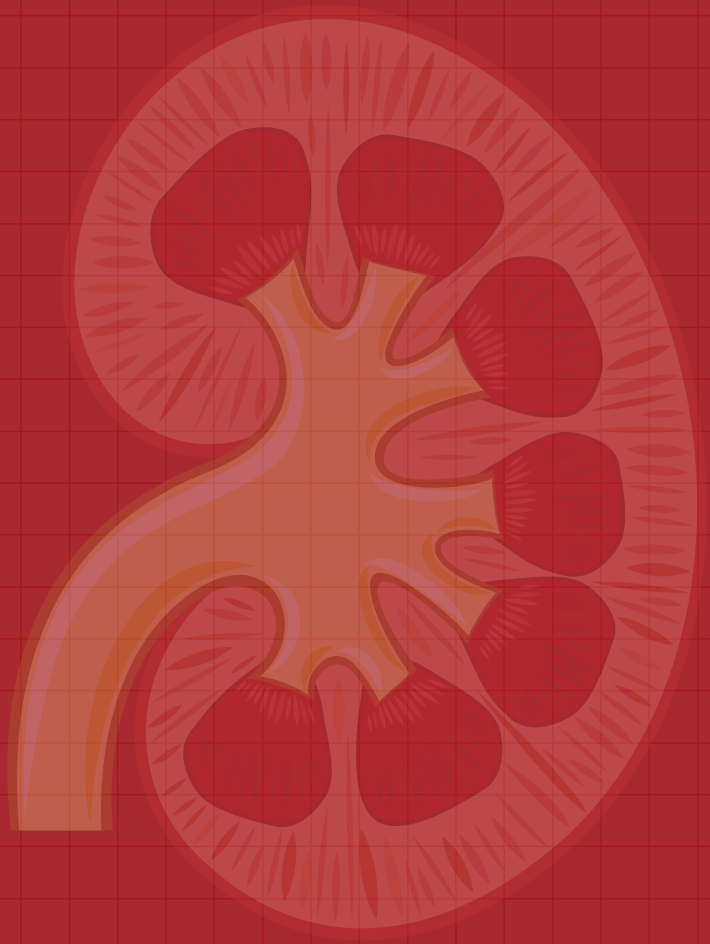
Strategies for Prevention and Management of CI-AKI and the Role of Contrast in Oncology CT Settings



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Strategies for Prevention and Management of CI-AKI and the Role of Contrast in Oncology CT Settings

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Preface

Contrast-induced acute kidney injury (CI-AKI) occurs in up to 30% cancer patients who receive iodinated contrast media (CM) for diagnostic, assessment, and management purposes. It is generally considered to be the third most common cause of hospital-acquired AKI. Accurate assessment of the incidence of CI-AKI is, however, obscured using different definitions and diagnostic criteria, the different populations studied and the prophylactic measures put in place. A deeper understanding of the mechanisms that underlie CI-AKI is required to enable reliable risk assessment for individual patients, as their medical histories will determine the specific pathways by which contrast media administration might lead to kidney damage. Here, we highlight the current definition of CI-AKI, as recommended by the International guidelines, common triggers and risk factors that prompt the development of CI-AKI in cancer patients, and optimal use of CM in cancer patients. We also discuss effective preventive measures, such as adequate hydration prior to CM administration, appropriate selection of CM, and avoidance of concomitant use of nephrotoxic agents. Understanding of how CI-AKI arises in different patient groups could enable a marked reduction in incidence and improved outcomes. The ultimate goal is to shape CI-AKI prevention strategies for individual patients. This compendium compiles the consensus report from India on Strategies for Prevention & Management of CI-AKI and the role of contrast in oncology CT setting. A panel of eminent nephrologists, radiologists, and oncologists were speakers during this meeting.

Synopsis

Cancer is the fourth leading cause of death in India. Contrast-based imaging plays a pivotal role in diagnosis, staging, response assessment, and follow-up of cancer patients. However, contrast-induced renal toxicity represents an important cause of acute kidney injury (AKI) in these patients, whose renal function is already compromised due to the disease per se, chemotherapy, comorbidities and other factors. Onco-nephrology is a rapidly growing area of nephrology where kidney disease in cancer patients has become an important source of consultations, with the trend occurring over the last 10–15 years [1].

A substantial proportion of patients receiving contrast media (CM) are at risk of CI-AKI — 1-7% of patients overall [2] 30–37% of patients with underlying chronic kidney disease [3, 4] >50% of patients with multiple additional risk factors* [4].

Vast database shows the rate of contrast-induced AKI (CI-AKI) in cancer patients to range between 8-30% [5-9]. This high variability in the rate of CI-AKI is largely attributable to inhomogeneity in the terminology and definition of CI-AKI. It is, therefore, important to increase awareness about CI-AKI, as well as homogenize the terminology and definition to develop best practices protocol and mitigate the damage induced by CM. According to the most recent guidelines, CI-AKI may be defined as an increase in serum creatinine (Cr) of ≥ 0.3 mg/dl, or of ≥ 1.5–1.9 times baseline (Kidney Disease: Improving Global Outcomes [KDIGO] definition of AKI) in the 48–72 h following CM administration. CI-AKI in oncology patients is associated with increased mortality, duration of hospital stays and hospital cost. Overall, early recognition of CI-AKI is recommended as it is a potentially preventable complication of CM use.

The choice of CM greatly influences the risk of CI-AKI in cancer patients. The osmolality of CM is a very important factor in preventing CI-AKI. Evolution of CT contrast has always focused on its osmolality. Closer the osmolality of the CM to that of blood, lesser will be the negative impact on volume balance. Also, care must be taken in cancer patients in terms of maintaining normal osmotic pressure in veins in order to minimize contrast-associated pain, which can be severe in oncology patients. It is also important to protect the kidneys from the ill-effects of CM. Hence, the choice of CM in these patients is of utmost importance.

Despite significant incidence of CI-AKI in cancer patients, there are only a few International expert groups that have provided recommendations on the management of CI-AKI in these patients. American Society of Nephrology (ASN) has laid down strong guidelines in the onco-nephrology curriculum around CI-AKI. These suggestions could be extrapolated to cancer patients.

Overall, while International guidelines on prevention and management of CI-AKI are available, currently there is an urgent need for developing an India-specific, multi-specialty consensus report/management algorithm for best practices on CI-AKI management in cancer patients. This booklet presents consensus report through panel discussions on the strategies for management of CI-AKI.

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*Additional risk factors include hypotension, intra-aortic balloon pump, congestive heart failure, age >75 years, anaemia, and diabetes.

Oncologists' Perspective on Kidney Injury in Cancer Patients

Burden of Cancer in India

The incidence of cancer is rising in India at an alarming rate. The cancer-related death rates have steadily increased over the past two decades. Currently, it stands at the 4th common cause of death in India. According to Indian Council for Medical Research (ICMR), India is likely to have over 17.3 lakh new cases of cancer and over 8.8 lakh deaths due to the disease by 2020, with cancers of breast, lung, and cervix topping the list.

Use of Imaging with Contrast in Oncology

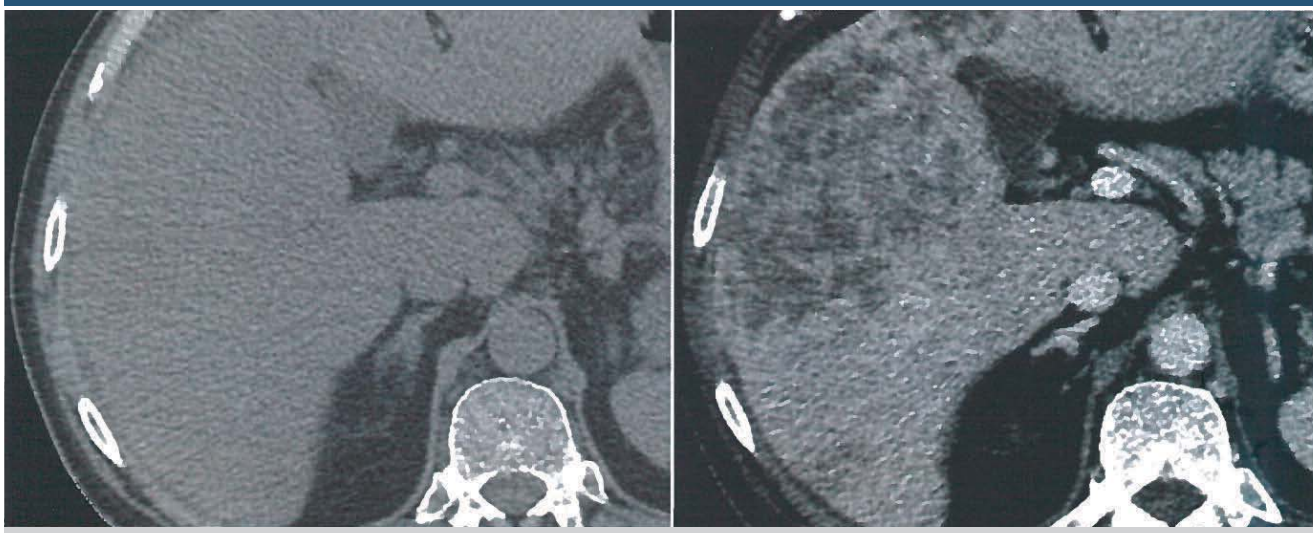
Over the last few years, the use of imaging has increased drastically in all fields of medicine, especially in oncology. Contrast-enhanced CT (CECT) not only helps in detection of a pathologic lesion but also in its characterization (Fig. 1). The contrast-based imaging in oncology is used but not limited to:

- Staging of cancers,
- Angiography of various tumors,
- Response evaluation after therapy,
- Follow-up of cancer patients,
- Characterizing optimum site of biopsy for diagnostic purposes,
- Characterization of suspicious lesions, and
- Screening for cancers.

Protecting Kidney in Cancer Patients

Certain cancers carry a much higher risk of acute kidney injury (AKI) than others [1]. Kidneys have a rich blood supply (25%

Lesions may be missed when non-enhanced CT scans are performed in cancer patients.*



Patient suffering from chronic liver disease was sent for a liver function test. The figures show the importance of an enhanced image because the carcinoma would have been missed without the contrast media enhancement.

Images courtesy of Sapienza University of Rome

**As well as increasing sensitivity for detection of pathologic lesions, contrast enhancement can improve accuracy in lesion characterization*

Fig. 1. Contrast-enhanced CT offers substantial benefits for detecting and characterizing pathologic lesions.

of cardiac output), which ensures high levels of toxicant delivery. High tubular re-absorptive capacity of kidneys can lead to high intracellular tubular cell concentrations of any drug. In addition, kidneys can concentrate toxins to high levels within the medullary interstitium; an important site for xenobiotic metabolism and may transform relatively harmless parent compounds into toxic metabolites.

Kidneys also have a high metabolic rate and the workload to renal cells results in increased sensitivity to toxicants and a high sensitivity to vasoactive agents. As kidneys are major elimination pathway for many antineoplastic drugs and their metabolites, any impairment in renal functions can result in delayed drug excretion and metabolism of chemotherapeutic agents, resulting in increased systemic toxicity. Understandably, many drugs require dose adjustment when administered in the setting of renal insufficiency.

In general, oncology patients are at heightened risk of nephropathy owing to the disease per se, its treatment or its follow-up. The various types of clinical settings where the risk of nephropathy in oncology patients is increased are:

- Tumor lysis syndrome (TLS);
- Hypercalcemia;
- Cancers, such as multiple myeloma where light chain are excreted via kidneys and cause renal failure;
- Pelvic tumors – hydronephrosis;
- Dehydration – vomiting, diarrhoea, and poor intake;
- Liver dysfunction due to metastases;
- Nephrotoxic chemotherapy drugs;
- Supportive care drugs – NSAIDs and zoledronic acid;
- Infections – sepsis and septic shock;
- Comorbidities – diabetes and metastatic involvement;
- Tumor or treatment-related microangiopathy;
- Tumor or treatment-related nephritic syndrome; and
- Contrast-induced acute kidney injury (CI-AKI).

Potentially, most of the anti-cancer drugs are nephrotoxic. But, few of them are more notorious for causing nephrotoxicity. These include methotrexate, cisplatin, ifosfamide, epirubicin, gemcitabine, carboplatin, doxorubicin, paclitaxel, oxaliplatin, irinotecan, bevacizumab, and trastuzumab.

Cisplatin merits further elaboration, as it can cause acute tubular necrosis (ATN), interstitial damage, and AKI due to dehydration-related hypovolemia (Tables 1–3).

Table 1. Drugs associated with tubular toxicity.

Drugs	Pathological findings	Clinical syndromes
Cisplatin	• Acute tubular necrosis • Chronic interstitial fibrosis and cyst formation	• Acute kidney injury • Hypomagnesemia • Renal sodium wasting • Chronic kidney disease
Ifosfamide	• Acute tubular necrosis	• Fanconi syndrome (partial/complete) • Acute kidney injury • End stage renal disease
Methotrexate	• Crystal nephropathy	• Nonoliguric acute kidney injury
Pemetrexed	• Acute tubular necrosis • Acute interstitial nephritis • Tubular atrophy and interstitial fibrosis	• Acute kidney injury • Chronic kidney disease • Nephrogenic diabetes insipidus
Ipilimumab	• Acute interstitial nephritis	• Acute kidney injury

American Society of Nephrology; Onco-Nephrology Curriculum; 2016.

Table 2. Drugs associated with glomerular toxicity.

Drugs	Pathological findings	Clinical syndromes
Gemcitabine	• Thrombotic microangiopathy	• Acute kidney injury • Microangiopathic hemolytic anemia • Hypertension
Mitomycin	• Thrombotic microangiopathy	• Dose dependent: Acute kidney injury, microangiopathic hemolytic anemia • Hypertension
Bevacizumab	• Thrombotic microangiopathy	• Proteinuria • Hypertension • Less common: Nephrotic syndrome, acute kidney injury, microangiopathic hemolytic anemia
Vascular endothelial growth factor multitarget tyrosine kinase inhibitors (VEGFR mTKI) Sunitinib Sorafenib Axitinib Pazopanib	• Thrombotic microangiopathy • MCD/cFSGS (minimal change disease and/or collapsing-like focal segmental glomerulosclerosis)	• Proteinuria • Hypertension • Less common: Nephrotic syndrome • Acute kidney injury, microangiopathic hemolytic anemia

American Society of Nephrology; Onco-Nephrology Curriculum; 2016.

Table 3. Drugs causing electrolyte abnormalities.

Drugs	Pathological findings	Clinical syndromes
Epithelial growth factor (EGFR) antibody	• Inhibition of transient receptor potential cation channel, subfamily M, member 6 (TRPM6) in distal convoluted tubule	• Hypomagnesemia
Cetuximab		
Panitumumab		
Imatinib	• Unknown	• Hypophosphatemia

American Society of Nephrology; Onco-Nephrology Curriculum;2016.

Intravenous iodinated contrast is a common cause of AKI in patients with cancer [1].

The risk for CI-AKI is likely to be relatively high among oncology patients.[2,3]

Exposure to nephrotoxic agents

– e.g. cytotoxic drugs, antibiotics, and analgesics [2]

Complicated by other issues

– e.g. anaemia, hypercalcaemia, and hyperuricaemia [2]

Compromised by advancing age

– predisposed to dehydration [3] and declining renal function [4]

Even when baseline SCr is normal/near normal, a significant portion of cancer patients still seem to be at risk for CI-AKI [3]

– with creatinine, a by-product of muscle metabolism, a low muscle mass may result in a low SCr that masks underlying renal insufficiency [3]

– renal function tests may remain within normal ranges, despite up to 50% of nephrons being lost and the kidney being susceptible to further insults [5]

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Fig. 2. Risk factors for AKI in patients with cancer.

Multiple Risk Factors for AKI in Cancer Patients

Patients with cancer are at an increased risk of AKI. **Manifestations of kidney disease from chemotherapy and targeted therapy include AKI, proteinuria, electrolytes derangements, and thrombotic microangiopathy (TMA). Nearly one-half of patients with multiple myeloma have evidence of AKI on initial presentation, and 10% require dialysis** [1]. A range of factors, including patient characteristics, such as age and comorbidities, as well as healthcare interventions may increase the risk of AKI in them. It may be possible to modify some of these factors before contrast-enhanced imaging, depending on the timeframe available (e.g. control of glucose levels and blood pressure). Figure 2 depicts multiple risk factors for AKI in oncology settings. At this juncture, it would be worthwhile to mention that creatinine is a by-product of muscle metabolism. A low muscle mass in cachexic cancer patients may result in a low serum creatinine (Cr), which may mask the underlying renal insufficiency.

Summary

Oncology patients might have higher incidence of CI-AKI compared to non-oncology patients. The benefits of contrast imaging, especially in oncology, have increased drastically. It is considered as "a 'guiding hand' of personalized medicine for cancer care." The data on association of CI-AKI with chemotherapy is accumulating and research shows that certain chemotherapeutic agents predispose to CI-AKI more than others. Despite advances in diagnosis, treatment, and prevention of chemotherapy-induced kidney injury, significant challenges remain about this entity. Future research should be directed towards the development of antidote agents that protect normal cells and allow continuation of chemotherapy without compromising antitumor effects.

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Nephrologists' Viewpoint on Recent Advances in CI-AKI

Burden of Nephrotoxicity

Acute kidney injury (AKI) is a common disorder in hospital settings and the most common cause of AKI is sepsis. However, causes like cardiorenal syndrome are taking over, with oncologic causes becoming an important component of AKI pathogenesis. Among the mechanisms of AKI, most are either ischemic, inflammatory or toxic. Renal toxicity by contrast media (CM) represents an important cause of AKI. It is important to increase awareness about this contrast induced AKI (CI-AKI) to homogenize the terminology and definition of CI-AKI as well as to develop best practices protocol and mitigate the damage induced by CM.

Terminology of CI-AKI

RIFLE Criteria for AKI

Variability in the definitions of CI-AKI have important consequences in terms of resource allocation (determining estimates of the incidence, costs, and outcomes of AKI), the timing of consultation and the methodology and comparability of clinical trials. Therefore, in 2004, the Acute Dialysis Quality Initiative (ADQI) sought a consensus definition that:

- Clearly established the presence or absence of the disease,
- Gave an idea of the severity of the disease,
- Correlated disease severity with outcome, and
- Was easy to understand and applicable in a variety of clinical and research settings.

The result was the Risk, Injury, Failure, Loss, End-stage renal disease (RIFLE) classification (Fig. 1).

Acute kidney injury network (AKIN) in 2007, led an initiative to develop uniform standards for defining and classifying AKI and to establish a forum for multidisciplinary interaction to improve care for patients with or at risk for AKI.

Acute kidney injury network proposed a modification to this system, i.e., RIFLE classification, to consider the evidence that lower serum creatinine (Cr) changes might be associated with adverse outcomes and allow patients to be staged. **AKIN**

As per the literature and recent guidelines, it is sufficient to label a patient as AKI once there is an absolute increase of 0.3 mg/dL in serum Cr value or 1.5 times increase in Cr value from the baseline within 48 hours of injecting the contrast. Clinicians should use consistent criteria to diagnose and classify AKI, based on the latest guidelines.

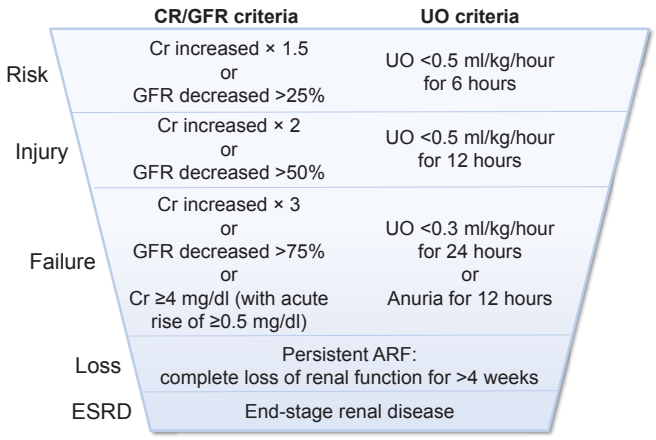


Fig. 1. RIFLE: Risk, Injury, Failure, Loss, ESRD.

ARF: acute renal failure; Cr: creatinine; ESRD: end-stage renal disease; UO: urinary output

Source: Figure adapted from Bellomo R, *et al. Crit Care.* 2004; 8: R204–R212.

Diagnostic criteria.
An abrupt (within 48 hours) reduction in kidney function currently defined as an absolute increase in SCr of more than or equal to 0.3 mg/dl (≥26.4 µmol/l), a percentage increase in SCr of more than or equal to 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 ml/kg/hour for more than 6 hours).

Classification/staging for AKI.		
Stage	**Serum creatinine criteria**	**Urine output criteria**
1	Increase in SCr of more than or equal to 0.3 mg/dl (≥26.4 µmol/l) or increase to more than or equal to 150% to 200% (1.5- to 2-fold) from baseline	Less than 0.5 ml/kg/hour for more than 6 hours
2	Increase in SCr to more than 200% to 300% (>2- to 3-fold) from baseline	Less than 0.5 ml/kg/hour for more than 12 hours
3	Increase in SCr to more than 300% (>3-fold) from baseline (or SCr of more than or equal to 4.0 mg/dl [≥354 µmol/l] with an acute increase of at least 0.5 mg/dl [44 µmol/l])	Less than 0.3 ml/kg/hour for 24 hours or anuria for 12 hours

Fig. 2. Acute kidney injury network (AKIN) diagnostic criteria and classification/staging for AKI.

AKI: acute kidney injury; SCr: serum creatinine

Source: Mehta R, *et al*. *Crit Care.* 2007; 11: R31.

Box 1: AKI biomarkers.
Inflammatory biomarkers
Neutrophil gelatinase-associated lipocalin (NGAL)
Interleukin-18 (IL-18)
Tubular proteins
Kidney injury molecule-1 (KIM-1)
Na+/H+ exchanger isoform 3 (NHE3)
Surrogate markers of tubular injury
Urinary low molecular weight proteins escaping reabsorption on tubular injury (cystatin C, or microglobulin, and retinol binding protein)
Urinary tubular enzymes released on tubular injury (NAG: N-acetyl--D-glucosaminidase; AP: alkaline phosphatase; GT: gamma-glutamyl-transferase, etc.)

added an absolute change in serum Cr of ≥0.3 mg/dl and removed criteria for GFR. The AKIN system also omitted the stages "loss" and "end-stage renal disease", as these were outcomes rather than stages (Fig. 2).

However, it needs to be clear that the term AKI covers a spectrum from subclinical to clinical kidney damage (i.e., not just overt injury). Clinicians should use consistent criteria to diagnose and classify AKI, based on the latest guidelines (i.e., using a serum Cr cutoff of 0.3 mg/dl or 25%). **Although there is concern that these cutoffs would result in a substantial increase in the number of reported cases, these patients need to have their risk recognized and managed, to avoid the long-term health and financial burden of progressive kidney disease.**

The patients with CI-AKI suffer from significant morbidity and mortality. The term CI-AKI is more universal currently and the term contrast nephropathy is no longer in use as it is imperative that the terminology is homogenized. **In addition, if the terminology is not consistent, comparison of the data will not be possible in this era of large database and pragmatic trials happening all over the world.**

Biomarkers in CI-AKI

To minimize the risk, healthcare professionals need to work together across disciplines, with nephrologists, radiologists, oncologists, and cardiologists, all involved in multidisciplinary decisions. Everyone needs to understand and recognize the potential long-term effects of nephron loss, and take steps to minimize such damage, even if the clinical consequences are not immediately apparent. Biomarkers are desperately needed to help clinicians identify patients with kidney damage before serum Cr levels are affected. While the kidney dysfunction can be indicated by Cr level, kidney damage will be identified with the help of biomarkers. Box 1 mentions AKI biomarkers. The Nephro Check diagnostic test for TIMP-2 and IGFBP-7 has been approved in the USA by the FDA.

Damage to kidneys can happen even when the Cr levels do not rise. Subclinical AKI, with no Cr rise but raised biomarkers is still AKI and needs attention. **eGFR cannot be used to describe acute changes in kidney function. In this regard, direct measurement of GFR is advised. However, eGFR is a excellent tool to describe baseline kidney function in steady state conditions and it is more reliable than Cr level. Evaluation of renal functional reserve can further help to clarify the conditions of the kidneys.** The CKD-EPI formula gives the most accurate eGFR:

$$eGFR = 141 \times min(Scr/k,1)^{a} \times max(Scr/k,1)^{-1.209} \times 0.993^{age} \times (1.018 \text{ if Female}) \times (1.159 \text{ if Black})$$

where SCr is serum creatinine (mg/dL), k is 0.7 for females and 0.9 for males, a is -0.329 for females and -0.411 for males, min indicates the minimum of SCr/k or 1, and max indicates the maximum of SCr/k or 1.

If serum Cr is measured in µmol/l, divide the Cr value obtained by 88. The simplified formula for eGFR is available online (https://www.kidney.org/apps/professionals/egfr-calculator). Figure 3 depicts biomarkers dynamics in CI-AKI.

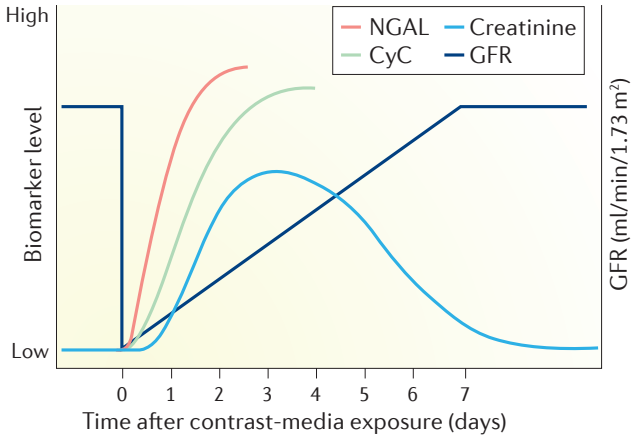


Fig. 3. Biomarkers dynamics in contrast-induced acute kidney injury (CI-AKI). Modelling serum creatinine time courses revealed a specific pattern during CI-AKI, which is characterized by a sharp decline in glomerular filtration rate (GFR) followed by slow GFR recovery. Typically, serum creatinine levels peak 2–3 days after contrast medium exposure. The tubular specific biomarker neutrophil gelatinase-associated lipocalin (NGAL) is particularly sensitive for the early diagnosis of acute kidney injury (AKI), including CI-AKI, showing an increase as early as 6 h post-procedure. Levels of cystatin C (CyC), an indicator of GFR, increase within 24 h after administration of contrast medium, thus constituting a further putative indicator of early stages of CI-AKI.

Renal Functional Reserve

The difference between baseline GFR and increased GFR (as in pregnancy, diabetes mellitus or increased protein intake and other conditions) is called as renal functional reserve. **Even if there is a loss of 50% of the nephrons functionally (as in case of damage to one out of two kidneys), the patient will have normal GFR, but, the renal functional reserve is lost completely.**

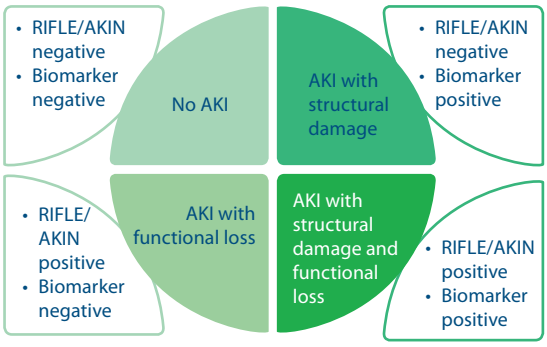
After an insult to kidney, complete recovery occurs when baseline GFR as well as renal function reserves recover completely. But, **a partial recovery is said to happen when baseline GFR recovers but renal function reserve does not.** The kidney which recovers partially is highly susceptible to kidney disease; any future insult to such a kidney results in increase in Cr but not GFR. This condition leads to chronic renal hypoperfusion, apoptosis, sclerosis, and progression to CKD.

In patients presenting for diagnosis of cancer or for treatment with chemotherapeutic drugs, the presence of renal function reserve will ensure that kidney functions are not affected even if a strong chemotherapeutic drug or a CM is used. **However, in patients with damage to renal function reserve, even a minor insult by a chemotherapeutic drug or CM will lead to AKI.** So, the development of AKI is always dependent on a balance between exposure to nephrotoxic agents and susceptibility of the kidney to damage.

Patients who develop AKI have almost 10 times more chances of developing CKD. The risk is influenced by decreasing renal functions and increasing comorbidities (especially the increasing rate of diabetes globally), as well as CM use due to the growing number of procedures. The risk of AKI in patients receiving CM for diagnostic imaging appears to be lower than in patients having interventional procedures; however, the risk is not zero and must not be ignored. Overall, recognition of full spetrum of AKI will improve its detection and management. Figure 4 depicts full spectrum of AKI.

It would be worthwhile to mention that prophylactic renal replacement therapy with hemodialysis or hemofiltration does not appear to prevent the development of CI-AKI. In a meta-analysis of studies involving hemodialysis/hemofiltration in patients scheduled for radiocontrast media administration,

Many subclinical insults or events happen to kidney which affect the renal functional reserve but do not affect the baseline GFR. But, when insults to kidney occur in future, the baseline GFR also starts getting affected and patient progresses on the slippery path of chronic kidney disease (CKD).



AKI: Acute Kidney Injury
AKIN: Acute Kidney Injury Network
RIFLE: Risk, Injury, Failure, Loss, End-stage renal disease

Fig. 4. Recognition of the full spectrum of AKI will improve detection and management.

Source: Ronco C, *et al. Eur Radiol.* 2013;23:319–323.

Summary
It needs to be clearly emphasized that patients must not be denied necessary procedures because of the fear of CI-AKI. CM exposure can be tailored to GFR.
Developments in imaging modalities are already offering improved image quality without the need for high dose of CM or radiation exposure.
If possible, a nephrologist should be involved in managing patients with AKI; there is evidence that mortality and complications are reduced if a nephrologist is involved. However, it is acknowledged that such support may not be acutely available; as an alternative, non-nephrologists need resources to help them understand and manage AKI themselves.
Management of CI-AKI should be based on locally-agreed protocols.
Hemodialysis (using a high-flux membrane) might be useful to remove CM after the procedure, although it may be too late to prevent some kidney damage.
The timing of follow-up assessments for AKI needs to be highlighted. Serum Cr should be measured within 48–72 hours, although ideally, a biomarker of damage that can be used within 4-6 hours, before patient is discharged, is awaited.
The patient should also be followed up after 90 days to identify whether acute kidney damage has progressed to CKD.
The young residents should be made aware that AKI, a previously neglected disease, has attained mammoth proportions and needs to be tackled at an early stage.

it was found that these prophylactic therapies offered no beneficial effects against CI-AKI. In fact, hemodialysis rather appeared to increase the risk of CI-AKI [1].

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The Optimal Use of Contrast Media in Cancer Patients – Radiologists' Perspective

Introduction

Imaging in patients with cancer has increased exponentially for diagnosis, staging, follow-up, and surveillance. The radiologist has to be prudent in choosing the modality for investigation and use of contrast media (CM) so that imaging studies do not further contribute to morbidity in patients undergoing chemo or immunotherapy. Radiologists have to work closely with oncologists and nephrologists to ensure optimum renal health in these patients.

In this chapter, we will discuss optimization of imaging protocols and contrast usage to reduce the risk of renal injury in an oncologic setting.

Computed Tomography (CT) Protocols

Low radiation-dose CT examinations would be the norm in not too distant future. Low-kVp CT protocols have been developed to decrease quantity of CM administered and radiation dose. Relative attenuation of iodinated CM is increased at lower kVp resulting in higher contrast enhancement than that obtained at higher kVp for a similar amount of administered CM. Iodine attenuation is higher at low-kVp and thus signal-to-noise ratio (SNR) can be kept constant with reduced radiation exposure. Use of high iodine concentration produces more noise but can be offset by lowering the mAs which in turn implies reduced radiation dose. The low kV and "low mAs–high iodine concentration" options can be combined to maximize the reduction in radiation dose and contrast volume.

Iterative Reconstruction (IR) [1]

Iterative reconstruction is a new technique of image reconstruction for reducing radiation exposure that utilizes an alternative image reconstruction algorithm to filtered back projection to reduce noise without impairing signal. This is available in all new generation scanners and is known by several acronyms like ASIR and ASIR-v (from GE Healthcare), IRIS and ADMIRE (Siemens), iDOSE4 (Philips Healthcare), and AIDR (from Toshiba).

Higher SNR can be used to improve image quality and visualization of small enhancing structures and arterially enhancing lesions. Low-kVp by itself can lead to an increase in image quality. With IR, further reduction of noise and thus an increase in SNR would be possible, resulting in increased image quality without compromising on diagnostic capabilities. IR additionally reduces radiation dose. SNR values are similar to "low-kVp alone" and low-mAs/high-iodine signal approaches. Another advantage is reduced iodine dose. The benefits of using low-kVp CT include reduction in the dose of CM and dose of ionizing radiation [2]. Combined with automatic kVp selection tools, reference mAs should be set at a lower level when using a contrast injection protocol that provides higher signal.

With IR, there is lowered radiation exposure and mAs can be reduced to obtain an SNR that is likely to be low-kVp without IR. IR additionally reduces radiation dose. SNR values are similar to "low-kVp alone" and low-mAs/high-iodine signal approaches. Another advantage is reduced iodine dose. The benefits of using low-kVp CT include reduction in the dose of CM and dose of ionising radiation [2].

This chapter has been written with expert scientific inputs by Dr Ravikanth Balaji (Head of Department - Radiology, Apollo Speciality Hospital, Chennai).

Combined with automatic kVp selection tools, reference mAs should be set at a lower level when using a contrast injection protocol that provides higher signal.

Importance of Iodine Delivery Rate [3]

Two injection parameters influence iodine enhancement in CT:

- Total iodine dose (D) which is calculated as volume (ml) x iodine concentration (g iodine/ml), and
- Iodine delivery rate (IDR) (g iodine/s) which is calculated as flow rate ml/s x iodine concentration (g iodine/ml)

where, dose D determines maximum enhancement in venous phase examinations.

Iodine delivery rate influences maximum enhancement in first pass examinations such as CT angiography (CTA), arterial phase imaging and perfusion CT.

Maintaining high iodine concentration and reducing only volume administered for same injection rate is that IDR remains high resulting in greater enhancement and potentially-improved image quality.

High iodine concentration and lower volume, more practically, permits the optimization of injection protocols.

Safety and Tolerability [4]

Safety and tolerability are influenced by iodine dose, injection volume and flow rate. High flow rate in elderly patients or in patients with poor venous condition may be difficult to achieve or potentially harmful. Higher concentration CM at reduced flow rate is potentially advantageous in reducing intolerability while maintaining a sufficiently high IDR. Reduced total volume of administered CM is beneficial in terms of lowered cardiac preload.

High flow rate is associated with:

- greater patient discomfort,
- increased heat sensation,
- higher post-examination heart rate, and
- increased number of premature heartbeats.

Here, it will be worthwhile to mention that, isosmolar CM is designed and studied to be more tolerable to patients, compared to high and low osmolar CM.

Contrast Medium Osmolality

Low-osmolar CM (LOCM) have more cytotoxic effects than iso-osmolarity contrast media (IOCM) based on consistent evidence from cultured tubular cells. In addition, in animal models, IOCM is associated with a lower induction of NOX4-dependent reactive oxygen species (ROS) generation. Also, IOCM exerts fewer vasoconstriction effects than LOCM [5].

Contrast Medium Viscosity [6]

The role of viscosity in contrast-induced acute kidney injury (CI-AKI) risk is still being debated. All CM, which are more viscous than plasma, and agents with increased osmolality that have lower viscosity may still lead to AKI [5]. Solution viscosity increases when iodine concentration is increased. Injection pressure increases with viscosity. Warming the CM reduces viscosity leading to higher injection rates and better patient tolerability.

Hydration Protocol

The contrast-induced nephropathy (CIN) Consensus Working Panel found that adequate intravenous (IV) volume expansion with isotonic crystalloids (1-1.5 mL/kg/h), 3-12 hours before the procedure and continued for 6-24 hours afterward, decreases the incidence of CI-AKI in patients at risk. For hospitalized patients, volume expansion should begin 6 hours prior to the procedure and be continued for 6-24 hours post procedure. For outpatients, administration of fluids can be initiated 3 hours before and continued for 12 hours after the procedure. Post-procedure volume expansion is more important than pre-procedure hydration [7].

Drug Interactions to be Avoided [8]

- Discontinue nephrotoxic drugs;
- Non-steroid anti-inflammatory drugs (NSAIDs) must be particularly avoided;
- Maintain an interval of 7 days between sessions of chemotherapy-platinum derivatives;
- Metformin to be avoided/stopped as it prevents renal clearance of lactic acid;

- Treatment with derivatives of metformin should be stopped for 48 hours following the injection of iodinated contrast medium (ICM). However, stopping the treatment 48 hours before the examination is based on the eGFR, and
- An interval of at least 3 days, up to 5 days if possible, between two injections of ICM is advised.

Route of Contrast Administration and Risk of CI-AKI

Contrary to previous belief, a recent study (published in 2016) suggested that intra-arterial administration of contrast material during cardiac catheterization had a similar risk of AKI as compared with that of CT scanning involving IV administration in a cohort of patients who underwent both procedures [9].

Summary
When a patient with malignancy who is at risk for CI-AKI requires an imaging study, the first determination that should be made is whether the desired clinical information can be obtained without use of intravascular contrast.
Low osmolar or iso-osmolar contrast agent should be used in conjunction with an IV saline hydration regimen.
Use the lowest dose of CM.
Low dose contrast-enhanced MRI examination should be performed using a low-risk agent as it has a clearer safety margin.
Multi-detector CT has dramatically short image acquisition time. Bolus duration should mimic the scanning duration.
Long injection leads to a waste of CM because CM administered after acquisition of data does not contribute to data acquisition.
Contrast medium should be at body temperature. At room temperature, in most radiology units, viscosity is high. High viscosity makes the patient more prone to AKI, contrast-induced side effects, as well increased extravasation of the contrast.

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Review of Clinical Evidence of Contrast Induced-Acute Kidney Injury (CI-AKI) in Oncology Settings

Imaging, especially with contrast-enhanced computed tomography (CECT), plays a pivotal role in cancer for diagnosis, staging, response assessment, and follow-up. Cancer patients are exposed to contrast medium (CM) many times, which may increase their already high risk of kidney impairment. Increased recognition of acute kidney injury (AKI) is recommended in the clinical setting as it is a potentially preventable complication of CM use and encourages best practice in risk assessment and prevention of AKI.

Clinical Evidence of AKI Risk in Cancer Patients

An American study investigated the incidence and outcomes of AKI in cancer patients admitted to the M.D. Anderson Cancer Center over 3 months in 2006; admission was defined as hospital stay for >23 hours (including midnight) [1]. For inclusion in this cross-sectional analysis, the patients were required to have had serum creatinine (Cr) measurement at the time of admission and at least one more measurement during their hospital stay. A total of 3,558 patients met these criteria. AKI was diagnosed using modified Risk, Injury, Failure, Loss, ESRD (RIFLE) criterion of an increase in serum Cr of ≥50% during hospital stay.

The rates of AKI and in-hospital mortality were noted to be 12% and 4.6%, respectively. AKI in comparison with no AKI significantly increased the risk of in-hospital mortality on both univariate and multivariate analyses (Fig. 1). Furthermore, worsening renal function, based on RIFLE categories, significantly increased the mortality risk. Approximately 55% of AKI cases occurred more than 48 hours after admission. AKI in comparison with no AKI was associated with approximately 2-fold increase in the length of hospital stay and hospital costs (Fig. 2).

Contrast medium administration was the most strongly associated risk factor for AKI, as depicted in Figure 3. The frequency of AKI was noted to be higher with agents already known to be associated with nephrotoxicity, such as cisplatin, carboplatin, methotrexate, interleukin-2, rituximab, and ifosfamide.

Based on the results of the meta-analysis, the investigators concluded that the rate of AKI is higher in cancer patients than non-cancer patients, with CM as the strongest risk factor for AKI, and an important step in minimizing the burden of AKI on healthcare resources in identification of patients at high risk.

Korean experts have also investigated the rate of AKI in cancer patients and potential predictors of CI-AKI in them [2]. They performed a retrospective analysis of 820 patients presenting at the emergency department at a tertiary care academic medical centre between October 2014 and March 2015. The studied patients had active cancer, were without CKD and had normal or near-normal serum Cr at baseline (≤1.5 mg/dl). These patients underwent CECT with

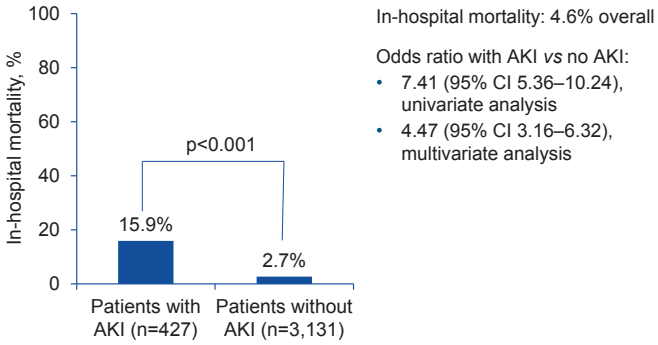
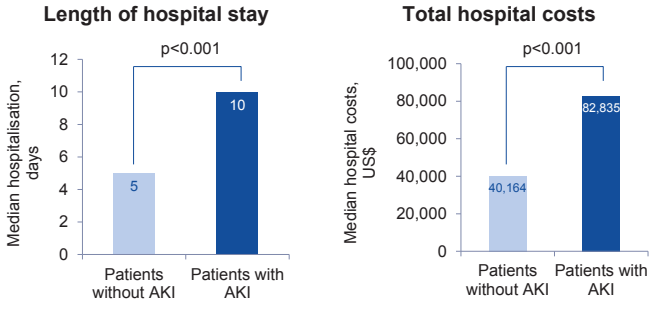


Fig. 1. Mortality in cancer patients with AKI: MD Anderson analysis.

Source: [1]



- Median length of stay increased 100% and median hospital costs increased 106% in patients with AKI *vs* those without AKI

Fig. 2. Healthcare use in cancer patients with AKI: MD Anderson analysis.

Source: [1]

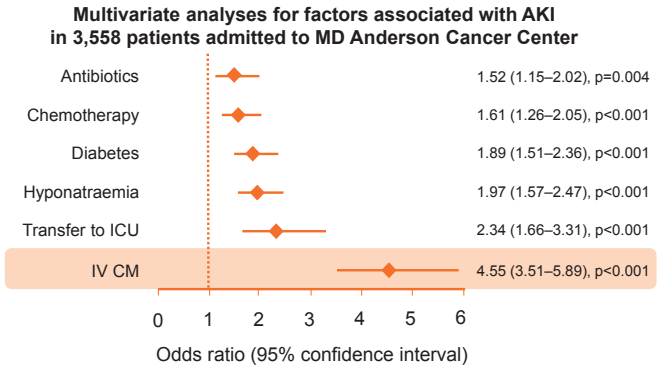


Fig. 3. Risk of AKI in cancer patients: MD Anderson analysis.

AKI: acute kidney injury (≥50% increase in serum creatinine); CM: contrast medium; ICU: intensive care unit; IV: intravenous

Source: [1]

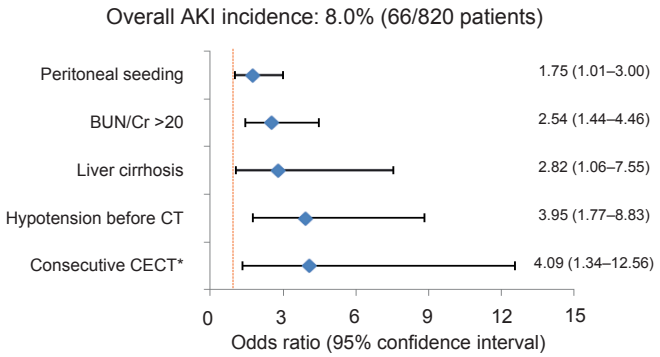


Fig. 4. AKI incidence in cancer patients in an emergency settings.

*Non-simultaneous CECT performed 24–72 hours after first scan

AKI: acute kidney injury (serum creatinine increase of ≥25% or ≥0.5 mg/dl over 48–72 hours); BUN/Cr: blood–urea–nitrogen/creatinine ratio; CECT: contrast-enhanced computed tomography; CT: computed tomography

Source: Figure adapted from [2]

non-ionic, low-osmolar contrast agents, such as iohexol, iopamidol, iopromide, and ioversol; 80–150 ml, depending on body region. Patients were hydrated with normal saline at the rate of 40–60 ml/hour. AKI was defined as a serum Cr increase of ≥25% or ≥0.5 mg/dl over 48–72 hours.

The incidence rate of CI-AKI in the study patients was 8% (Fig. 4). However, the authors acknowledged that exclusion of patients without Cr follow-up measurements may have influenced this incidence rate. Except for liver cirrhosis which was more prevalent in AKI-positive patients than non-AKI patients (9.1% vs 3.6%, respectively), there was no difference in comorbidities between the two groups. Furthermore, no relationship was found between the development of AKI and the type of CT, volume of CM used or number of CT scans performed. **Mortality was higher in patients who developed AKI than those who did not (10.6% vs 2.3%, respectively; p=0.002).**

Based on the findings, it was concluded that **even in patients with normal or "near normal" baseline serum Cr levels, the rate of AKI could be substantial.**

Similarly, a prospective Turkish study has assessed the specific risk of CI-AKI in cancer patients with normal or near-normal kidney function at baseline [3]. The study patients had GFR >50 ml/min, were well-hydrated prior to undergoing CECT, and were not receiving nephrotoxic drugs other than chemotherapy. Contrast agent employed was iopromide or iohexol, in the amount of 50–100 ml depending on body region. AKI was defined as ≥25% or ≥0.5 mg/dl increase in serum Cr within 72 hours of CECT.

The rate of AKI in this study was quite high (20%) compared with other reports, even though the patient population was selected to have good renal function at baseline. AKI developed in 26% patients who received chemotherapy vs 11% who did not receive it (p=0.1). The time between the last chemotherapy treatment and contrast administration, showed a significant association with the development of AKI. While the mean time between CECT and the last chemotherapy administration was 27 days (median 10, range 1–160) in patients who developed AKI, it was 66 days (median 25, range 1–350) in those who did not (p=0.1) develop it. **The risk of AKI was significantly increased in patients who had CECT within 45 days vs those who had CECT >45 days after the last chemotherapy administration or those who never had chemotherapy (Fig. 5).** Also, the risk of AKI was significantly increased among patients who had CECT within 45 days vs all other patients in the study. **On logistic regression analysis, only CT within 45 days**

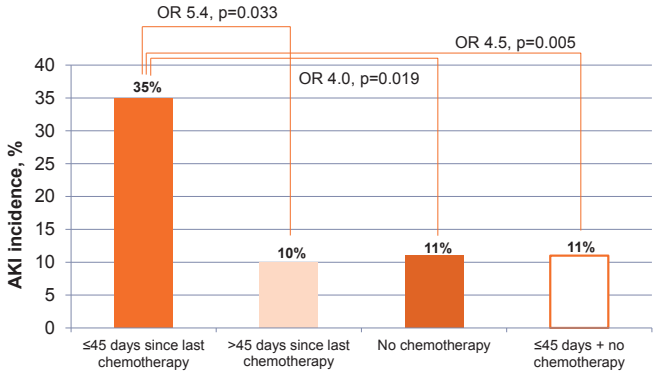


Fig. 5. Effect of chemotherapy and CM on the incidence of AKI in hospitalized cancer patients undergoing CECT.

AKI: acute kidney injury (≥25% or ≥0.5 mg/dl increase in serum creatinine within 72 hours); CECT: contrast-enhanced computed tomography; CM: contrast medium; OR: odds ratio

Source: [3]

Overall AKI rate:
- 29% (58/197 patients)

2.56-fold increased risk with CM ≤1 week before cisplatin *vs* no CM exposure

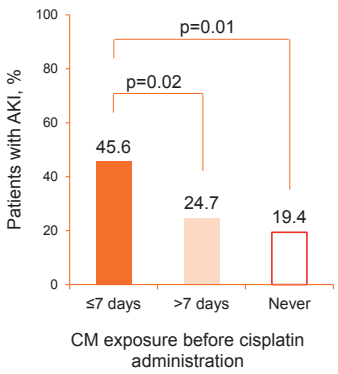


Fig. 6. AKI in cancer patients receiving cisplatin.

Source: [4]

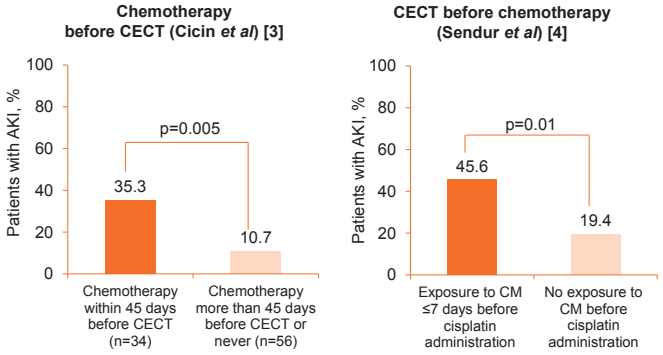


Fig. 7. Cumulative effect of chemotherapy and CM on AKI.

AKI: acute kidney injury (Cicin, *et al*: ≥25% or ≥0.5 mg/dl increase in serum creatinine within 72 hours of CECT; Sendur, *et al*: ≥25% decrease in glomerular filtration rate from baseline); CECT: contrast-enhanced computed tomography; CM: contrast medium

Source: [3, 4]

after the last chemotherapy administration was found to be an independent risk factor for AKI (odds ratio 4.3, p=0.016). Additionally, there appeared to be a higher risk of AKI in patients with hypertension and those receiving the combination of irinotecan and bevacizumab.

It was concluded that CI-AKI is a serious problem associated with the use of CM in oncological patients undergoing CT examination, and the risk is increased if CECT is performed within 45 days of the last chemotherapy.

Cisplatin is a widely used potent chemotherapeutic agent. It, however, is nephrotoxic and is notorious for causing AKI. Renal tubular dysfunction and cumulative renal impairment are important dose-limiting effects of cisplatin, which were noted to be affecting >50% of patients in early trials (before intensive hydration regimens were introduced). A yet another Turkish study assessed the incidence of AKI in hospitalized cancer patients receiving cisplatin and aimed to develop a risk prediction methodology for cisplatin-induced AKI to guide decisions on patient management and preventive measures [4].

Acute kidney injury occurred in 29.4% of cisplatin-treated patients. The authors looked at several potential risk factors for AKI, including demographic and tumor characteristics, comorbidities, cancer treatments, and previous CM exposure. Only CM use was found to be statistically greater in patients with AKI than in those without it (p=0.01). A significant difference was found when CM was administered <1 week prior to cisplatin therapy vs no CM exposure (45.6% vs 19.4%; p=0.01) or CM administered >1 week prior to cisplatin therapy (45.6% vs 24.7%; p=0.02).

Overall, there was 2.56-fold increased risk when CM was administered ≤1 week before cisplatin vs no CM exposure (Fig. 6).

It was concluded that CM exposure within 1 week of cisplatin-based chemotherapy significantly increased the risk of AKI.

The above-described clinical trials also indicate that proximity between chemotherapy and CM use increases the risk of AKI, regardless of whether CM use precedes or follows chemotherapy (Fig. 7) [3, 4].

Summary
Increased recognition of AKI is recommended in the clinical setting as it is a potentially preventable complication of CM use and encourages best practice in risk assessment and prevention of AKI.
Contrast medium administration was the most strongly associated risk factor for AKI.
The incidence and severity of renal toxicity increases with repeated usage of cisplatin-based chemotherapy and can become irreversible.
Death was more common in patients who developed AKI.
The studies suggest that proximity between chemotherapy and CM use increases the risk of AKI.
There is a clinical need to predict the probability of AKI to make decisions about patients' management and take measures to prevent or mitigate the nephrotoxic effects.

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Burden of AKI in Oncology Patients – Does the Choice of Contrast Media Matter?

Researchers point out that the mechanisms of nephropathy due to chemotherapy and contrast medium (CM) use are similar, involving vasoconstriction, inflammation, tissue damage, and direct cytotoxic effects. Thus, it is not surprising that acute kidney injury (AKI) develops more frequently in chemotherapy recipients exposed to CM.

Structures and Properties of CM

- Contrast media are tri-iodinated benzene derivatives with iodine atoms in positions 2, 4, and 6.
- Other ring positions are occupied by side chains, aimed at improving solubility, osmolality, protein binding, and tolerance.

Contrast Media Profiles

Many iodinated CM are available, each with its own unique profile, including pharmacological characteristics such as structure, ionicity, iodine content, viscosity, and osmolality.

Pharmacokinetic Properties of CM

- Following intravenous (IV) administration, CM have a short distribution half-life ($t½_{d}$).
- Usually, the time for the CM to distribute evenly over the fluids ranges from 2 to 30 mins.
- Plasma protein binding is approximately 1-3%.
- Patients with normal renal function can excrete approximately 100% of the CM in the first 24 h after administration.
- In patients with decreased renal function the $t½_{el}$ can increase to 40 h or more.

Osmolality of CM

While the viscosity and osmolality of these agents vary, all have iodine concentrations between 270 and 400 mg/ml, which is sufficient to provide adequate radiographic opacification. High-osmolar contrast media (HOCM) and low-osmolar contrast media (LOCM) are hyperosmolar to blood, whereas iso-osmolar contrast media (IOCM), such as iodixanol has same physiological osmolality as blood (290 mOSm/kg H_2O). **When a CM has a higher osmolality than blood, water can be drawn from the vascular endothelial cells, red blood cells and extravascular interstitium.** Consequently, these agents may pose a significant risk in patients with low cardiac output and pulmonary congestion, as the osmotic pressure (and the amount) of contrast material may have negative effects on the volume balance in these patients. Iodixanol is isosmolar to blood and induces less fluid shift from the red blood cells (RBCs) and across the vessel walls. The net transfer of fluid from the RBCs may lead to morphological changes making them less able to bend and conform as they pass through smaller capillaries (Fig. 1). Table 1 describes the structure and properties of various CM used in radiological settings.

Is Isosmolar Contrast Medium (IOCM) Better Than Low Osmolar Contrast Medium (LOCM) – Clinical Evidence

A retrospective study recently compared the rates of AKI, emergent dialysis, and mortality between patients who

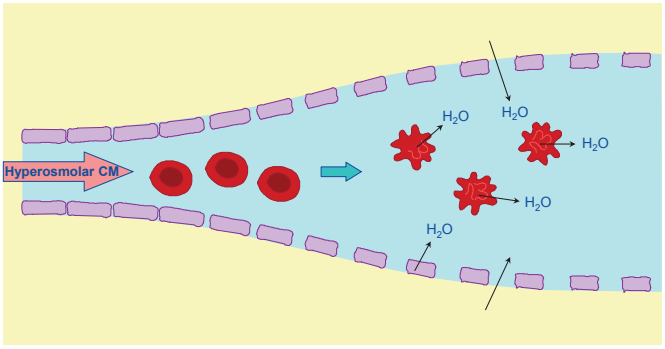

Fig. 1. Fluid shifts across osmotic gradients.
Source: Adapted from Tsai, *et al*. 2008; Swanson, *et al*. 1990; Rienmuller, *et al*. 2001

Table 1: Structure and properties of various contrast media used in radiological settings.

Name	Benzene rings	Ionicity	Iodine content, mg/ml	Viscosity at 37°C, mPa·s	Osmolality mOsm/kg H_2O
Diatrizoate	Monomer	Ionic	140–462	1.4–19.5	550–2,938
Iothalamate	Monomer	Ionic	141–480	1.5–9.0	600–2,400
Ioxitalamate	Monomer	Ionic	120–380	1.1–8.5	610–2,160
Ioxaglate	Dimer	Ionic	160–350	1.7–10.5	295–680
Iohexol	Monomer	Non-ionic	200–350	2.4–10.6	410–780
Iopamidol	Monomer	Non-ionic	150–370	1.5–9.5	300–832
Ioversol	Monomer	Non-ionic	160–350	1.6–9.0	355–790
Iopromide	Monomer	Non-ionic	150–370	1.2–9.5	340–780
Iobitridol	Monomer	Non-ionic	250–350	4.0–10.0	585–915
Iomeprol	Monomer	Non-ionic	150–400	1.4–12.6	301–730
Iodixanol	Dimer	Non-ionic	270–320	5.7–11.1	290

CM: contrast media
Adapted from Davidson C, *et al*. *Am J Cardiol*. 2006;98(Suppl): 42K–58K.

Important Physicochemical Characteristics of CT CM and Their Clinical Relevance

- Solubility of CM is high with non-ionic agents with hydrophilic side chains and low with ionic media with lipophilic side chains. The adverse reaction profile is better with non-ionic agents.
- Osmolality of CM increases with ionicity as well as iodine concentration. It is advised to use the CM with osmolality closer to blood.
- Viscosity of CM increases with iodine concentration and molecular size and decreases with temperature. So warming the CM before administration is always recommended.

underwent CECT using IOCM iodixanol and those who underwent non-contrast CT scans [1]. The study patients (n = 5758) had been admitted in the neurosurgery department between January 2003 and December 2014. Propensity score matching was used to maximize the homogeneity between the CECT and non-contrast CT groups. Based on the baseline eGFR, the patients were further stratified into subgroups of stages 1-2 CKD (eGFR ≥60 ml/min/1.73 m^2), stage 3 CKD (eGFR < 60 ml/min/1.73 m^2), and stage 5 CKD (eGFR <30 ml/min/1.73 m^2), respectively.

Remarkably, **the rates of AKI, dialysis, and mortality were noted to be similar between the patients who underwent CECT using iodixanol and those who had non-contrast CT scans**. It was concluded that use of iodixanol does not increase the risk of AKI, emergent dialysis, or mortality even in patients who are at high risk of developing CI-AKI.

> "Mayo Clinic guidelines [1] recommend use of the IOCM iodixanol for patients at high risk of developing post-contrast AKI (PC-AKI), including patients with greatly elevated baseline SCr levels, reduced eGFR, and other risk factors, in lieu of the use of our standard low-osmolar contrast material."

Another retrospective observational study assessed the risk of CI-AKI in high-risk cancer patients with underlying renal insufficiency, undergoing diagnostic CT examination at a US cancer institute [2]. The comparison group comprised of cancer patients undergoing diagnostic CT scan, but having **normal baseline renal function**. For comparative analyses, patients were divided into three groups according to their risk profile: patients with elevated baseline serum Cr levels (receiving iodixanol); patients at high risk of CI-AKI with normal baseline serum Cr levels (receiving iodixanol); and patients at low risk of CI-AKI with normal baseline serum Cr levels (receiving iohexol, LOCM). Renal insufficiency was indicated by serum Cr > 1.2 mg/dL in females and > 1.5 mg/dL in males; and CI-AKI was denoted by an absolute elevation of 0.5 mg/dL or 25% elevation in serum Cr level.

The AKI rate (Fig. 2) was highest in patients with raised baseline serum Cr levels who additionally had other risk factors, such as diabetes mellitus (23%) and use of nephrotoxic medications (48%); these patients were also generally older than those in the other two groups and had a higher rate of cardiovascular disease. Nonetheless, **the authors concluded**

that if iodixanol is used in such patients, the rate of AKI is not prohibitively high to preclude this group from receiving diagnostic imaging, if clinically required.

A prospective randomized, double-blind trial investigated the effects of IV administration of IOCM (iodixanol, n = 61) vs LOCM (iopromide, n = 56) on renal functions in high-risk patients undergoing IV CECT; renal functions were assessed in terms of change in serum Cr and GFR [3]. The high-risk study patients had decreased renal function at baseline. The use of measures to protect the kidney (e.g. hydration and prophylactic treatments) was at the discretion of the referring clinician requesting the scan. Outcome measures were serum Cr increase or GFR decrease for 3 days after CT, a serum Cr increase (of ≥0.5 mg/dL [25%] or ≥1.0 mg/dL [50%]), a GFR reduction (of ≥5 mL/min), and patient outcome at 30- and 90-day follow-up. AKI was defined as ≥25% or 0.5 mg/dl increase in serum Cr from baseline.

Even though iodixanol group included higher proportion of patients with diabetes and hypertension than iopromide group, the rate of AKI was lower in iodixanol group than iopromide group (Fig. 3). Another interesting observation was that serum Cr levels decreased within 24 hours of iodixanol use, whereas they increased over the same period following iopromide use. It was concluded that IV CM use even in high-risk patients is unlikely to be associated with permanent adverse outcomes. Furthermore, **use of iodixanol produces significantly less rise in serum Cr levels than iopromide use.**

More recently, a randomized controlled trial assessed the safety profile of IOCM versus LOCM in cancer patients at very low risk of AKI (eGFR of > 60 ml/min), undergoing

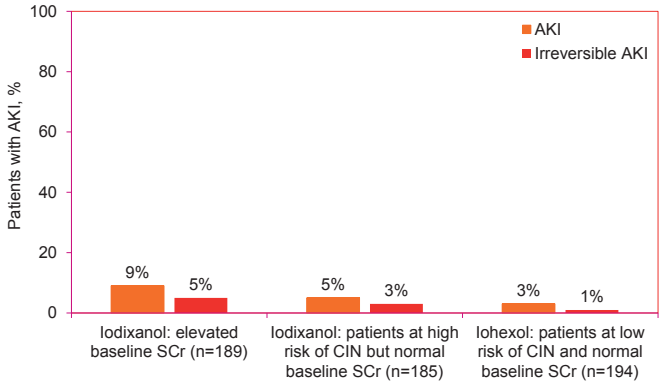

Fig. 2. Risk of AKI with iodixanol in high-risk patients.

AKI: acute kidney injury (increase in SCr ≥25% or ≥0.5 mg/dl from baseline)
SCr: serum creatinine

Source: [2]

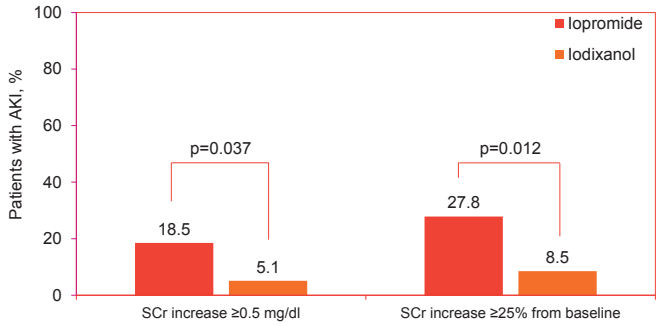

Fig. 3. Risk of AKI with iodixanol vs iopromide in high-risk patients.

AKI: acute kidney injury; SCr: serum creatinine

Source: [3]

CECT [4]. This study was **prospective, multicentre, double-blind, and randomized** in patients with a clinical indication for CT. Out of total 497 patients who were eligible for the study, 247 were randomized to iodixanol (IOCM) and 250 to iopromide (LOCM).

Primary outcomes were development of CI-AKI at 24 and/or 72 hours. Other outcomes assessed were irreversible CI-AKI, average eGFR percentage variation (%Δ), and adverse events. Seven and three CI-AKI at 24 hr ($p = 0.34$) and 8 and 2 CIN at 72 hr ($p = 0.11$) occurred in the iopromide and iodixanol groups, respectively (Fig. 4). Within the subgroup of individual patients who developed CI-AKI (N: 17), the event rate was higher in the iopromide arm ($p = 0.045$; Fig. 4). No cases of permanent CI-AKI or significant differences in terms of AEs or GFR %Δ were observed.

Favourable safety profile of iodixanol was reflected by comparative lower rate of CI-AKI in iodixanol group than iopromide group ($p = 0.045$).

Safety and Tolerability of Iodixanol in Clinical Settings

Tangible evidence shows IOCM iodixanol to have favourable safety profile as compared with LOCM iopromide when administered intra-arterially. Patients with cancer often experience severe pain and heat sensations because of chemotherapy or CM on their venous integrity. Therefore, it is important to assess the safety profile of IV administration of CM in these patients. Weiland, *et al.* in a prospective, randomized, double-blind, multicenter study sought to evaluate and compare the frequency and intensity of patient

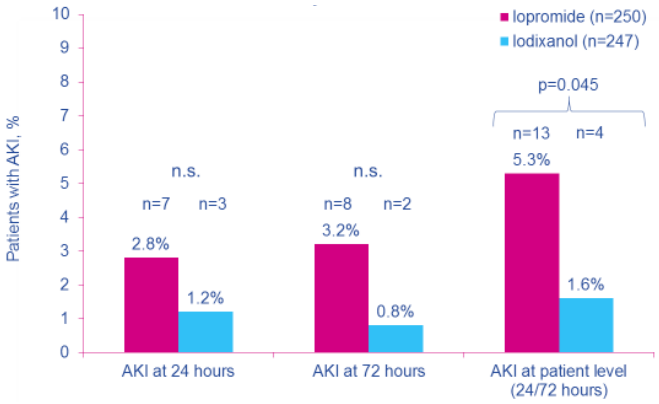

Fig. 4. Risk of AKI with iodixanol vs iopromide in low-risk patients.

AKI: acute kidney injury (increase in SCr ≥25% or ≥0.5 mg/dl from baseline); SCr: serum creatinine; n.s.: not significant

Source: [4]

discomfort following IV administration of iodixanol or iopamidol in patients undergoing CECT as part of their routine medical care [5]. The presence of discomfort (heat, pain, and coldness) and intensity was verbally rated by patients on a 0-10 scale and converted into four categories (none: 0; mild: 1-3; moderate: 4-7; and severe: 8-10, severe).

A total of 299 patients were enrolled in the study, out of which 151 patients received iodixanol and 148 patients received iopamidol. The rates of moderate-to-severe discomfort and severe discomfort were significantly less in iodixanol groups than iopamidol group – moderate-to-severe discomfort rates: 35.1% vs 67.3%, respectively, p<0.0001; severe discomfort rates: 2.6% vs 16.3%, respectively; p=0.0004. Heat was the main factor prompting reports of discomfort. A statistically higher proportion of patients in iodixanol group than iopamidol group experienced no discomfort (21.2% vs 7.5%, p=0.0008). Another remarkable observation was higher rate of excellent overall image quality in iodixanol group, although the difference did not reach statistical significance (95.4% vs 89.9%, respectively, p=0.0508). Overall, **the rate of severe discomfort with iopamidol was about 6 times greater than that with iodixanol.**

A post-marketing surveillance study aimed to determine the frequency and severity of adverse drug reactions (ADRs) and discomfort with iodixanol use for CECT scans by radiologists in private practice in Germany [6]. Patients were asked to report immediate or delayed adverse reactions after CM administration. Patients were also asked to rate discomfort (pain, heat, and coldness), if any, on a scale of 0-10.

The overall incidence of ADRs was 0.74%, with immediate ADRs accounting for 0.30% and delayed ADRs for 0.42% incidence. Serious ADRs were observed in only 0.05% patients. No contrast-related deaths occurred. Discomfort was generally reported as mild and the composite score of discomfort ranged between 0-3 in majority of the patients (72%). **Based on the findings, it was concluded that iodixanol shows excellent safety and tolerability profile.**

Summary
Acute kidney injury is a significant burden in cancer, dramatically increasing patient mortality and hospital costs.
The risk of AKI in cancer patients is increased if they receive CM and nephrotoxic chemotherapy.
In renally impaired cancer patients, the rate of CI-AKI with Iodixanol may not preclude them from having CECT.
In patients with apparently normal renal function but with other risk factors for AKI, iodixanol can help address renal complications.
Because iodixanol has been designed to maintain normal osmotic pressure in the veins, it also minimizes contrast-associated pain, which can be severe in oncology patients.
Iodixanol has been developed to protect the kidneys and improve patient tolerability.

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Note on International Guidelines on AKI Management

Few International expert groups have provided recommendations on the management of acute kidney injury (AKI) specifically in cancer patients.

Onco-nephrology curriculum of American Society of Nephrology (ASN) offers the following guidance on prevention and management of AKI and contrast-induced nephropathy (CIN) [1]:

- The Kidney Disease Improving Global Outcomes (KDIGO) work group has combined components of the RIFLE and AKIN classifications, to define AKI as: (1) a rise in serum creatinine (Cr) ≥ 0.3 mg/dL within 48 hours; (2) ≥ 1.5 times increase in serum Cr values from baseline within the prior 7 days; or (3) a urine output of < 0.5 mL/kg/h for 6 hours.
- Estimated glomerular filtration rate (eGFR) provides resonable estimate of renal function.
- In adults, the **CKD-EPI or MDRD** formula are most commonly used to estimate GFR.
- In children, the revised Schwartz formula is used to estimate GFR.
- Use the lowest dose of CM consistent with a diagnostic result.
- Risk factors for AKI include underlying CKD, diabetes mellitus, volume depletion, and co-administration of other nephrotoxins.
- In addition, **high osmolar (>1400 mOsm/kg) and low osmolar (600–800 mOsm/kg) contrast agents are associated with a higher incidence of AKI in comparison to iso-osmolar (300 mOsm/kg) contrast**.
- Preventive measures should be taken in patients with GFR, <60 mL/min including limiting contrast volume, using iso-osmolar contrast, prehydration with normal saline, and discontinuation of concurrent nephrotoxic agents.
- Several meta-analyses have examined the use of N-acetylcysteine in the prevention of CIN but results remain inconclusive, as is the use of bicarbonate. There is insufficient evidence to recommend hemodialysis or hemofiltration for the prevention or treatment of CIN.

In a very recent consensus statement from Italy, titled "Methods to Address Computed Tomography-Related Risk Factors in Oncology Patients: An Expert Opinion Based on Current Evidence" [2], practical methods to reduce risks in cancer patients related to CT examinations were derived from expert opinions based on the current literature, recently developed guidelines and technological advancements. The consensus mentions the following on the choice of CM in cancer patients:

- The use of CM with the lowest osmolarity is advisable, particularly in high-risk patients. **Patients with cancer must be considered as a high-risk group**, and **iso-osmolar contrast media (IOCM) should be considered the first choice**, particularly if the patients are affected by at least one of the following conditions: intra-arterial injection, diabetes mellitus, liver diseases, hypertension, pre-existing CKD (serumCr levels >2 mg/dL), hematocrit <30%, age over 70 years, cardiac diseases, and recent myocardial infarction (<1 month). **Iodixanol is the first choice for patients with myeloma or patients with monoclonal gammopathies, independent of additional risk factors**.

Figure 1 depicts algorithm for the prevention and management of CI-AKI in interventional cardiac settings, as proposed by Peter McCullough and his colleagues. Taking into consideration the multitude of risk factors in cancer patients, there is a compelling need to develop this kind of an algorithm for cancer patients as well. **Also, there is an emergent need for developing an India-specific, multi-specialty consensus report/management algorithm for best practices on CI-AKI management in oncology patients.**

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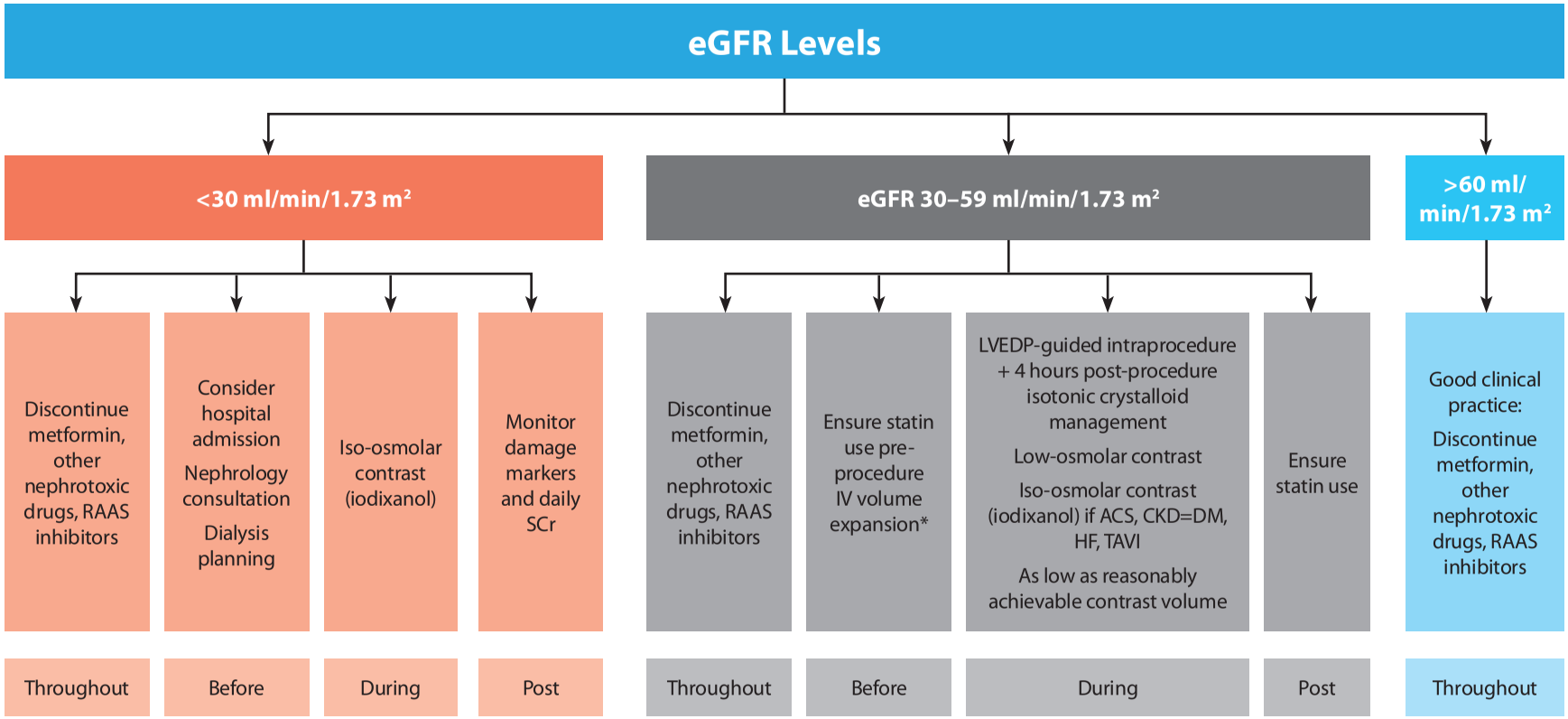

Fig. 1. Algorithm for the Prevention and Management of Contrast-Induced Acute Kidney Injury.

*Adapted from Algorithm for the Prevention and Management of CI-AKI. McCullough, P.A., *et al. J Am Coll Cardiol.* 2016;68(13):1465–1473.

Expert Opinion/Recommendations to Prevent CI-AKI in Oncology Patients.

Expert Opinion

- ✓ Oncology patients are at heightened risk of acute kidney injury (AKI) due to the disease per se, chemotherapy, comorbidities, and frequent use of contrast-based imaging studies.
- ✓ Most of the anti-cancer drugs, including methotrexate, cisplatin, ifosfamide, epirubicin, gemcitabine, carboplatin, doxorubicin, paclitaxel, oxaliplatin, irinotecan, bevacizumab, and trastuzumab, are nephrotoxic.
- ✓ The most recent guidelines define contrast-induced AKI (CI-AKI) as an increase in serum creatinine (Cr) of ≥ 0.3 mg/dl, or of ≥ 1.5–1.9 times baseline (KDIGO definition of AKI) in the 48–72 h following contrast media (CM) administration.
- ✓ Damage to kidneys can occur even when the serum Cr levels do not rise. Subclinical AKI, with no rise in serum Cr but raised biomarkers, is still AKI and needs attention.
- ✓ Estimated glomerular filtration rate (eGFR) is the best marker of renal functions, since serum Cr may vary based on various factors such as age, sex, muscle mass, drug inhibitions, inter laboratory variations, etc.
- ✓ Patients must not be denied necessary procedures because of the fear of CI-AKI. CM exposure can be tailored to GFR.
- ✓ Adequate hydration is one of the major factors in preventing CI-AKI. Decision on use of nephrotoxic and other concomitant drugs during contrast based-imaging, should be carefully evaluated.
- ✓ The choice of CM should be based on various factors such as demographics and disease condition, comorbidities, concomitant medications, risk of CI-AKI, complications, etc.
- ✓ Isosmolar contrast media (IOCM) have osmolality as that of blood and benefit the patients by improving tolerability and reducing the risk of CI-AKI in high risk patients. Hence in patients with high risk of CI-AKI, IOCM can be preferred over low osmolar contrast media (LOCM).
- ✓ The incremental cost of IOCM over LOCM is well-justified among high-risk patients.

Do's and Don'ts Before, During, and After Contrast-Based Imaging to Prevent CI-AKI.

Do's and Don'ts

- ✓ Assess the risk for CI-AKI in all patients who are considered for a procedure that requires intravascular/intra-arterial administration of iodinated contrast medium (CM). Use eGFR to assess kidney function of the patient.
- ✓ Use a uniform definition-based on serum creatinine (Cr) and urine output to diagnose AKI.
- ✓ Use the lowest dose of CM consistent with the diagnostic results.
- ✓ The incidence of CI-AKI will decrease dramatically when the right volume expansion protocols are implemented.
- ✓ The recommendation of "nil per os after midnight" before a planned imaging examination should, therefore, be reconsidered.
- ✓ Metformin needs to be withheld to avoid lactic acidosis, ACE/ARBs may, however, be continued.
- ✓ Administration of nephrotoxic drugs should be based on the benefit-risk ratio.
- ✓ Isosmolar contrast media (IOCM) should be preferred over low osmolar contrast media (LOCM) in patients with high risk of CI-AKI.

Notes:-