



# Acute kidney injury from contrast-enhanced CT procedures in patients with cancer: white paper to highlight its clinical relevance and discuss applicable preventive strategies

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## ABSTRACT

Patients with cancer are subjected to several imaging examinations which frequently require the administration of contrast medium (CM). However, it has been estimated that acute kidney injury (AKI) due to the injection of iodinated CM accounts for 11% of all cases of AKI, and it is reported in up to 2% of all computed tomography (CT) examinations. Remarkably, the risks of developing AKI are increased in the elderly, in patients with chronic kidney disease or diabetes, and with dehydration or administration of nephrotoxic chemotherapeutics. Given the common occurrence of post-contrast acute kidney injury (PC-AKI) in clinical practice, primary care physicians and all specialists involved in managing patients with cancer should be aware of the strategies to reduce the risk of this event. In 2018, a panel of five experts from the specialties of radiology, oncology and nephrology were speakers at the annual meeting of the Italian Society of Medical Radiology (Società Italiana di Radiologia Medica e Interventistica), with the aim of commenting on existing evidence and providing their experience on the incidence and management of PC-AKI in patients with cancer. The discussion represented the basis for this white paper, which is intended to be a practical guide organised by statements describing methods to reduce renal injury risks related to CM-enhanced CT examinations in patients with cancer.

## INTRODUCTION

The role of contrast medium-enhanced computed tomography (CECT) is extremely important throughout the whole natural history of patients with cancer, being key to correctly characterise and stage the disease, to monitor response to anticancer treatments and to monitor the risk of progression or relapse during follow-up.

Furthermore, the increased survival achieved in the past decades, due to improvements in the treatment of a number of malignancies, is associated with a growing number of patients with cancer with an active disease, or in follow-up after treatment, or aged 70

years or more<sup>1</sup>; these patients are therefore expected to present a number of comorbidities,<sup>2</sup> including acute and chronic kidney disease (CKD).

Thus, contrast medium (CM)-related renal damage is worthy of attention, representing one of the key topics covered by the recently born subspecialty of onconephrology.<sup>3</sup>

A consensus-based paper, established on a modified Delphi approach, on methods to reduce risks related to computed tomography (CT) examinations in patients with cancer has already been recently published.<sup>2</sup> In order to better focus on CM-induced renal damage, a multidisciplinary panel of experts from the specialties of radiology, oncology and nephrology assembled in 2018. Their specific aim was to comment on existing evidence and to provide their experience on the incidence and management of acute kidney injury (AKI) in patients with cancer who receive iodinated CM. The discussion represented the basis for this white paper, which is intended to be a practical guide organised by statements (some of which were already provided in the article by Del Mastro *et al*<sup>2</sup>). In particular, clinical questions, which were derived from clinical needs, and an integration of all the expert's suggestions, are stated further. The statements and the recommendations appear in italics in the boxes.

Patients with cancer are subjected to several imaging examinations, which frequently require the administration of iodinated CM.<sup>4,5</sup> However, it has been estimated that AKI due to injection of iodinated CM accounts for 11% of all cases of AKI, and it is reported in up to 2% of all CT examinations.<sup>5</sup>

There are many causes of AKI following iodinated CM administration, not directly caused by CM, so that AKI is often mistakenly

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## Should an iodinated CM injection be considered a relevant risk factor for AKI?

- ▶ The administration of iodinated CM is a well-known risk factor for AKI.
- ▶ AKI in patients undergoing iodinated CM injections may be due to the CM itself or to other concomitant risk factors, leading to different definitions of AKI in this setting: contrast-induced AKI (CI-AKI) versus post-contrast AKI (PC-AKI).
- ▶ Whenever it is impossible to clearly differentiate between these two definitions, the term PC-AKI should be used.

attributed to CM; this led to the development of the European Society of Uroradiology (ESUR) definition of 'PC-AKI', which is used to describe a decrease in renal function that follows intravascular administration of CM, but it is not strictly caused by CM; PC-AKI is thus defined as an increase in serum creatinine (SCr) of  $>0.3$  mg/dL (or  $>26.5$   $\mu$ mol/L), or  $>1.5$  times the baseline, within 48–72 hours of intravascular administration of a contrast agent.<sup>6</sup>

Instead, the term CI-AKI should only be used when the causative relationship between AKI and CM administration is proven, a relationship which is often difficult to establish. Thus, throughout the whole manuscript, we did use the term PC-AKI.

In oncological patients, PC-AKI is often multifactorial, highlighting the need to consider and weight each of the possible causes involved (age, oncological treatments, use of other nephrotoxic agents and dehydration).<sup>7</sup>

As far as PC-AKI in clinical practice is concerned, primary care physicians and all specialists involved in managing patients with cancer should be aware of the strategies to reduce the risk of this event.

## Is AKI a clinical issue in patients with cancer?

- ▶ AKI should be defined as SCr levels of  $\geq 0.3$  mg/dL or  $\geq 25\%$  within 48–72 hours.
- ▶ The incidence of AKI in patients with cancer ranges from 12% to 17%, and it is higher than the incidence observed in patients without cancer (5–8%).
- ▶ Risk factors include the type of cancer, comorbidities, cotreatment with other drugs (eg, furosemide, antibiotics, chemotherapy and iodinated CM administration).
- ▶ Specific cancer locations (eg, kidney, liver, oesophagus, pancreas and uterus) and cancer types (lymphomas, leukaemias, mixed lymphosarcoma and multiple myeloma) have been linked with an increased risk of AKI.
- ▶ Among commonly used anticancer agents (either cytotoxic chemotherapeutics, targeted agents or immune checkpoint inhibitors), an increased risk of AKI has been documented particularly in patients treated with pemetrexed, ifosfamide, cisplatin, bevacizumab and cetuximab.
- ▶ A short time span between chemotherapy administration and CM injection is associated with an increased risk of AKI. Closely repeated administrations of iodinated CM are associated with a higher risk of PC-AKI.

AKI is highly prevalent in patients with cancer, particularly in the case of renal cell cancer, liver cancer, multiple myeloma, leukaemias and lymphomas.<sup>8,9</sup> In a Danish population study, including 37267 patients with cancer, the risk of AKI (defined as  $>50\%$  increase in SCr levels) was approximately 17.5% within 1 year of a cancer diagnosis and 27% after 5 years.<sup>8</sup> The rate of AKI in hospitalised patients with cancer seems to be higher than the rate reported for hospitalised patients without cancer (12 vs 5–8%, respectively).<sup>9–11</sup>

Therefore, patients with cancer should be considered a population at high risk of developing AKI, and this condition is associated with major consequences on patients' status and a great impact on the healthcare system.<sup>9</sup> Salahudeen *et al*.<sup>9</sup> evaluated the effects of AKI on the clinical outcomes and costs related to hospital stays for patients with cancer. They reported a 4.7-fold increase in death, a 3-day increase in the length of hospital stay and a US\$42671 increase in costs for hospitalised patients with cancer, in comparison with those without. Moreover, the mortality rate in patients with AKI is higher in patients with cancer (42.8%) than in patients without cancer (22.5%) ( $p=0.014$ ).<sup>12</sup>

A number of factors and patient characteristics contribute to the increased risk of developing AKI in patients with cancer.<sup>13</sup> Furthermore, the odd ratio (OR) for developing AKI is significantly higher for cancer patients with diabetes (OR 1.89, 95% CI 1.51 to 2.36), those undergoing chemotherapy (OR 1.61, 95% CI 1.26 to 2.05), patients with hyponatraemia (OR 1.97, 95% CI 1.57 to 2.47), patients who use antibiotics (OR 1.52, 95% CI 1.15 to 2.02) and those undergoing an intravenous injection of iodinated CM (OR 4.55, 95% CI 3.51 to 5.89) compared with those without the aforementioned characteristics.<sup>9</sup> Other risk factors are heart failure, a recent myocardial infarction ( $<1$  month), hypertension, pre-existing CKD and age over 70 years.<sup>14</sup> Moreover, some types of cancer are associated with higher risk of developing AKI; namely, patients with cancer originating in the oesophagus, kidney, liver, pancreas or uterus and patients affected by lymphomas, leukaemia, mixed lymphosarcoma or multiple myeloma are considered to be at a very high risk, with a  $\geq 15\%$  probability of developing AKI compared with those with other types of cancer.<sup>9</sup>

According to all the aforementioned data, it is possible to identify some characteristics that make a patient with cancer particularly prone to develop AKI. Table 1 summarises characteristics of patients which, according to existing evidence and the clinical experience of the authors, can be associated with a high risk of developing AKI. In addition, current ESUR guidelines extensively discuss the different risks of developing PC-AKI.<sup>6</sup>

Medications play a critical role in inducing AKI; indeed, according to the Renal Insufficiency and Anticancer Medications study,<sup>15</sup> 50–60% of patients with cancer who are undergoing antineoplastic treatment develop a renal impairment, a figure higher than the incidence of PC-AKI itself. Beyond anticancer agents, oncological patients

**Table 1** Identification of patients at risk of developing PC-AKI, who should undergo prevention strategies

Factor	High-risk features	Medium-risk features	Low-risk features
Renal function	Established CKD or GFR <30 mL/min/1.73m <sup>2</sup> or <45mL/min/1.73 m <sup>2</sup>	GFR 30-45 mL/min/1.73 m <sup>2</sup>	GFR 45-60 mL/min/1.73 m <sup>2</sup>
Age (years)	≥70	≥60	<60
Heart failure	NYHA class ≥III or EF <30%	NYHA class <III or EF <35%	NYHA class I or EF <45%
Volume of CM (mL)	≥250	140–250	<140
Diabetes	Uncontrolled	Controlled with concomitant systemic diseases	Controlled without concomitant systemic diseases
Hb (g/L)	<95	<110	<145
Nephrotoxic drugs	Three concomitant	Two concomitant	One
Time of administration of oncological therapy and iodinated CM (days)	<8	<45	<45

Patients at high risk are those with at least one high-risk feature+one medium-risk feature, those with at least three medium-risk features or those carrying at least five low-risk features.

CKD, chronic kidney disease; CM, contrast medium; EF, ejection fraction; GFR, glomerular filtration rate; Hb, haemoglobin; NYHA, New York Heart Association; PC-AKI, post-contrast acute kidney injury.

are indeed exposed to multiple nephrotoxic insults, including antibiotics, analgesics and drugs for supportive therapy (eg, bisphosphonates).

Cisplatin is by far the most common cause of acute nephrotoxicity from anticancer agents; it typically causes glomerular impairment and tubulopathy, which ultimately leads to magnesuria and hypomagnesaemia.<sup>16</sup> The incidence and severity of renal toxicity increases with the repeated use of cycles of cisplatin-based chemotherapy, ultimately leading to an irreversible damage.

Cisplatin-treated patients with cancer receiving iodinated CM during radiological procedures are at a higher risk of PC-AKI. Indeed, exposure to iodinated CM within 1 week before cisplatin administration increased the risk of AKI by 2.56-fold.<sup>17</sup> Furthermore, the risk of PC-AKI was 2.56-fold higher (95% CI 1.28 to 5.11) in patients exposed to CM within 1 week before cisplatin administration than in patients without such exposure (p=0.009).<sup>18</sup>

Cicin *et al* reported an incidence of PC-AKI after chemotherapy in hospitalised patients with cancer of 20%.<sup>13</sup> Moreover, AKI developed 4.5 times more frequently in patients with cancer who had undergone injection of iodinated CM and underwent a CT scan within 45 days after their last chemotherapy treatment (p=0.005), thus proving iodinated CM injection to be an independent risk factor (p=0.017). In patients with cancer who require CECT in an emergency setting, the OR of developing PC-AKI (in this case defined as an increase in SCr levels of ≥0.5 mg/dL or ≥25% within 48–72 hours) was 4.09 (95% CI 1.34 to 12.56) in patients requiring serial examinations on consecutive days, compared with patients who only underwent scans on 1 day.<sup>19</sup> However, the presence of a confounding factor must be acknowledged; that is, patients requiring serial examination are often undergoing multiple treatments and are in a poorer health status and hence are at an inherently higher risk of AKI.

Despite this, the aforementioned evidence highlights the need to prevent the risk of PC-AKI in patients with cancer, especially in at-risk patients, such as those treated with cisplatin or other potentially nephrotoxic agents, or in those with pre-existing CKD and diabetes, or in elderly subjects.<sup>20–22</sup>

We should highlight that, in the real world, we simply cannot wait 45 days between chemotherapy and iodinated CM administration, especially considering that many cytotoxic agents are administered at intervals of 2, 3 or 4 weeks.

Another key point to keep in mind is that, beyond cisplatin, a number of other anticancer agents (eg, targeted agents and immune checkpoint inhibitors) may induce glomerular injury, tubulopathies as well as interstitial nephritis.<sup>23–25</sup> Thus, since almost all patients with cancer on active treatment undergo a number of CECT scans, the risk of an increased nephrotoxicity is particularly high, not to take into account the fact that patients on clinical trials usually undergo very closely repeated iodinated CM administration in order to monitor the activity of experimental treatments.

### Role of hydration and N-acetylcysteine

Prehydration with saline infusion is the only recommended measure to prevent AKI in the setting of CM infusion, as demonstrated by the results of the PRESERVE (Prevention of Serious Adverse Events Following Angiography) study, which enrolled patients scheduled for angiography.<sup>26</sup> The proposed dose regimen for pre-CM administration was 1–3 mL/kg/hour, to be started between 2 and 12 hours before the radiological procedure.

A systematic review and meta-analysis showed that, in patients undergoing any contrast-enhanced procedure, sodium bicarbonate significantly decreased the risk of PC-AKI, without a significant difference in need for renal

**PC-AKI prevention strategy: which kind of prophylaxis and on which patients?**

- ▶ PC-AKI should be prevented, whenever possible, in cancer patients at risk of AKI.
- ▶ Overall, prehydration and the use of tailored dose of iodinated CM in patients at high risk are recommended.
- ▶ A preventive strategy using saline prehydration, as well as the use of the CM with the lowest osmolarity, is highly advisable, particularly in high-risk patients.
- ▶ Iso-osmolar contrast medium (IOCM) should thus be considered the first choice in this setting, particularly if patients with cancer present a high risk of developing AKI (eg, they present diabetes, liver diseases, hypertension, pre-existing CKD, low hematocrit, age over 70 years, cardiac diseases and recent myocardial infarction (<1 month)).

replacement therapy, in-hospital mortality or congestive heart failure compared with controls. Similar results were seen for the risk of PC-AKI when sodium bicarbonate was compared with normal saline alone, but not when sodium bicarbonate/N-acetylcysteine combination was compared with N-acetylcysteine/normal saline combination.<sup>27</sup>

However, these results have been challenged by another meta-analysis,<sup>28</sup> as well as by the already mentioned PRESERVE study<sup>26</sup> and by the AMACING randomised trial,<sup>29</sup> and thus cannot be considered as definitive. In particular, in the AMACING trial, no prophylaxis was found to be non-inferior and cost-saving in preventing PC-AKI when compared with intravenous hydration.<sup>29</sup>

Although studies on oral hydration are limited, preliminary evidence on this strategy suggests that it is as safe and effective as intravenous prophylaxis.<sup>30</sup> For this reason, when it is not possible to hydrate the patient by the intravenous route, at least oral hydration is recommended.

As far as N-acetylcysteine is concerned, its role to reduce the incidence of PC-AKI is controversial.<sup>31</sup> At the current time, there is insufficient evidence of its efficacy to recommend its use.<sup>32 33</sup>

Finally, renal replacement therapy has not been shown conclusively to reduce the risk of PC-AKI in patients receiving intravenous or intra-arterial CM, and its use is not recommended.<sup>32</sup>

**Selection of iodinated CM according to different guidelines**

Current guidelines (eg, ESUR, The American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), Kidney Disease: Improving Global Outcome (KDIGO), American Society of Nephrology (ASN) and American College of Radiology (ACR)) do

not provide consistent recommendations for the selection of iodinated CM in patients with cancer in order to limit the risk of developing AKI. Furthermore, the ESUR guidelines consider low the risk of PC-AKI in the general population, and for this reason, they suggest prevention only in patients with a glomerular filtration rate (GFR) of <30 mL/min.<sup>32</sup> Several other guidelines recommend that iodinated CM with the lowest osmolarity and the lowest toxicity should be used, and that Iso-osmolar contrast medium (IOCM) should be administered in high-risk patients. The guidelines of ACCF and AHA recommend the use of IOCM as a strategy to prevent AKI in patients with stable ischaemic heart disease,<sup>34</sup> and KDIGO confirms a preference towards the use of IOCM in patients with CKD.<sup>22</sup> Based on the Onconephrology Curriculum of the ASN, high-osmolar (>1400 mOsm/kg) and low-osmolar (600–800 mOsm/kg) CM are associated with a higher incidence of AKI compared with IOCM (300 mOsm/kg).<sup>20</sup> In addition, the Geriatric Nephrology Curriculum of the ASN suggests the preference of iodixanol when iodinated CM is used in elderly patients.<sup>21</sup>

The 2018 ACR Manual on Contrast Media highlights the fact that a number of studies have failed to establish a clear advantage of intravenous IOCM over intravenous low-osmolarity contrast medium (LOCM) with regard to PC-AKI or CIN.<sup>33</sup> Indeed, a 2009 meta-analysis using data pooled from 25 trials found no difference in the rate of PC-AKI between iodixanol and low-osmolarity agents after intravenous administration.<sup>35</sup>

As a whole, radiologists' guidelines have a more generalist approach in comparison with cardiological and nephrological guidelines; the latter defines the risk in specific settings of patients and suggests preventive measures, such as hydration and IOCM use in at-risk patients.

Given the lack of consistent indications, we review here current evidence on the selection and optimisation of iodinated CM in patients with cancer.

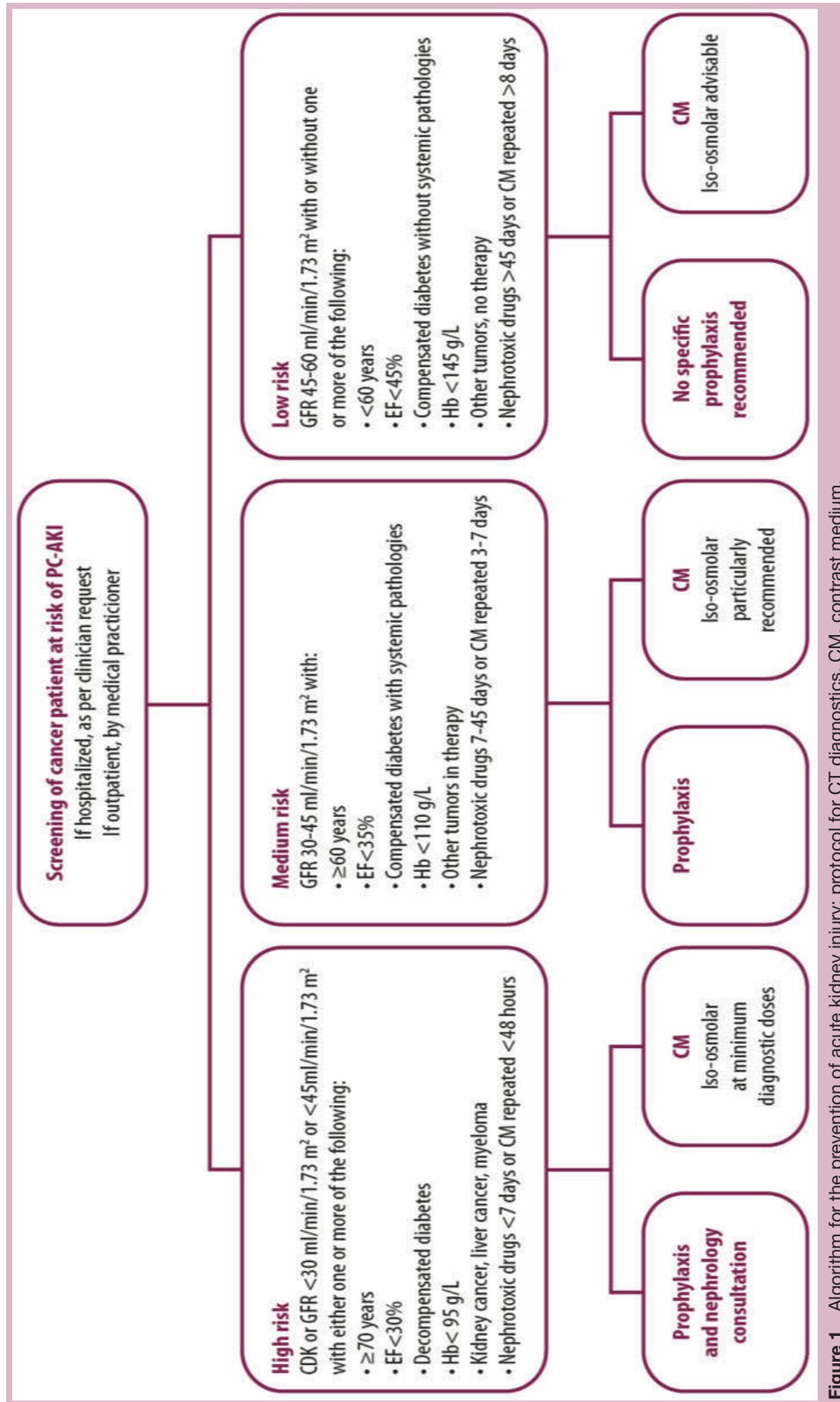
**Dose**

It has been demonstrated that the enhancement of liver parenchyma, during portal phase, should increase by at least 50–60 Hounsfield units to allow an accurate identification of focal lesions.<sup>36 37</sup> The parenchymal enhancement is determined by the concentration of iodine in the extracellular and vascular volumes; thus, it is also influenced by the patient's weight. Therefore, the amount of iodinated CM should be tailored for each patient. The CM dose should be calculated according to milligrams of iodine (mgI) rather than volume in millilitres. Studies

**Table 2** Formulas for lean body mass calculation

Formula	Males	Females
James <sup>39 45</sup>	eLBM=1.1 W-128(W/H) <sup>2</sup>	eLBM=1.07W-148(W/H) <sup>2</sup>
Boel <sup>36 42</sup>	eLBM=0.407W+0.267 hour - 19.2	eLBM=0.252W+0.473 hour - 48.3

eLBM, estimated lean body mass; H, body height (cm); W, body weight (kg).



**Figure 1** Algorithm for the prevention of acute kidney injury: protocol for CT diagnostics. CM, contrast medium.

suggested tailoring the amount of CM based on patients' lean body weight (LBW) rather than on total body weight (TBW).<sup>38,39</sup> Indeed, injecting 750 mgI/kg of patient LBW to maximise lesion detection rate was suggested.<sup>40</sup> This approach seems to overcome the limit of the previous strategy whereby the CM amount required was estimated based on TBW. In fact, the estimation of CM dose at CT based on LBW reduces the contribution of highly variable but poorly perfused adipose tissue, especially in obese patients. Different methods are available to calculate LBW, and the James formula is one the most commonly used (table 2).<sup>38,41</sup> However, this formula seems to have shortcomings in obese patients (body mass index of  $>30\text{ kg/m}^2$ ), underestimating patients' LBW and consequently the amount of CM to be injected. Thus, other formulas, like the Boer formula,<sup>42</sup> may be more appropriate.<sup>42–45</sup> Finally, a recent study demonstrated that the adoption of a bioimpedance device to tailor CM dose based on LBW in obese patients can result in an optimal liver enhancement in the portal phase during MDCT (multidetector computed tomography) of the liver and it should be preferred to the approach of calculating LBW with formulas.<sup>15</sup>

Another parameter influencing hypervascular liver lesion enhancement and thus their detectability is the iodine delivery rate (IDR). A minimum IDR of 1.2 gram of iodine (gI) per second has been suggested using a standard acquisition protocol at 120 kV.<sup>17,46</sup>

Recent technological developments (ie, availability of new image reconstruction algorithms, such as iterative reconstructions of second and third generations, and more powerful tube generators), allow lowering of the tube voltage (ie, kV) during the CT acquisition protocol. A low kV scanning protocol (ie, 80 kV) increases tissue contrast enhancement, since iodine better absorbs X-ray photons at low energy because X-rays are closer to the iodine k-edge, and, at the same time, low kV means lower radiation exposure compared with conventional 120 kV acquisition protocols. In two recent papers, the authors delivered between 330 and 360 mgI/kg, achieving the same image quality of traditional protocols, but being also able to reduce radiation exposure by 50%.<sup>47,48</sup>

Further developments can be expected by the use of dual-energy scanners with optimisation of low kilovoltage peak virtual monochromatic images.<sup>49</sup>

### Osmolarity of iodinated CM

Though the nephrotoxicity of first-generation iodinated CM, which were characterised by high osmolarity, has been clearly demonstrated, several recent propensity score-matched controlled observational studies have failed to show any association between AKI and modern iodinated CM.<sup>50</sup> The lack of association between AKI and modern CM administered intravenously before CT examination may be the result of a better adherence to existing guidelines, with proper patient selection and preventive measures.<sup>50</sup>

A bulk of evidence suggests that the osmolarity of iodinated CM does play a major role in the risk of developing AKI.<sup>50–52</sup> From a mechanistic viewpoint, consistent evidence from cultured tubular cells suggests that LOCM has more severe cytotoxic effects than IOCM.<sup>50</sup> In addition, in animal models, IOCM is associated with a lower induction of Nox4-dependent reactive oxygen species generation. Furthermore, IOCM also exerts fewer vasoconstriction effects than LOCM.<sup>53</sup>

Indeed, evidence suggests that AKI is more frequent when using LOCM, but may not occur when using IOCM together with an adequate prophylaxis. In a large meta-analysis of 25 studies, the relative risk of developing CI-AKI (defined by the authors as an increase in SCr of either  $\geq 0.5\text{ mg/dL}$  or  $\geq 25\%$  from baseline) with intra-arterial iodixanol—an IOCM—compared with LOCM was 0.462 (95% CI 0.272 to 0.786,  $p=0.004$ ).<sup>52</sup> Similar findings were reported in another meta-analysis,<sup>51</sup> although this superiority may lose significance according to the type of analysis. Concerning intravenous administration, a study conducted by Nguyen *et al*, which enrolled patients with decreased renal function, showed an inferior incidence of PC-AKI in patients treated with iodixanol (8.5%) compared with the iopromide group (27.8%,  $p=0.012$ ).<sup>54</sup> To date, a single randomised, prospective, comparative study has been conducted in relatively young ( $<60$  years old) patients with cancer at a very low risk of PC-AKI, defined here as a GFR of  $>60\text{ mL/min}$ . The mean GFR was  $98.8\text{ mL/min}$  in the iopromide group and  $96.5\text{ mL/min}$  in the iodixanol group. These results suggested a lower incidence of AKI in patients who have undergone an intravenous injection of IOCM (4/247; ie, 1.6%), compared with iopromide ( $p=0.045$ ), suggesting a more favourable safety profile of iodixanol versus iopromide.<sup>55</sup> IOCM proved also to be safe for kidney function in two studies involving chronic dialysis patients, independently of the route of administration (intravenous *vs* intra-arterial); indeed, the use of iodixanol did not result in further increase of SCr.<sup>56,57</sup> The CONNECT (Clinical Evaluation Of Remote Notification to rEduCe Time to Clinical Decision) Italian observational study showed that in the setting of hospital CT radiology units, where guideline-recommended strategies for PC-AKI prevention may not be consistently followed, the use of the IOCM iodixanol appears to be associated with a lower incidence of PC-AKI in at-risk patients. The majority (76.4%) of patients referring to CT radiology units had one risk factor and 19.8% had two risk factors; while relatively few patients had three risk factors (3.4%) or four risk factors (0.4%). Notably, the concomitance of two risk factors has an additive effect on PC-AKI risk.<sup>58</sup>

### CONCLUSIONS

AKI is a serious and frequent concern in patients with cancer who often present comorbidities or receive drugs that may increase the risk of developing this event. Therefore, it should be mandatory to try to

prevent PC-AKI (as recently defined by Lencioni *et al*<sup>58</sup>) in patients with cancer at risk, with the implementation of dedicated protocols (an example, based on the experience of the authors, is presented in figure 1). In particular, prehydration and the choice of specific CM doses and classes (IOCM *vs* LOCM) in patients at high risk are recommended: a preventive strategy using saline prehydration, as well as the use of the CM with the lowest osmolarity, is highly advisable, particularly in high-risk patients. IOCM should thus be considered the first choice in this setting.

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**Correction notice** This paper has been updated since first published to update Figure 1.

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