Acute Kidney Injury in Pediatric Cancer Patients

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Objective To analyze the incidence of acute kidney injury (AKI) in the first year after cancer diagnosis in children and to evaluate the short-term and long-term effects on renal function and proteinuria.

Study design Retrospective review of medical records was done on children who were diagnosed and treated for cancer at Seoul National University Hospital between 2004 and 2013. AKI was defined according to the Kidney Disease: Improving Global Outcomes criteria. Impaired renal function of estimated glomerular filtration rate less than 90 mL/minute/1.73 m^2 and development of proteinuria of cancer survivors were also assessed.

Results This study included 1868 patients who were diagnosed with cancer at a median age of 7.9 years. During the course of treatment, 983 patients (52.6%) developed 1864 episodes of AKI, and the cumulative incidence at 2 weeks, 3 months, and 1 year after diagnosis was 28.9%, 39.6%, and 53.6%, respectively. The 1-year cumulative incidence was the highest in patients with acute myeloid leukemias (88.4%). In all, 6.1% of patients had more than 4 episodes of AKI and 11.8% of patients had stage 3 AKI. Among the 1096 childhood cancer survivors, 22.6% were found to have impaired renal function. A greater number of AKI episodes (≥4 times) and nephrectomy were independent risk factors of impaired renal function. Also, 8.2% of the survivors developed proteinuria among 742 childhood cancer survivors.

Conclusions A large percentage of children with cancer experience AKI during the course of treatment, and AKI is associated with impaired long-term renal function. *(J Pediatr 2019;208:243-50).*

Patients with cancer may experience various adverse events during the course of their disease, including acute kidney injury (AKI). Cancer is a known risk factor of AKI.[1-5] AKI occurs in such patients because of tumor lysis syndrome (TLS), the use of nephrotoxic agents (eg, chemotherapeutics, antimicrobials, and contrast media), direct infiltration of the genitourinary system by cancer cells, or multiorgan failure following sepsis or other morbidities.[1,5,6] When AKI occurs during cancer treatment, certain treatment agents may require dose adjustments or complete elimination from the treatment strategy, which may adversely affect the outcome of cancer treatment. In critically ill patients, AKI itself may be associated with increased length of hospital stay and odds of mortality and may have a negative impact on prognosis.[7-9] Moreover, AKI is a known risk factor of chronic kidney disease (CKD), further affecting the long-term quality of life of cancer survivors.[10]

AKI has been investigated in patients with cancer in various studies. In a population-based cohort study that included patients of all ages, the incidence of AKI in the first year of cancer diagnosis was 25.8% among 37 267 patients with cancer, and their 1-year cumulative risk was 17.5%.[11,12] In another recent study, 12% of 3558 adults admitted to a cancer center developed AKI.[9] However, the incidence of AKI has not been well established in the pediatric population of patients with cancer. In the few available studies, the incidence of AKI ranged between 11% and 84%, but these studies were limited to patients with hematologic malignancies.[13-16]

Cancer among children differs from that among adults in aspects such as biology, host, and epidemiology. Children rarely have epithelial tumors in solid organs, such as the lung, colon, and breast, but usually have embryonal tumors in the hematopoietic system and the central nervous system.[17] Concomitant medical conditions, such as diabetes, hypertension, and CKD, are rare in children, and children seldom smoke or drink. The epidemiology of diseases in children is, thus, expected to be different from that in adults. In addition, the impact of AKI on the development of CKD can be

AKI	Acute kidney injury	HSCT	Hematopoietic stem cell transplantation
ALL	Acute lymphoblastic leukemia		
AML	Acute myeloid leukemia	KDIGO	Kidney Disease: Improving Global Outcomes
CKD	Chronic kidney disease		
Cr	Creatinine	NBL	Neuroblastoma
CT	Computed tomography	RRT	Renal replacement therapy
eGFR	Estimated glomerular filtration rate	TLS	Tumor lysis syndrome

expected to be different in children because of the differences in underlying medical conditions. In general, AKI has been shown to be more common in children than in adults, as indicated in a systematic review of 312 studies reporting a higher incidence of AKI in children in hospital settings compared with adults (33.7% vs 21.6%).[18] The incidence of AKI in hospitalized children has recently been reported to be 34%-40%, with two-thirds of them being stages 2 or 3.[18-21] Nonetheless, more focused and comprehensive data on AKI among children with cancer are limited. We, thus, aimed to evaluate the characteristics of AKI in children with cancer, including its incidence, change during the course of cancer treatment, and risk factors. We further analyzed the influence of AKI on long-term renal outcomes, including CKD and proteinuria, in this patient group.

Methods

We performed a retrospective review of the electronic medical records of Seoul National University Hospital, Seoul, South Korea, with approval by the institutional review board (No. H-1509-051-702). This analysis included patients who were diagnosed with cancer between January 1, 2004 and December 31, 2013. Patients who were younger than 18 years at cancer diagnosis and who had creatinine (Cr) levels measured at least twice in the first year after diagnosis were eligible. Patients who had previously been diagnosed with CKD with an initial estimated glomerular filtration rate (eGFR) of lower than 15 mL/minute/1.73 m^2 or who had previously received renal replacement therapy (RRT) were not eligible.

The following clinical data were collected: initial blood test results, all available serum Cr levels and urinalysis, development of TLS, performance of nephrectomy as a part of cancer treatment, use of contrast for computed tomography (CT) scans, use of RRT such as intermittent hemodialysis, and continuous RRT. Data on cancer treatment were also collected, including chemotherapy, overall duration of chemotherapy treatment, administration of 5 chemotherapeutic agents that are widely used in children and are known to be nephrotoxic (carboplatin, cisplatin, cyclophosphamide, ifosfamide, and methotrexate), administration of high-dose chemotherapy and hematopoietic stem cell transplantation (HSCT), and treatment outcome of cancer. Mortality data were obtained from both the institutional electronic medical record and the Vital Statistics reported on July 2016 by the Statistics Korea, a governmental organization for national statistics.

Definitions and Measurements

Cancer types of the patients were categorized into 7 groups: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), lymphoma, neuroblastoma (NBL), Wilms tumor, brain tumor (including medulloblastoma, primitive neuroectodermal tumor, intracranial germ cell tumor, and

other brain tumors), and other cancers (including retinoblastoma, hepatoblastoma, osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, nonrhabdomyosarcoma soft tissue sarcoma, extracranial germ cell tumor, and other unspecified cancers).

AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria with some modifications.[20] Stage 1 AKI was defined as a rise of Cr by 0.3 mg/dL in 2 days or by 1.5 times in 7 days, stage 2 as a rise of Cr by 2 times, and stage 3 as a rise of Cr above 4 mg/dL or by 3 times. Cr had to be at least 0.5 mg/dL for the patients to be diagnosed with AKI when the fold-change criterion was used, to avoid over-diagnosis in young patients whose baseline Cr values were low.[22,23] When the Cr at presentation was high, a recovery of Cr by more than 50% or by 0.3 mg/dL was used for the diagnosis of AKI, as proposed in the KDIGO criteria. For the purpose of this study, the application of RRT was not used as a criterion of stage 3 AKI because it is often transiently used for prompt management of TLS or toxic methotrexate levels in children with cancer, even without presumable actual renal dysfunction. In addition, the criterion concerning the urine output could not be used because of the retrospective nature of this study. Data on maximum AKI stage, number of AKI episodes, and time from cancer diagnosis to AKI were obtained. Deterioration of renal functions in the timeframe of 4 weeks from the onset of AKI was considered a single episode.

Serum Cr level measured either 1 year after the completion of cancer therapy or 5 years after the initial diagnosis was used as the final Cr to determine the long-term renal outcome. Final eGFRs of survivors were estimated with the CKD in Children "bedside Schwartz" equation, using their final serum Cr level and their height at the time of Cr measurement.[24] For patients age 18 years or older at final Cr measurement, the CKD Epidemiology Collaboration equation was used to estimate the eGFR.[25] A final eGFR of less than 90 mL/minute/1.73 m^2 was defined as impaired renal function. An albumin dipstick test result of greater than 1+ on at least 2 occasions at the time of final serum Cr measurement was defined as proteinuria.

Outcomes

The primary outcome measure was the development of AKI. Kaplan-Meier cumulative incidence curves of AKI were plotted at 2 weeks, 3 months, and 1 year after diagnosis by each cancer group. The Kaplan-Meier cumulative incidence curve was also plotted for stage 3 AKI. The maximum stage and number of episodes of AKI were assessed for each cancer group. In the comparison analysis of patients who developed AKI and those who did not, the correlation between AKI and baseline patient characteristics, use of CT scans, and treatments were assessed. The application of RRT was described separately.

The secondary outcome measure was the development of renal impairment or proteinuria in childhood cancer survivors. For the risk factor analysis, patient characteristics,

time interval from cancer diagnosis to first onset of AKI, number of AKI episodes, maximum stage of AKI, and use of RRT were assessed.

Statistical Analyses

Continuous variables were presented as a median with IQR regarding their normality, and categorical variables were presented as counts and percentages. Groups were compared with a t test, χ^2 test, or Mann-Whitney U test, as appropriate. All variables with a P value of <.25 in the bivariate analysis were included in the multivariable analysis. A P value of <.05 was considered statistically significant. Statistical analysis was done by using R-project version 3.3.2 (R core team, Vienna, Austria), and cumulative incidence of AKI was calculated with the package *survival*.

Results

A total of 2170 children were diagnosed with cancer during the study period, and 1877 of them had their serum Cr levels measured at least twice in the first year after cancer diagnosis. Of these patients, 9 patients with CKD stage V were excluded. A total of 1868 patients (1059 male and 809 female) were eligible for analysis (**Figure 1**; available at www.jpeds.com). These patients were diagnosed with cancer at a median age of 7.9 years old. Brain tumor, acute leukemia (ALL and AML), and lymphoma were the most common cancer types in our study population (**Table I**; available at www.jpeds.com). The median initial eGFR of the eligible patients was 90.0 mL/minute/1.73 m^2 (IQR 74.6-110.4). It is notable that 145 patients (7.8%) had an initial eGFR below 60 mL/minute/1.73 m^2. These patients were younger (median age of 1.7 years old), but distribution of their cancer types were not significantly different from that of those without low initial eGFR.

Patients were followed up for a median duration of 5 years (IQR 2.26-6.16), and 1093 patients (58.5%) were followed up for more than 5 years. During the course of the treatment, 144 patients (7.7%) received RRT. Of these patients, 106 patients (73.6%) had RRT applied in the timeframe of 1 year, and 69 patients (47.9%) had it applied in the first month after cancer diagnosis. At 5 years from cancer diagnosis, a total of 1481 patients (79.3%) were alive.

Incidence of Acute Kidney Injury

A total of 983 patients (52.6%) developed AKI, and they had a total of 1864 AKI episodes in the first year after cancer diagnosis (**Figure 2**, A). A total of 293 patients (15.7%) had high serum Cr at presentation and actually presented with AKI at diagnosis, and the onset of the first episode of AKI had a median of 9 days (IQR 0-90.5) after cancer diagnosis. The cumulative incidence of AKI at 2 weeks, 3 months, and 1 year after diagnosis was 28.9% (95% CI 26.9-31.1), 39.6% (95% CI 37.5-41.9), and 53.6% (95% CI 51.3-55.9), respectively. The 2-week cumulative incidence of AKI was the highest in ALL (58.5%, 95% CI 53.1-64.0), followed by

AML (45.2%, 95% CI 37.5-53.6) and medulloblastoma (45.0%, 95% CI 35.9-55.3). The 1-year cumulative incidence of AKI was the highest in AML (88.4%, 95% CI 82.4-93.0), followed by ALL (77.2%, 95% CI 72.4-81.7) and medulloblastoma (67.0%, 95% CI 57.6-76.1). Overall, the 1-year cumulative incidence of AKI was the lowest in other cancers, more specifically in retinoblastoma (14.1%, 95% CI 8.7-22.3) (**Figure 2**, B and **Table II**).

Stage and Number of Acute Kidney Injury Episodes

Of the total of 1864 AKI episodes, 860 episodes (46.1%) were stage 1 AKI, 714 (38.3%) were stage 2, and 290 (15.6%) were stage 3. The cumulative incidence of stage 3 AKI in the first year after diagnosis was 12.3% (95% CI 10.9-13.9, **Figure 2**, C). The cumulative incidence of stage 3 AKI was the highest in ALL (27.9%, 95% CI 23.2-33.3) and the lowest in Wilms tumor (2.1%, 95% CI 0.3-14).

In the first year after cancer diagnosis, AKI occurred once in 520 patients (27.8%), 2 or 3 times in 349 patients (18.7%), and more than 4 times in 114 patients (6.1%). Among the patients who experienced AKI more than 4 times, AML was the most frequent cancer type (23.1%), followed by ALL (13.4%) (**Figure 3**, A and **Table III**; available at www.jpeds.com). The highest stage of AKI that a patient experienced in the first year of cancer diagnosis was stage 1 in 349 patients (18.7%), stage 2 in 413 patients (22.1%), and stage 3 in 221 patients (11.8%). Among the patients who experienced stage 3 AKI, ALL was the most frequent diagnosis (27.1%), followed by AML (25.9%) (**Figure 3**, B and **Table IV**; available at www.jpeds.com).

Risk Factors of Acute Kidney Injury

In the bivariate analysis, a greater proportion of patients who experienced AKI had hematologic malignancies (ALL, AML, and lymphoma), lower eGFR at diagnosis, experienced TLS, had undergone a greater number of CT scans, had nephrotoxic chemotherapeutic agents administered (especially cyclophosphamide, ifosfamide, and methotrexate), had received HSCT, and had experienced cancer relapse. In the current study, nephrectomy and the use of carboplatin and cisplatin did not increase the risk of AKI. In the multivariable analysis, statistically significant risk factors of AKI were cancer group (especially ALL and AML), lower eGFR at diagnosis, occurrence of TLS, use of methotrexate, administration of HSCT, and greater number of CT scans performed (**Table V**).

Long-Term Renal Outcome

Final eGFR values were available in a total of 1096 patients. At a median 5.17 years (IQR 5.02-5.47) after diagnosis, patients had a median eGFR of 107.63 mL/minute/1.73 m^2 (IQR 91.57-125.09). A total of 248 patients (22.6%) had impaired renal function of eGFR below 90 mL/minute/1.73 m^2. Impaired renal function was most frequent in survivors of Wilms tumor (36.8%), followed by nonrhabdomyosarcoma soft tissue sarcoma (34.6%). In the bivariate analysis, patients who had renal impairment had the following
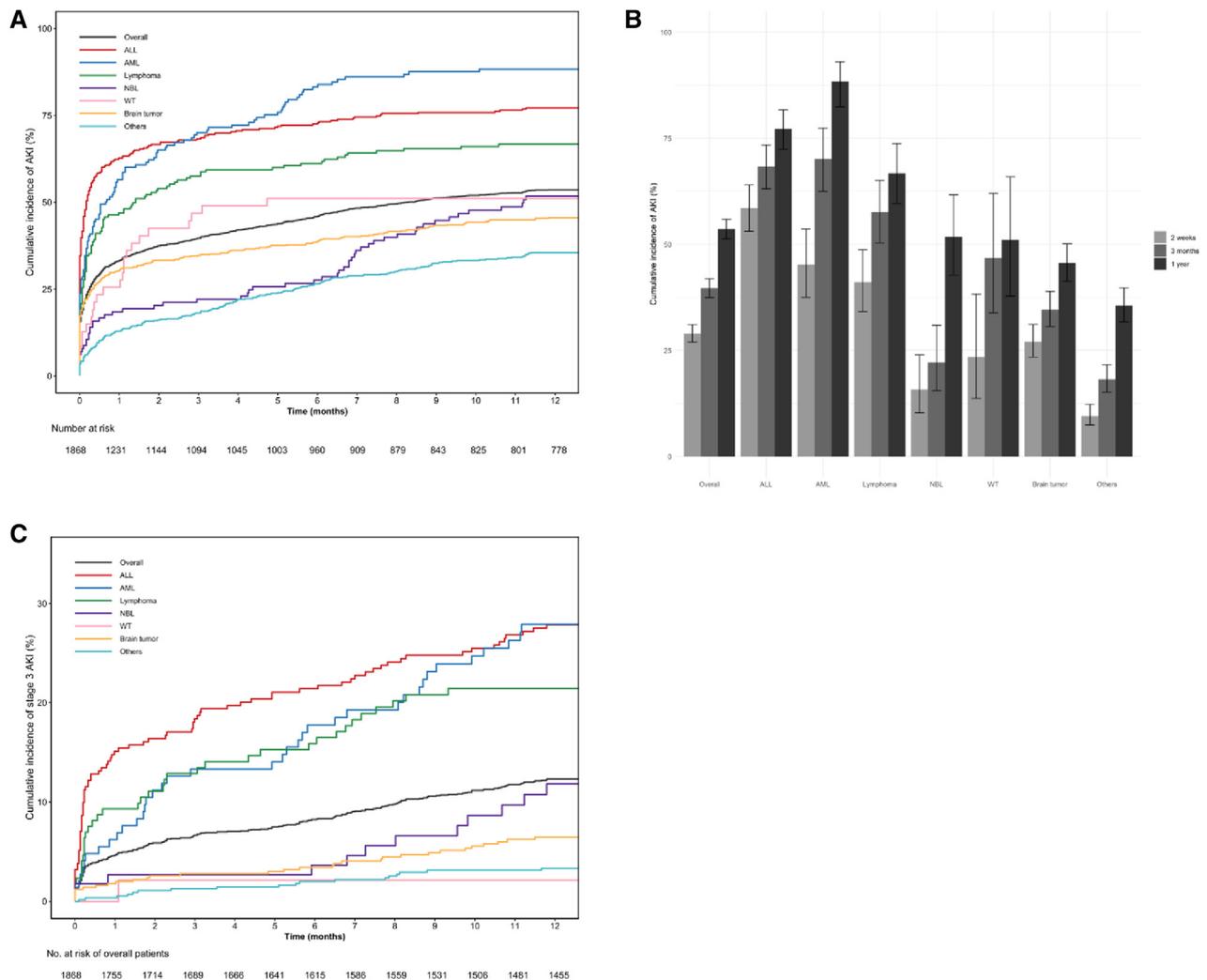
Figure 2. A, Kaplan-Meier cumulative incidence curve of AKI according to cancer group; **B,** 2-week, 3-month, and 1-year cumulative incidence of AKI according to cancer group, with 95% CI; **C,** Kaplan-Meier cumulative incidence curve of stage 3 AKI, according to cancer group. *WT*, Wilms tumor.

characteristics: male sex, lower eGFR at diagnosis (below 60 mL/minute/1.73 m^2), chemotherapeutic agents administered (especially cyclophosphamide), and nephrectomy performed. In the multivariable analysis, the statistically significant risk factors of renal impairment were male sex, lower eGFR at diagnosis, greater number of AKI episodes (more than 4 times), and nephrectomy (**Table VI**; available at www.jpeds.com). Cancer survivors with or without final eGFR measured did not differ in their percentages of patients who underwent nephrectomy or had AKI. However, the group with final eGFR was more likely to have undergone HSCT or have experienced relapse. Two of the survivors had final eGFR below 15 mL/minute/1.73 m^2. A boy who was treated surgically for colon cancer and who also had underlying Crohn's disease and complicated renal amyloidosis, is on close observation for his renal dysfunction, although he is not on RRT yet. Another girl with lymphoma who had

experienced AKI more than 4 times, lost her kidney function about 2.5 years from cancer diagnosis and is currently on peritoneal dialysis. All other patients had final eGFRs between 60 mL/minute/1.73 m^2 and 90 mL/minute/1.73 m^2. Urinalysis data were available for 742 survivors, and a total of 61 patients (8.2%) had proteinuria. Proteinuria was most frequent in survivors of AML (13.6%), followed by lymphoma (9.3%).

Discussion

Our study provides a comprehensive evaluation of the characteristics of AKI, including the incidence, risk factors, and short-term and long-term outcome of AKI in children with cancer, including a large group of patients diagnosed with inclusive cancer types using established criteria for AKI—the KDIGO criteria. Reports on the incidence of AKI in children with cancer have offered variable results

**Table II.** Cumulative incidence of acute kidney injury, specified*

Variables	2-wk risk of AKI% (95% CI)	3-mo risk of AKI% (95% CI)	1-y Risk of AKI% (95% CI)
Overall	28.9 (26.9-31.1)	39.6 (37.5-41.9)	53.6 (51.3-55.9)
Acute leukemia			
ALL	58.5 (53.1-64.0)	68.3 (63.1-73.4)	77.2 (72.4-81.7)
AML	45.2 (37.5-53.6)	70.1 (62.4-77.4)	88.4 (82.4-93.0)
Lymphoma	41.1 (34.1-48.8)	57.6 (50.3-65.0)	66.7 (59.6-73.7)
NBL	15.8 (10.3-23.9)	22.1 (15.5-30.9)	51.8 (42.7-61.6)
WT	23.4 (13.7-38.3)	46.8 (33.8-61.9)	51.1 (37.8-65.9)
Brain tumor			
Intracranial germ cell tumor	19.5 (13.5-27.7)	28.5 (21.3-37.3)	36.7 (28.9-45.9)
Medulloblastoma	45.0 (35.9-55.3)	50.1 (40.8-60.2)	67.0 (57.6-76.1)
Primitive neuroectodermal tumor	23.6 (14.5-37.2)	31.0 (20.5-45.1)	48.7 (35.8-63.3)
Other brain tumor	24.0 (19.0-30.1)	31.9 (26.3-38.4)	40.4 (34.3-47.1)
Ewing sarcoma	7.9 (2.6-22.5)	13.2 (5.7-28.8)	59.8 (43.9-76.3)
Extracranial germ cell tumor	14.3 (8.0-24.9)	24.3 (15.9-36.1)	35.9 (25.9-48.4)
Hepatoblastoma	20.8 (12.1-34.3)	28.4 (18.2-42.6)	47.9 (35.4-62.2)
Nonrhabdomyosarcoma soft tissue sarcoma	6.8 (2.6-17.1)	10.2 (4.7-21.2)	23.1 (14.1-36.5)
Osteosarcoma	2.9 (1.0-8.8)	20.8 (14.1-30.1)	53.4 (43.8-63.6)
Retinoblastoma	6.5 (3.1-13.1)	7.4 (3.8-14.2)	14.1 (8.7-22.3)
Rhabdomyosarcoma	9.3 (3.6-22.9)	21.2 (11.7-36.9)	30.8 (19.2-47.1)
Other unspecified cancers	13.0 (7.6-21.8)	22.9 (15.6-33.0)	35.5 (26.6-46.4)

WT, Wilms tumor.
*Cumulative incidence was calculated using survival analysis.

depending on the criteria used for the diagnosis of AKI. For example, although the incidence of AKI in recipients of HSCT was 78% within 1 year after cancer diagnosis in our study, the reported incidence of AKI in recipients of HSCT was much lower, about 11% and 21%, within a 2-year period in studies that defined AKI as the doubling of Cr levels.[13,14] However, when the pRIFLE (Pediatric Risk, Injury, Failure, Loss, End Stage Renal Disease) criteria were used, the reported incidence of AKI was 84% in recipients of HSCT within 100 days after transplantation, which was slightly higher than the result of our study, although the different timeframe should be considered for a more accurate comparison.[16] In a study that used the KDIGO criteria for AKI diagnosis, as in our study, 64% of patients with AML
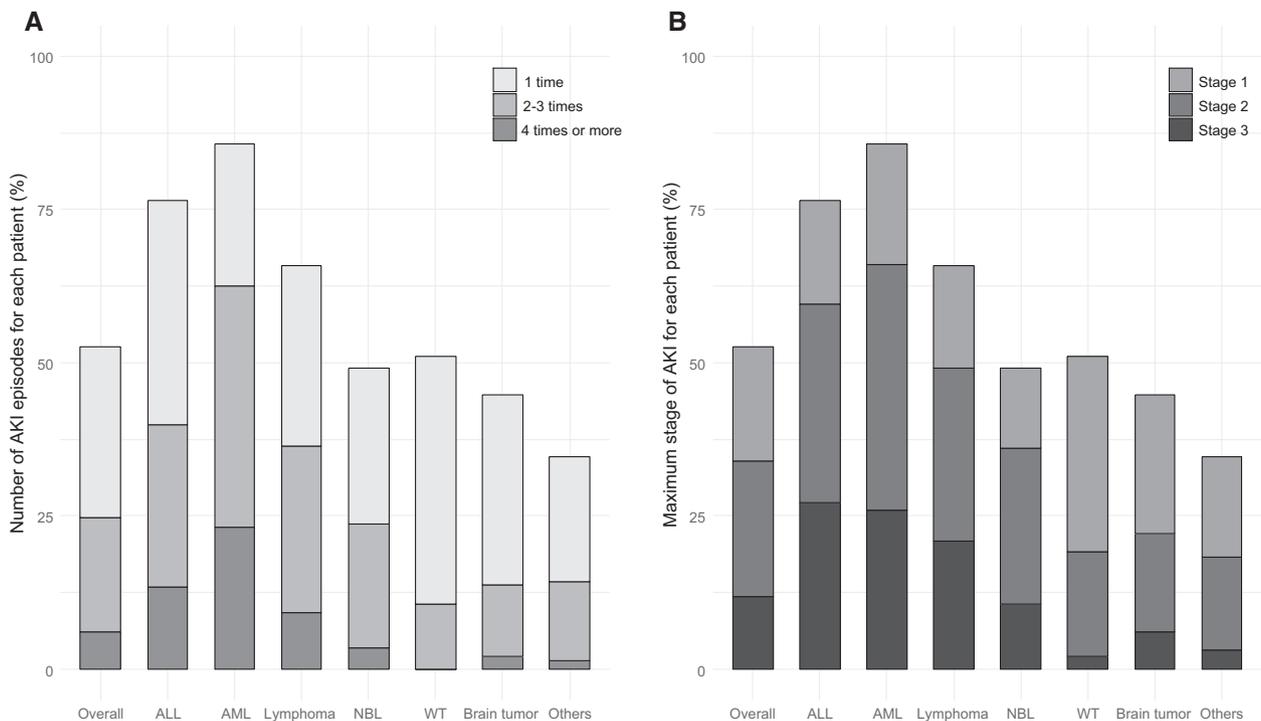
Figure 3. A, Number of AKI episodes; **B,** Maximum stage of AKI according to cancer group.

Table V. Patient characteristics according to the occurrence of acute kidney injury

Variables	Patients who did not experience AKI (n = 885)	Patients who experienced AKI (n = 983)	P value	Multivariable analysis (95% CI)*
No. (%) of female patients	399 (45.1)	410 (41.7)	.16	1.02 (0.88-1.19)
Age at diagnosis, median (IQR), years	8.0 (2.3-13.3)	7.8 (2.9-12.3)	.59	
Initial eGFR at diagnosis, median (IQR), ml/min/1.73 m²	94.9 (79.6-114.9)	85.7 (70.3-105.3)	<.001	0.99 (0.98-0.99)
No. (%) of patients by cancer group†				
ALL	74 (8.4)	240 (24.4)	<.001	1.71 (1.10-2.68)
AML	21 (2.4)	126 (12.8)		3.35 (1.94-5.97)
Lymphoma	59 (6.7)	114 (11.6)		1.12 (0.70-1.78)
NBL	58 (6.6)	56 (5.7)		0.65 (0.40-1.05)
WT	23 (2.6)	24 (2.4)		0.95 (0.50-1.82)
Brain tumor	280 (31.6)	227 (23.1)		Ref.
Other cancer	370 (41.8)	196 (19.9)		0.41 (0.31-0.56)
No (%) of patients who received CTx	659 (74.5)	880 (89.5)	<.001	1.29 (0.91-1.82)
No. (%) of patients who received specific chemotherapeutic agents‡				
Carboplatin	264 (29.8)	283 (28.8)	.66	
Cisplatin	272 (30.7)	296 (30.1)	.81	
Cyclophosphamide	434 (49.0)	628 (63.9)	<.001	0.91 (0.68-1.21)
Ifosfamide	171 (19.3)	239 (24.3)	.011	1.20 (0.89-1.61)
Methotrexate	190 (21.5)	454 (46.2)	<.001	1.78 (1.29-2.46)
No. of CT scans performed, median (IQR), count	1 (0-4)	2 (0-6.5)	<.001	1.05 (1.03-1.07)
No. (%) of patients who experienced TLS	1 (0.1)	53 (5.4)	<.001	14.79 (3.11-265.1)
No (%) of patients who received HSCT	63 (7.1)	330 (33.6)	<.001	3.75 (2.67-5.34)
No (%) of patients who had nephrectomy performed	28 (3.2)	28 (2.8)	.79	
No (%) of patients who experienced cancer relapse	92 (10.4)	205 (20.9)	<.001	1.22 (0.88-1.70)

CTx, chemotherapy.

*The covariates assessed for the multivariable logistic-regression model were sex, initial eGFR at diagnosis, cancer group, chemotherapy, chemotherapy with cyclophosphamide, ifosfamide, or methotrexate; CT scans, HSCT, or relapse.

†Reference to OR in multivariable analysis is brain tumor in the cancer group and the absence of the corresponding risk factor.

‡Patients could have received more than 1 of the specified chemotherapeutic agents. Reference to such patients is patients who did not receive any of the specified chemotherapeutic agents.

treated with conventional chemotherapy developed AKI, whereas 74% of the patients with AMLs treated with only conventional chemotherapy in our study developed AKI within 1 year after cancer diagnosis (data not shown).[26] Because the KDIGO criteria are currently regarded as the standard criteria for evaluating AKI, the findings of our study may be a useful clinical reference in the future.

The 1-year cumulative incidence of AKI in our study population of children with cancer was 52.6%, which was higher than the 12%-18% in adults with cancer.[11,27] It is notable that one-half of the AKIs occurred within 2 weeks after diagnosis, with the first onset at a median 9 days after cancer diagnosis. This emphasizes the importance of closely monitoring renal functions and using the best possible nephroprotective measures, especially early after diagnosis.

The incidence of AKI differed between cancer types. Overall, the cumulative incidence of AKI was the highest in patients with hematologic malignancies both at 2 weeks and at 1 year after cancer diagnosis. The range of cumulative incidence among AKI in patients with acute leukemia was high, ranging between 45.2% and 58.5% at 2 weeks, and it was extremely high, ranging between 77.2% and 88.4%, at 1 year after diagnosis. Moreover, the severity of AKI was also higher in this patient group. This implies that cautious nephroprotective measures early after diagnosis and throughout the course of treatment is particularly crucial in this group of patients. This is in accordance with a study on adults with cancer, in which patients with hematologic malignancy had a higher cumulative incidence of AKI than

those with other cancer types.[11] In comparison, renal tumor was the most AKI-prone cancer in an adult study.[11] Interestingly, Wilms tumor, renal tumor in children, had a cumulative incidence of AKI of 51.5% at 1 year after diagnosis, which was eighth in ranking among the cancer types in our study (Table II). At our institute, most of the patients with Wilms tumor did not have nephrotoxic chemotherapeutics administered and they did not undergo intensive treatment periods, which may explain their low incidence of AKI.

In addition to the cancer group, the occurrence of TLS, greater number of CT scans performed, administration of chemotherapy, and administration of HSCT were found to be significant risk factors of AKI, as expected from the clinical experience.[2,5,28,29] Notably, methotrexate was found to be a significant risk factor of AKI, as found in a previous study.[30] The use of high-dose methotrexate from day 14 from the initial cycle of chemotherapy and throughout the treatment course for osteosarcoma in our institute may have contributed to the gradual increase in the cumulative incidence of AKI of this cancer type. Cisplatin and carboplatin were not shown to be risk factors of AKI in current study. One of our speculations is that they were used more often for solid tumors than for hematologic malignancies. Because AKI occurs more frequently in hematologic malignancies, the effects of cancer types may have offset the risks of chemotherapeutics. On the other hand, cyclophosphamide was shown to be associated with unexpectedly high incidence of AKI in bivariate analysis.

In fact, cyclophosphamide is often used for hematologic malignancies and for many of the aggressive and refractory cancers where patients can be vulnerable to AKI because of either prolonged treatment or intense therapies. Administration of HSCT was another significant risk factor of AKI in our study, as previously reported.[24] In our institute, most patients with AML undergo HSCT after 2 cycles of induction chemotherapy and 2 cycles of consolidation chemotherapy over a 4-week interval, and patients with advanced NBL undergo HSCT after 7-8 cycles of chemotherapy, with a 3- to 4-week interval. Although it should be interpreted with caution, it is interesting to note that the time points when the stepwise increment of the cumulative incidence of AKI in AML and in NBL coincide with the usual time points of HSCT in these diseases are at about 5.0 months and 6.5 months from diagnosis, respectively (**Figure 2**, A). Patients who experienced relapse had high incidence of AKI in bivariate analysis. This may have been due to their high initial cancer stage and their intensive treatment periods. However, it was not shown to be significant in multivariable analysis.

On long-term follow-up, more than one-fifth of the patients developed renal impairment and/or proteinuria. The occurrence of AKI was significantly associated with the development of long-term renal impairment, in accordance with a well-known finding that AKI is a risk factor of CKD.[10] In particular, the experience of multiple episodes of AKI, but not the onset time or the severity of AKI, was a risk factor of long-term renal impairment. Notably, among the risk factors of long-term renal impairment, the recurrence and, thus, the number of AKI episodes may be the only potentially modifiable risk factor. It is also notable that patients with low initial eGFR was significantly associated with the development of long-term renal impairment. Close monitoring of renal function after the course of treatment in these patients may be helpful to mitigate poor outcomes. Although Wilms tumor was ranked eighth regarding the development of AKI among the 17 different cancer types in our study, a high proportion (37%) of patients with Wilms tumor developed renal impairment in the long-term follow-up (**Table II**). Moreover, nephrectomy was found to be an independent risk factor of long-term renal impairment. Decreased number of nephrons has direct effect on decreased renal function, although it is partly compensated by the increase in GFR per nephron.[31,32] One study reported that one-half of the nephrectomized patients with Wilms tumor or NBL had a final eGFR of less than 90 mL/minute/1.73 m^2.[33] Thus, close monitoring of renal function and applications of nephroprotective measures are necessary in these patients. However, most of the patients had only mild kidney dysfunction, partly because of the lack of enough follow-up time. Our data should be interpreted with caution because the complete final eGFR data was missing in a large portion of survivors and the patients with this data tended to be those who have undergone prolonged or intensive treatment courses such as HSCT because of high

cancer stage or relapse. The reported prevalence of proteinuria in cancer survivors is 3.2%.[34] In our study, a total of 8.2% of the patients developed proteinuria. However, our results may have been biased and overestimated because patients who have not experienced clinically overt renal insults may not have had their urinalysis followed-up routinely. Also, as it is the result from random urinalysis, much of these findings may be due to the benign proteinuria which does not require specific management. Nonetheless, because proteinuria is a well-known risk factor of CKD progression, this subset of patients might need further evaluation to detect pathologic proteinuria in early stage to improve long-term renal outcome.

This study has the inherent limitation that it was a retrospective medical chart review and single center study. The results should be interpreted with caution because the study population may have been a biased group of patients because of our institutional status as a referral center for pediatric patients in South Korea. In addition, the evaluation of AKI in this study is not fully comprehensive because the criterion involving urine output was not included. Also, defining impaired renal function as eGFR less than 90 mL/minute/1.73 m^2 may be imprecise given the limited accuracy of Cr based eGFR in patients with mildly impaired kidney function, although it was partly due to the lack of patients with severely impaired kidney function for statistical analysis. Furthermore, not all of the factors that may have affected the development of AKI and the long-term renal outcome were sufficiently analyzed. For instance, the study did not evaluate the cancer stage, all the chemotherapeutic agents and regimens used (eg, dosages and schedules), or all the possibly nephrotoxic medications (eg, antimicrobial agents).

AKI is very common in children with cancer, especially early after diagnosis; it is associated with adverse long-term renal outcomes. Further studies are needed to prospectively evaluate the trend of changes in renal functions throughout the treatment course in children with cancer and to further focus on long-term renal outcomes in childhood cancer survivors.[35,36] ∎

References

1. Lameire NH, Flombaum CD, Moreau D, Ronco C. Acute renal failure in cancer patients. Ann Med 2005;37:13-25.
2. Campbell GA, Hu D, Okusa MD. Acute kidney injury in the cancer patient. Adv Chronic Kidney Dis 2014;21:64-71.
3. Cohen EP. Cancer and the kidney: the frontier of nephrology and oncology. Oxford University Press; 2010.
4. Humphreys BD, Soiffer RJ, Magee CC. Renal failure associated with cancer and its treatment: an update. J Am Soc Nephrol 2005;16:151-61.
5. Rosner MH, Perazella MA. Acute kidney injury in patients with cancer. N Engl J Med 2017;376:1770-81.

6. Lahoti A, Humphreys BD. AKI Associated With Malignancies. J Am Soc Nephrol, 2016. https://www.asn-online.org/education/distancelearning/curricula/onco/Chapter3.pdf. Accessed February 1, 2018.

7. Rustagi RS, Arora K, Das RR, Pooni PA, Singh D. Incidence, risk factors and outcome of acute kidney injury in critically ill children–a developing country perspective. Paediatr Int Child Health 2017;37:35-41.

8. Lahoti A, Nates JL, Wakefield CD, Price KJ, Salahudeen AK. Costs and outcomes of acute kidney injury in critically ill patients with cancer. J Support Oncol 2011;9:149-55.

9. Salahudeen AK, Doshi SM, Pawar T, Nowshad G, Lahoti A, Shah P. Incidence rate, clinical correlates, and outcomes of AKI in patients admitted to a comprehensive cancer center. Clin J Am Soc Nephrol 2013;8:347-54.

10. Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med 2014;371:58-66.

11. Christiansen CF, Johansen MB, Langeberg WJ, Fryzek JP, Sørensen HT. Incidence of acute kidney injury in cancer patients: a Danish population-based cohort study. Eur J Intern Med 2011;22:399-406.

12. Jhaveri K, Salahudeen AK. Onconephrology: cancer, chemotherapy and the kidney. New York, NY: Springer; 2015.

13. Kist-van Holthe JE, Goedvolk CA, Brand R, van Weel MH, Bredius RG, van Oostayen JA, et al. Prospective study of renal insufficiency after bone marrow transplantation. Pediatr Nephrol 2002;17:1032-7.

14. Michael M, Kuehnle I, Goldstein SL. Fluid overload and acute renal failure in pediatric stem cell transplant patients. Pediatr Nephrol 2004;19:91-5.

15. Fisher BT, Zaoutis TE, Leckerman KH, Localio R, Aplenc R. Risk factors for renal failure in pediatric patients with acute myeloid leukemia: a retrospective cohort study. Pediatr Blood Cancer 2010;55:655-61.

16. Kizilbash SJ, Kashtan CE, Chavers BM, Cao Q, Smith AR. Acute kidney injury and the risk of mortality in children undergoing hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2016;22:1264-70.

17. Pizzo PA, Poplack DG. Principles and practice of pediatric oncology. Philadelphia, PA: Lippincott Williams & Wilkins; 2015.

18. Susantitaphong P, Cruz DN, Cerda J, Abulfaraj M, Alqahtani F, Koulouridis I, et al. World incidence of AKI: a meta-analysis. Clin J Am Soc Nephrol 2013;8:1482-93.

19. Sutherland SM, Byrnes JJ, Kothari M, Longhurst CA, Dutta S, Garcia P, et al. AKI in hospitalized children: comparing the pRIFLE, AKIN, and KDIGO definitions. Clin J Am Soc Nephrol 2015;10:554-61.

20. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012;120:c179-84.

21. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11:R31.

22. Holmes J, Roberts G, May K, Tyerman K, Geen J, Williams JD, et al. The incidence of pediatric acute kidney injury is increased when identified by a change in a creatinine-based electronic alert. Kidney Int 2017;92:432-9.

23. Downes KJ, Cowden C, Laskin BL, Huang Y-S, Gong W, Bryan M, et al. Association of acute kidney injury with concomitant vancomycin and piperacillin/tazobactam treatment among hospitalized children. JAMA Pediatr 2017;171:e173219.

24. Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol 2009;20:629-37.

25. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-12.

26. Du Plessis L, Rassekh SR, Mammen C. High incidence of acute kidney injury during chemotherapy for childhood acute myeloid leukemia. Pediatr Blood Cancer 2018;65:e26915.

27. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure–definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8:R204.

28. Hingorani S. Renal complications of hematopoietic-cell transplantation. N Engl J Med 2016;374:2256-67.

29. Gleeson TG, Bulugahapitiya S. Contrast-induced nephropathy. Am J Roentgenol 2004;183:1673-89.

30. Perazella MA. Onco-nephrology: renal toxicities of chemotherapeutic agents. Clin J Am Soc Nephrol 2012;7:1713-21.

31. Bailey S, Roberts A, Brock C, Price L, Craft A, Kilkarni R, et al. Nephrotoxicity in survivors of Wilms' tumours in the North of England. Br J Cancer 2002;87:1092.

32. Ben-Haim S, Sopov V, Stein A, Moskovitz B, Front A, Mecz Y, et al. Kidney function after radical nephrectomy: assessment by quantitative SPECT of 99mTc-DMSA uptake by the kidneys. J Nucl Med 2000;41:1025-9.

33. Schell M, Cochat P, Hadj-Aïssa A, Bouffet E, Dubourg L, Brunat-Mentigny M. Renal function following unilateral nephrectomy for neuroblastoma and Wilms' tumour. Pediatr Nephrol 1995;9:579-82.

34. Ramirez MD, Mertens AC, Esiashvili N, Meacham LR, Wasilewski-Masker K. Yield of urinalysis screening in pediatric cancer survivors. Pediatr Blood Cancer 2016;63:893-900.

35. Jones DP, Spunt SL, Green D, Springate JE. Renal late effects in patients treated for cancer in childhood: a report from the Children's Oncology Group. Pediatr Blood Cancer 2008;51:724-31.

36. Arjmandi-Rafsanjani K, Hooman N, Vosoug P. Renal function in late survivors of Iranian children with cancer: single centre experience. Indian J Cancer 2008;45:154.
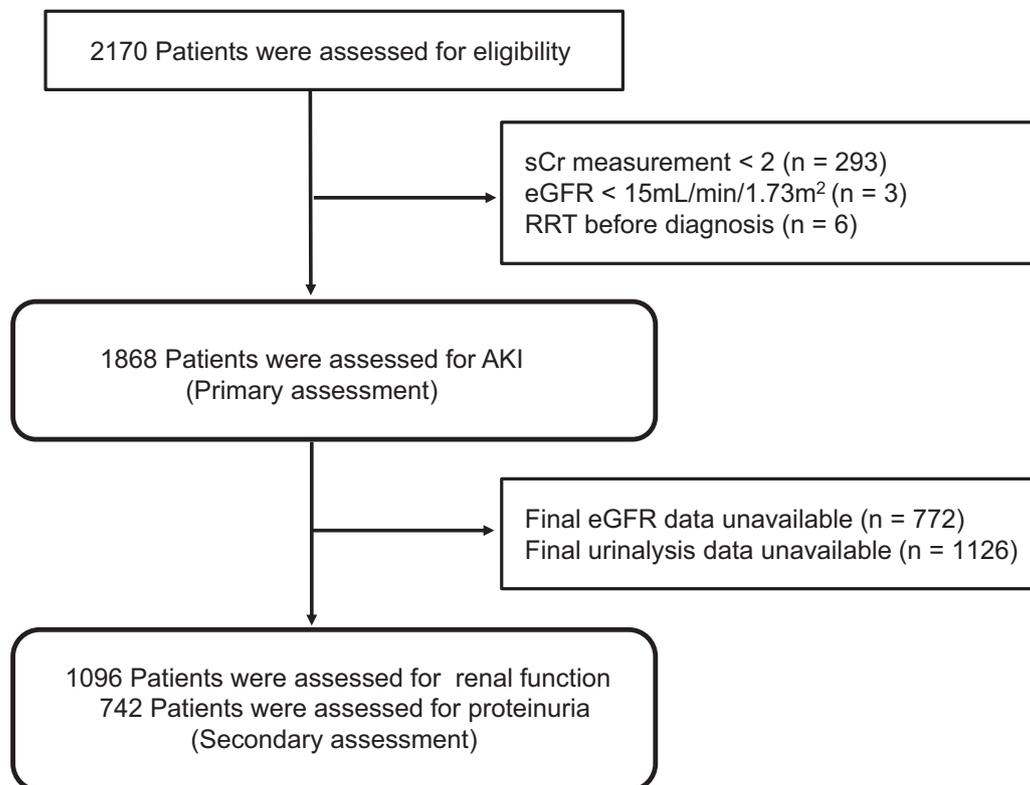
Figure 1. Flow of assessed and eligible patients. *sCr*, serum creatinine.

Table I. Baseline patient characteristics

Variables	Value
Number of patients	1868
No. (%) of male patients	1059 (56.7)
Age at diagnosis, median (IQR), y	7.9 (2.5-12.7)
Age distribution, no (%)	
Under 1 y	197 (10.5)
1-4 y	532 (28.5)
5-9 y	406 (21.7)
10-14 y	484 (25.9)
15-18 y	249 (13.3)
Initial eGFR at diagnosis, median (IQR), mL/min/1.73 m^2	90.0 (74.6-110.4)
No (%) of patients according to cancer group	
Acute leukemia	
ALL	314 (16.8)
AML	147 (7.9)
Lymphoma	173 (9.3)
NBL	114 (6.1)
WT	47 (2.5)
Brain tumor	
Intracranial germ cell tumor	123 (6.6)
Medulloblastoma	100 (5.4)
Primitive neuroectodermal tumor	55 (2.9)
Other brain tumor	229 (12.3)
Ewing sarcoma	38 (2.0)
Extracranial germ cell tumor	70 (3.7)
Hepatoblastoma	53 (2.8)
Nonrhabdomyosarcoma soft tissue sarcoma	59 (3.2)
Osteosarcoma	102 (5.5)
Retinoblastoma	109 (5.8)
Rhabdomyosarcoma	43 (2.3)
Other unspecified cancers	92 (4.9)

WT, Wilms tumor.

Table IV. Maximum stage of acute kidney injury in first year after cancer diagnosis

Variables (no)	Stage 1, no (%)	Stage 2, no (%)	Stage 3, no (%)
Overall cancer (1868)	349 (18.7)	413 (22.1)	221 (11.8)
Acute leukemia			
ALL (314)	53 (16.9)	102 (32.5)	85 (27.1)
AML (147)	29 (19.7)	59 (40.1)	38 (25.9)
Lymphoma (173)	29 (16.8)	49 (28.3)	36 (20.8)
NBL (114)	15 (13.2)	29 (25.4)	12 (10.5)
Wilms tumor (47)	15 (31.9)	8 (17.0)	1 (2.1)
Brain tumor			
Intracranial germ cell tumor (123)	33 (26.8)	9 (7.3)	3 (2.4)
Medulloblastoma (100)	27 (27.0)	32 (32.0)	7 (7.0)
Primitive neuroectodermal tumor (55)	9 (16.4)	8 (14.5)	8 (14.5)
Other brain tumor (229)	46 (20.1)	32 (14.0)	13 (5.7)
Ewing sarcoma (38)	10 (26.3)	8 (21.1)	3 (7.9)
Extracranial germ cell tumor (70)	12 (17.1)	10 (14.3)	3 (4.3)
Hepatoblastoma (53)	5 (9.4)	17 (32.1)	3 (5.7)
Nonrhabdomyosarcoma soft tissue sarcoma (59)	8 (13.6)	4 (6.8)	1 (1.7)
Osteosarcoma (102)	29 (28.4)	20 (19.6)	3 (2.9)
Retinoblastoma (109)	5 (4.6)	10 (9.2)	0
Rhabdomyosarcoma (43)	8 (18.6)	5 (11.6)	0
Other unspecified cancers (92)	16 (17.4)	11 (12.0)	5 (5.4)

Percentages do not add up to 100% because the patients who did not experience AKI were not included.

Table III. Number of acute kidney injury episodes in first year after cancer diagnosis

Variables (no)	1 time, no (%)	2-3 times, no (%)	≥4 times, no (%)
Overall (1868)	520 (27.8)	349 (18.7)	114 (6.1)
Acute leukemia			
ALL (314)	115 (36.6)	83 (26.4)	42 (13.4)
AML (147)	34 (23.1)	58 (39.5)	34 (23.1)
Lymphoma (173)	51 (29.5)	47 (27.2)	16 (9.2)
NBL (114)	29 (25.4)	23 (20.2)	4 (3.5)
WT (47)	19 (40.4)	5 (10.6)	0
Brain tumor			
Intracranial germ cell tumor (123)	34 (27.6)	9 (7.3)	2 (1.6)
Medulloblastoma (100)	33 (33.0)	27 (27.0)	6 (6.0)
Primitive neuroectodermal tumor (55)	15 (27.3)	8 (14.5)	2 (3.6)
Other brain tumor (229)	75 (32.8)	16 (7.0)	0
Ewing sarcoma (38)	10 (26.3)	10 (26.3)	1 (2.6)
Extracranial germ cell tumor (70)	15 (21.4)	10 (14.3)	0
Hepatoblastoma (53)	13 (24.5)	11 (20.8)	1 (1.9)
Nonrhabdomyosarcoma soft tissue sarcoma (59)	12 (20.3)	0	1 (1.7)
Osteosarcoma (102)	27 (26.5)	20 (19.6)	5 (4.9)
Retinoblastoma (109)	10 (9.2)	5 (4.6)	0
Rhabdomyosarcoma (43)	9 (20.9)	4 (9.3)	0
Other unspecified cancers (92)	19 (20.7)	13 (14.1)	0

Percentages do not add up to 100% because the patients who did not experience AKI were not included.

Table VI. Patient characteristics according to the development of renal impairment*

Variables	Patients who did not develop renal impairment (n = 848)	Patients who developed renal impairment (n = 248)	P value	Multivariable analysis (95% CI)†
No (%) of female patients	386 (45.5)	78 (31.5)	.013	0.65 (0.52-0.81)
Age at diagnosis, median (IQR), y	7.2 (2.3-13.0)	8.7 (3.3-11.9)	.57	
No (%) of patients with Initial eGFR at diagnosis below 60 mL/min/1.73 m²	56 (6.6%)	28 (11.3%)	.021	1.80 (1.08-2.95)
No (%) of patients by cancer group‡			.21	
ALL	166 (19.6)	40 (16.1)		0.70 (0.43-1.14)
AML	62 (7.3)	16 (6.5)		0.52 (0.25-1.03)
Lymphoma	100 (11.8)	25 (10.1)		0.63 (0.35-1.10)
NBL	49 (5.8)	12 (4.8)		0.61 (0.28-1.24)
WT	24 (2.8)	14 (5.6)		0.43 (0.10-1.80)
Brain tumor	183 (21.6)	65 (26.2)		Ref.
Other cancer	264 (31.1)	76 (30.6)		0.70 (0.46-1.06)
No (%) of patients who received CTx	763 (90.0)	210 (84.7)	.027	0.63 (0.37-1.06)
No (%) of patients who received specific chemotherapeutic agents§				
Carboplatin	253 (29.8)	82 (33.1)	.37	
Cisplatin	246 (29.0)	64 (25.8)	.36	
Cyclophosphamide	549 (64.7)	138 (55.6)	.011	0.69 (0.47-1.02)
Ifosfamide	153 (18.0)	52 (21.0)	.34	
Methotrexate	335 (39.5)	90 (36.3)	.40	
No of CT scans performed, median (IQR), count	1 (0-5)	2 (0-6.5)	.17	1.02 (0.99-1.04)
No (%) of patients according to time point at first onset of AKI				
Within 1 y	107 (12.6)	31 (12.5)	.78	
Within 3 mo	90 (10.6)	26 (10.5)		
Within 2 wk	239 (28.2)	78 (31.5)		
No (%) patients according to number of AKI episodes				
1 time	228 (26.9)	65 (26.2)	.081	1.04 (0.72-1.50)
2-3 times	169 (19.9)	48 (19.4)		1.19 (0.77-1.82)
4 times or more	39 (4.6)	22 (8.9)		2.12 (1.09-4.03)
No (%) patients according to maximum AKI stage experienced				
AKI stage 1	164 (19.3)	48 (19.4)	.71	
AKI stage 2	195 (23.0)	59 (23.8)		
AKI stage 3	77 (9.1)	28 (11.3)		
No (%) of patients who had RRT applied	37 (4.4)	18 (7.3)	.095	1.56 (0.80-2.96)
No (%) of patients who experienced TLS	40 (4.7)	12 (4.8)	>.99	
No (%) of patients who received HSCT	210 (24.8)	61 (24.6)	>.99	
No (%) of patients who had nephrectomy performed	27 (3.2)	19 (7.7)	.004	3.68 (1.05-13.72)
No (%) of patients who experienced cancer relapse	79 (9.3)	30 (12.1)	.24	1.29 (0.78-2.06)

*Impaired renal function was defined as final eGFR of less than 90 mL/min/1.73 m², which was calculated either at 1 year after the completion of cancer therapy or at 5 years after initial diagnosis of cancer.
†The covariates assessed for the multivariable logistic-regression model were sex, initial eGFR at diagnosis, cancer group, chemotherapy, cyclophosphamide containing regimen, CT scans, AKI frequency, RRT, nephrectomy, or relapse.
‡Reference to OR in multivariable analysis is brain tumor in cancer group and the absence of the corresponding risk factor.
§Patients could have received more than 1 of the specified chemotherapeutic agents. Reference to such patients is patients who did not received any of the specified chemotherapeutic agents.