrolizumab was the most commonly used drug (n = 37, 52.9%), followed by nivolumab (n = 22, 31.4%).

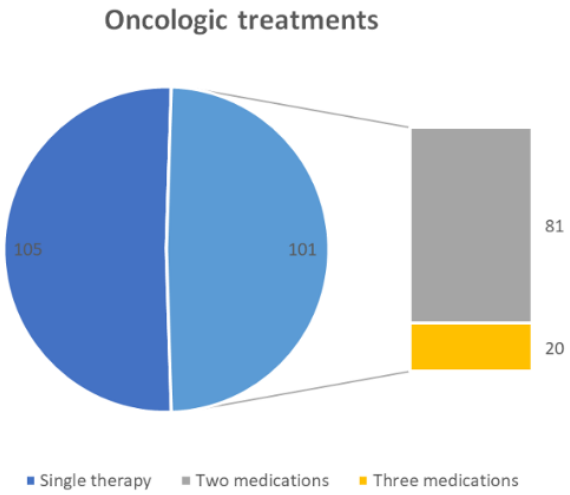

Figure 2. Distribution of oncologic treatments in patients referred to our onconephrology clinic.

First Onconephrology Visit

The primary reason for the first onconephrology referral was AKI in 153 patients (60.2%). The second most common reason (n = 47, 18.5%) was the general management of patients with pre-existing renal issues (45 with pre-existing CKD and 2 with a solitary kidney and normal renal function) (Figure 3). Table II summarized patients' serological characteristics at the first visit.

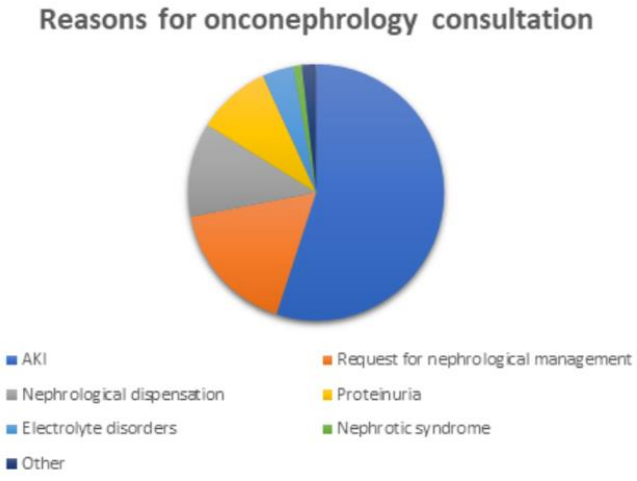

Figure 3. Reasons for first nephrological referral.

	No AKI (N = 101)	AKI (N = 153)	Overall (n = 254 pts)
sCreat, mg/dl	1.47 (0.42)	1.89 (0.57)	1.73 (0.55)
GFR, ml/min/1.73m2	47.78 (18.40)	35.64 (16.59)	40.47 (18.29)
sCys C, mg/dl	2.04 (0.71) n = 15 pts	2.12 (0.71) n = 34 pts	2.09 (0.71) n = 45 pts
CKD EPI Cys, ml/min/1.73m^2	33.47 (15.33) n = 15 pts	33.47 (23.56) n = 34 pts	33.47 (21.21) n = 45 pts
CKD EPI Cr-Cys C, ml/min/1.73m^2	38.47 (14.92) n = 15 pts	35.18 (20.93) n = 34 pts	36.18 (19.19) n = 45 pts

Table II. Laboratory at first onconephrology referral, divided into AKI and no AKI. Abbreviations: sCreat, serum Creatinine; GFR, Glomerular Filtration Rate; sCys C, serum Cystatin C.

Therapeutic Decisions

Among the 206 patients receiving specific oncological therapy, the treatment regimen was not modified in 124 (60.19%), permanently discontinued in 27 (13.10%), temporarily suspended in 26 (12.62%), switched due to renal damage in 24 (11.65%), and the dosage or frequency adjusted in 5 (2.42%). Nephrological dispensation was requested for 35 patients and granted to all but one. Adjunctive steroid therapy was initiated in 49 patients (19.31%), RAAS inhibitor therapy was discontinued in 28 patients (24.14%) and continued in 88 (75.86%), and renal biopsy was performed in 20 patients (7.9%). The predominant histological finding was tubulointerstitial nephritis (TIN) observed in 10 patients (47.21%), followed by thrombotic microangiopathy (TMA) in 4 (19.04%) and acute tubular necrosis (ATN) in 3 (15%). Minor histological changes were observed in 2 patients. Diagnoses also included diabetic nephropathy (DN) in two cases, IgA nephropathy (IgAN) in one, focal segmental glomerulosclerosis (FSGS) in one, and minimal change disease (MCD) in one (Figure 4). Among the 153 patients referred for AKI, the renal damage was likely related to ongoing oncological therapy in 71 (46.4%), while an alternative cause was identified as more probable in the remaining 82 (53.6%). In 34 patients (23.12%), AKI was attributed to prerenal causes; in 15 (10.20%) to obstruction; in 12 (8.12%) it was likely related to previous oncological therapies; in 8 (5.44%) to other nephrotoxic non-oncological drugs; in 2 (1.36%) to infection secondary to pyelonephritis; and in 11 (7.48%) to other possible causes, including neoplasm progression, paraneoplastic syndromes, and vasculometabolic damage related to comorbidities (Figure 5). In patients receiving oncological therapy at the time of the first visit (n = 140), the mean time to renal damage onset was 4.9 months in cases of suspected oncological toxicity and 11.43 months in cases with alternative etiologies. In the subgroup of 71 patients with AKI attributed to pharmacological toxicity, the specific oncological therapy was modified in 54 (76.06%) and continued in 17 (23.94%). Adjunctive steroid therapy was initiated in 10 of these patients. In patients with AKI from other causes (n = 82), therapy was continued in 60 (73.17%) and modified in 22 (26.82%).

Among the 26 patients referred for proteinuria, drug-related toxicity was suspected in 18 (69.23%), while an alternative cause in 8 (30.77%). Among the 18 patients with suspected drug-related proteinuria, 12 were receiving bevacizumab, either alone or in combination. Oncological therapy was continued in 9 (50%) and modified in the remaining.

Forty-six patients were lost to follow-up. Among the remaining 208 patients, the last follow-up occurred after a median of 11 months (range 1-36). At the last follow-up, mean serum creatinine was 1.57 ± 0.8 mg/dl, mean eGFR was 46.82 ± 20.04 ml/min/1.73m², and median proteinuria was 240 mg/day (IQR 110-561.5 mg/day). Seventy-one-point three percent of patients experienced an eGFR decline of <30% after the renal event, while 9.6% had a decline >30%. Five patients progressed to ESKD and required hemodialysis. Eighty-three patients (34.5%) died during follow-up, including 18 with AKI secondary to drug toxicity, 28 with AKI due to other causes, and 37 patients without AKI.

Notably, renal disease was not the primary cause of death in any of these 83 patients.

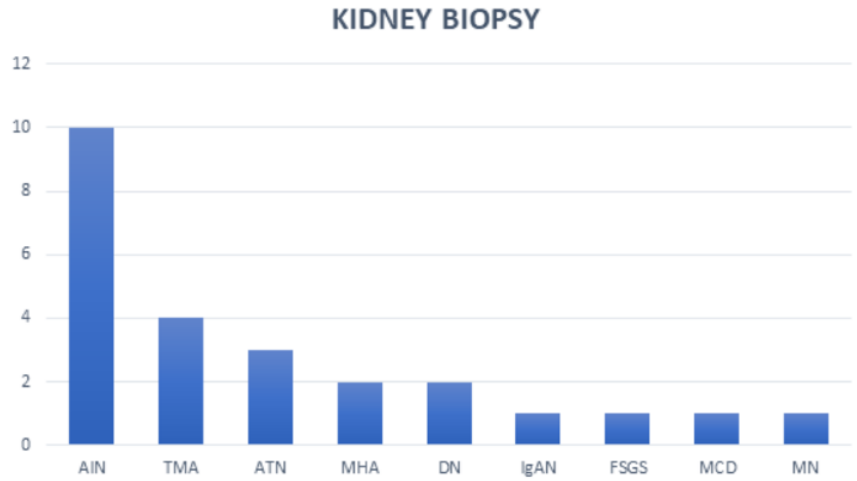

Figure 4. Histological findings. Abbreviations: AIN: Acute Interstitial Nephritis; TMA, Thrombotic Microangiopathy; ATN, Acute Tubular Necrosis; MHA, Minimal Histologic Abnormalities; DN, Diabetic Nephropathy; IgAN, IgA Nephropathy; FSGS, Focal Segmental Glomerulosclerosis; MCD, Minimal Change Disease; MN, Membranous Nephropathy.

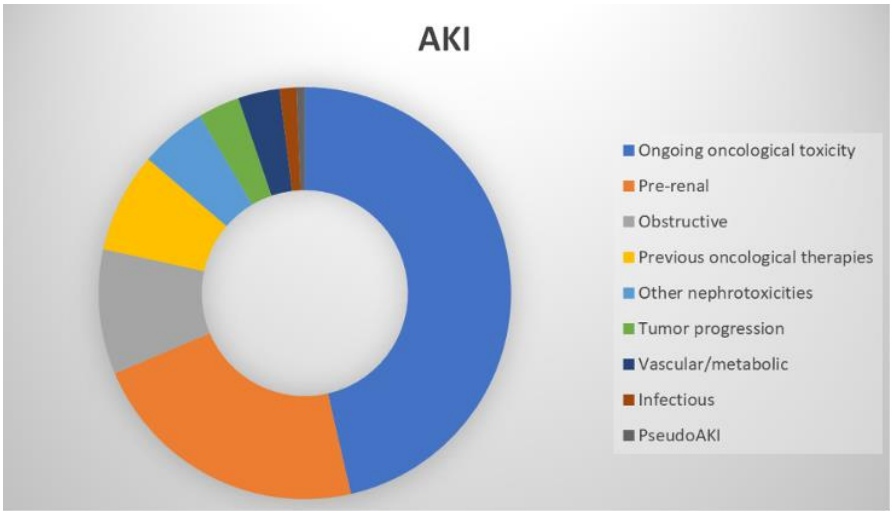

Figure 5. Acute Kidney Injury (AKI) etiology.

Discussion

Among cancer patients, systematic data on the prevalence of CKD were provided by a 2007 French multicenter, retrospective, and observational study, the Renal Insufficiency and Anticancer Medications (IRMA), which showed a prevalence of CKD between 12% and 25% in a population of 4684 cancer patients. However, this study only included patients younger than 65 years [5]. A subgroup analysis of the American NHANES study showed a prevalence of CKD of 47.8% among cancer patients older than 70 years [10].

Regarding the Italian situation, there are currently no prevalence data on renal abnormalities in cancer patients. The only published experience to date comes from the Cremona center, which published data on a cohort of patients seen in the onconephrology outpatient clinic during the first half of 2023 [11]. The demographic profile of our cohort, characterized by an older age (mean 68 years), male predominance, and a high burden of comorbidities, particularly hypertension (66.1%),

underscores the frailty of this patient group. The frequent use of RAAS inhibitors at baseline (45.7%) further highlights the pre-existing cardiovascular and renal risk factors present in a substantial portion of our study population. Interestingly, the average baseline eGFR of 62 ml/min/1.73 m² was only moderately reduced for their age, suggesting that referral was often triggered by acute events or specific concerns rather than solely by pre-existing chronic kidney disease.

The distribution of primary tumor types in our cohort showed a slight deviation from general population trends in Italy, with gynecological cancers being the most prevalent, followed by lung cancer [8]. This observed higher prevalence is likely attributable to the institution's status as a premier national referral center. As a leading tertiary care facility, it handles a disproportionately high volume of complex oncology cases, which often involve advanced disease stages, more aggressive treatment regimens (including nephrotoxic chemotherapies), and comorbidities that predispose patients to renal impairment. The relatively high proportion of lung cancer (17.5%) might reflect the increasing utilization of immune checkpoint inhibitors (ICIs) in this malignancy, a class of drugs known to be associated with a higher incidence of renal adverse events, particularly tubulointerstitial nephritis [12, 13]. Indeed, a significant proportion of our lung cancer patients were receiving ICIs, often in combination with other agents like pemetrexed, platinum compounds and PPIs, the latter also implicated in TIN development [14]. The pattern of oncological therapies administered mirrored general trends, with a majority of patients receiving chemotherapy, followed by immunotherapy and targeted therapies [2, 15]. The comparable prevalence of these drug classes to broader oncology populations suggests that nephrotoxicity is likely a class effect, manifesting through diverse mechanisms rather than being solely attributable to a single type of antineoplastic agent. The high number of initial referrals lacking baseline urine analysis (n = 99) is a notable finding, highlighting a potential area for improved inter-specialty communication and the need for standardized initial work-up of oncology patients at risk for renal complications. Acute kidney injury was the most common reason for referral (60.2%), with a significant proportion (46.4% of AKI cases) attributed to ongoing oncological therapy. Comparing these data with the Spanish group, the prevalence of AKI secondary to drug-related toxicity is lower (56%) [16]. However, the comparison is partial, as the authors had histological based diagnoses for each patient. Our relatively low rate of renal biopsies (7.9%) represents a limitation in definitively characterizing the underlying renal pathology. While clinical and laboratory data allowed for presumptive diagnoses of AKI etiology, a higher biopsy rate could have provided more granular insights into the specific mechanisms of renal injury [17, 18]. Notably, in a substantial proportion of AKI cases (53.6%), causes other than direct oncological drug toxicity were identified, including prerenal factors, obstruction, and other nephrotoxic agents. This underscores the importance of a comprehensive differential diagnosis in this complex patient group.

The predominant AKI stages observed were AKIN I-II, indicating that while often not severe enough to warrant immediate dialysis, these episodes are clinically significant and carry implications for long-term renal outcomes and mortality, as seen in the general population [19]. In cases where AKI was attributed to drug toxicity, oncological therapy was frequently modified (76.06%), highlighting the proactive role of the onconephrology team in attempting to mitigate renal damage. Interestingly, antineoplastic treatment was not permanently discontinued in any case of AKI, suggesting a careful balancing act between oncological necessity and renal preservation, often involving dose adjustments, temporary suspensions, or therapeutic shifts. In a significant minority (23.94%), therapy was continued due to the perceived risk of tumor progression outweighing the renal risks, with implementation of nephroprotective strategies.

Proteinuria was another common reason for referral, and in the majority of these cases, it was suspected to be secondary to oncological therapy, particularly with bevacizumab. Among all 18 patients, therapy was discontinued in half of them. Discontinuation was motivated by the

concomitant appearance of hypertension, AKI, massive nephrotic syndrome, or in cases of taking other specific oncological therapies, in line with the indications in the literature [20].
Notably, the association of nephrotic syndrome stresses a possible paraneoplastic involvement, which aligns with existing literature, emphasizing the diverse ways in which malignancy can affect the kidney [21].

The follow-up data revealed a concerning trend of declining GFR in a significant proportion of surviving patients (71.3% with a decline <30%), and a smaller but still important percentage with a more substantial decline (>30%). The progression to ESKD in 5 patients and the high mortality rate (34.5%), with a significant association with prior AKI, further emphasize the adverse impact of renal complications on the prognosis of cancer patients. It is important to note that in our cohort, renal disease was not identified as the primary cause of death, suggesting that renal complications often contribute to overall morbidity and mortality in the context of advanced malignancy and other comorbidities.

Several limitations inherent to this study warrant consideration. Firstly, its retrospective and single-center design may restrict the generalizability of our findings to the broader oncological population, as the observed patterns of renal complications might not fully reflect the experiences of patients in other settings or geographical regions. Secondly, a selection bias is likely present, as the referral for nephrological evaluation was determined by the treating oncologist. Consequently, the true incidence of acute kidney injury and other renal abnormalities within the overall oncological population of our institution remains undetermined. Finally, the limited number of renal biopsies performed precludes a definitive characterization of the underlying causes of acute kidney injury and the precise mechanisms of proteinuria observed in our cohort. This diagnostic constraint necessitates cautious interpretation of the etiological attributions based solely on clinical and laboratory data.

Despite its limitations, this study possesses several notable strengths. Firstly, it represents the first national report detailing the clinical activity of a dedicated onconephrology outpatient clinic over a 3-year period within Italy. This provides valuable initial insights into the management of renal complications in Italian cancer patients within a specialized setting. Secondly, our findings underscore the critical need for enhanced communication and collaboration between oncologists and the nephrology community. The observed impact of even acute kidney injury events on the potential development of chronic kidney disease highlights the importance of timely nephrological involvement in the care pathway of oncological patients. The complex interplay between cancer therapies, the underlying malignancy, and pre-existing conditions necessitates a multidisciplinary approach to optimize both oncological outcomes and renal function preservation.

Conclusions

Cancer is one of the leading causes of death worldwide, and the increase in life expectancy makes it one of the top causes of death in 2050 [8]. CKD, as well as other age-related comorbidities, is showing a progressing trend [22]. In this context, the direct or indirect toxic effect of cancer on renal function and the increased susceptibility of nephrology patients to oncological diseases make the role of the nephrologist essential.

The task of the onconephrologist is complex as it requires knowledge not only of the mechanisms of interaction between cancer and the kidneys but also of the pharmacokinetics and pharmacodynamics of both established and emerging drugs and their possible interactions. Potential toxic effects, especially in relation to new categories (immunotherapeutics, immuno-targeted therapies), are often speculative in nature and involve complex immunopathological

mechanisms, which represent a true challenge for the nephrologist [23]. The lack of specific diagnostic markers that correlate renal damage to a particular pathophysiological process must be addressed by careful study of the suitability of the fragile multimorbid patient, timely evaluation of the cancer patient with AKI, and the use of invasive biopsy procedures. These procedures allow for the exclusion or confirmation of drug-related toxicity and, based on the histological findings, a probable pathophysiological process [24]. The goal is to counteract potential drug toxicities with increasingly targeted therapeutic approaches, which in some ways are akin to the concept of targeted therapy used in the treatment of oncological diseases. The nephrologist's mission is ultimately to preserve renal function and reduce the unfavorable outcomes that cancer-related kidney disease can have. It is necessary to define the identity of onconephrology not only in international contexts but also nationally, in order to monitor, through dedicated registries, the increasingly significant interaction between cancer, cancer therapy, renal function, and renal outcomes [25].

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