

Review Article

CT Contrast in Radiation Oncology Simulation

Gregory J Kubicek, MD^{1*}, James E Kovacs, DO², Tamara LaCouture, MD¹

¹ Department of Radiation Oncology, Cooper University Hospital, Camden, New Jersey, United

² Department of Radiology, Cooper University Hospital, Camden, New Jersey, United

Abstract

Objectives: With IMRT and advanced radiation planning, anatomy and contouring is becoming increasingly important in the field of radiation oncology. The use of iodinated computed tomography (CT) contrast for radiation simulation CT scans can help define anatomy more precisely and thus improve contouring. The major risks of CT contrast (which at least partly accounts for the aversion by some departments to its routine use) are contrast induced nephropathy and allergic-like reactions.

Results: The evidence of complications attributable to standard doses of contrast for diagnostic CT examinations is weak. The preponderance of data on contrast induced nephropathy has been compiled from interventional cardiology procedures, and the current guidelines regarding diagnostic CT contrast require extrapolation on mostly retrospective data. The evidence available suggests that CT contrast related adverse events are rare, and contrast related nephropathy most often spontaneously resolves without further decline in baseline renal function.

Conclusion: The current data regarding safety of CT contrast provides a limited foundation on which to make evidence-based recommendations. We have reviewed the literature on CT contrast. By following some simple algorithms CT contrast can be safely utilized.

Keywords: CT Contrast; contrast induced nephrotoxicity; contouring; simulation

Academic Editor: Xiaoning Peng, Department of Internal Medicine, Hunan Normal University School of Medicine

Received: January 15, 2015; **Accepted:** March 13, 2015; **Published:** April 20, 2015

Competing Interests: The authors have declared that no competing interests exist.

Copyright: 2015 Kubicek GJ. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

***Correspondence to:** Gregory J Kubicek, Cooper University Hospital, Department of Radiation Oncology, One Cooper Plaza, Camden NJ, 08103, United States; **Email:** greg.kubicek@gmail.com

Introduction

CT based treatment planning is becoming today's standard in radiation oncology. An understanding of cross-sectional anatomy has becoming increasingly important for the radiation oncologist. With the shift from 2D to 3D treatment planning, radiation oncologists have to conceptualize anatomy in multiple planes, and this is even more vital with IMRT.

Anatomy and contouring are one of the most vital and important processes in radiation oncology today. Improved quality of the CT images used for simulation results in greater tumor conspicuity, and instills a greater confidence in the contouring process. One common method to maximize the quality of a simulation CT scan is to administer contrast, especially intravenously (IV) administered contrast. CT contrast can effectively delineate vessels and often increases tumor discrimination from normal tissue because of differential tissue enhancement. In this way contouring becomes optimal, which in theory translates to better outcomes.

However, radiation oncology departments are generally much less experienced with IV contrast than are diagnostic radiology departments. A consequence of this is that departments may be disinclined to use contrast merely because they lack the experience in its delivery. A report on IV contrast usage in UK radiation oncology departments reported suboptimal IV contrast use [1]. The objective of this review is to outline common indications within radiation oncology for which CT images can be substantially improved by the use of CT contrast, to propose a few simple algorithms for different body sites, to summarize the potential toxicities of CT contrast, and offer guidelines for how to improve safety in administering CT contrast.

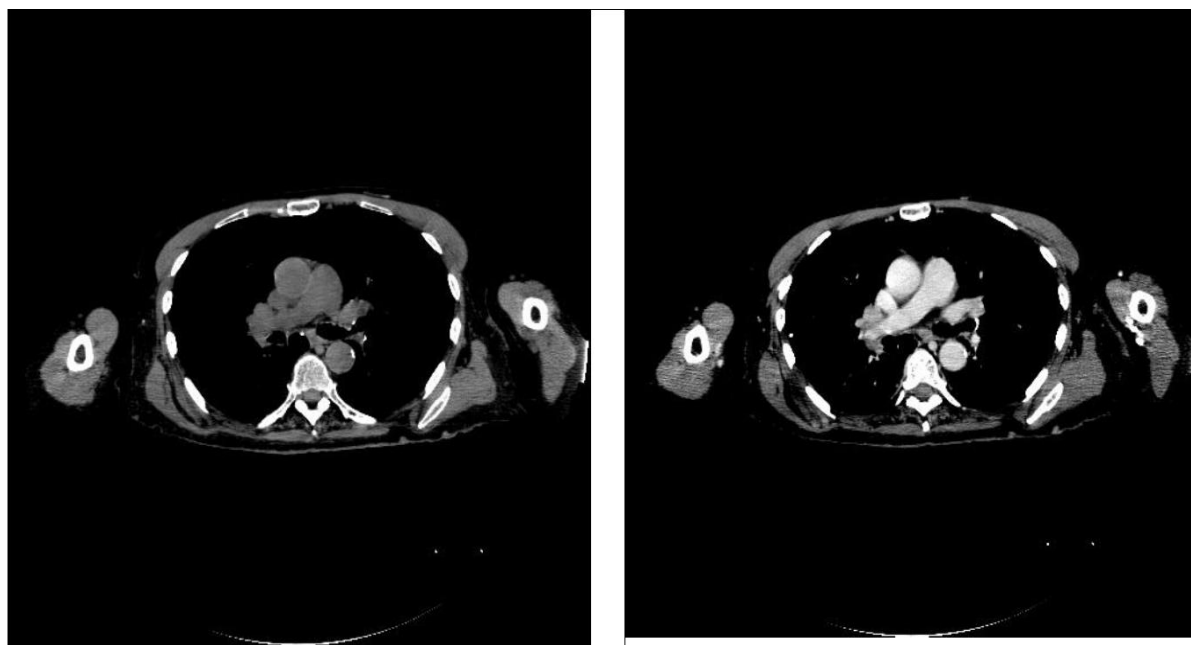


Figure 1 axial CT scan without and with contrast. This is an example of how IV contrast (right) can make visualization of the hilar lymph node much easier and more accurate than the scan without contrast (left).

Table 1 Recommendations for when to use IV contrast

Treatment Site	Use Contrast for simulation?	CTNote
CNS	No	Most times will have MRI that can be used for fusion. In cases where MRI cannot be performed, IV contrast should be utilized
Head& Neck	Yes	
Breast	No	
GI	Yes	
Thoracic	Yes	IV contrast should be used to determine mediastinal and hilar lymph nodes. In patients in whom there is no lymph node disease or elective nodal treatments IV contrast can be held.
Prostate	Variable	Can help define vessels but not necessary
Gyn	Variable	Can help define vessels but not necessary
Soft tissue	Variable	

Role of IV contrast

Contrast for CT comes in several forms and may be administered by a variety of routes. For the purpose of this review, only iodinated contrast for intravascular administration will be discussed. Briefly, the photons emitted by the fan beam of the CT scanner are attenuated by the iodinated contrast media within the patient from reaching the detector opposite the fan beam, and the degree to which the beam is attenuated is measured in Hounsfield units. CT contrast is almost always injected into the venous system, and depending on the timing of scan acquisition it can help enhance vessels to a greater degree than other non-vascular anatomical structures (**Figure 1**). A second major advantage to contrast is that many tumors will either hypo- or hyperenhance with CT contrast relative to surrounding structures, allowing clearer distinction of tumor margins. This is especially crucial in tumors which do not have an exophytic component. However, not all body sites require or derive benefit from administration of CT contrast as outline in **Table 1**.

CNS

Most patients with CNS tumors (e.g. glioblastoma multiforme) will have previously undergone an MRI examination. While MRI for brain tumor is usually acquired with a gadolinium-based contrast agent, as most CNS tumors are contrast-enhancing, MRI is not typically done in the radiation oncology department. Assuming that a high-quality MRI examination is available for fusion with simulation CT scan, there is little benefit to performing the CT scan with contrast. In the event that an MRI with contrast cannot be performed (e.g. implanted cardiac pacemaker which is a contraindication to MRI), the simulation CT scan should be performed with IV contrast.

Head and Neck

Nowhere in the body is the use of contrast more crucial. The multiplicity of vessels, muscles, salivary glands, and lymph nodes, their relative small size, and the paucity of space between them poses a challenge to the radiation oncologist. Elective nodal radiation is a critical aspect to head and neck cancer treatments, and IV contrast will help delineate lymph nodes, adding precision to contouring. In addition to this, abnormal lymph nodes may enhance differently than normal lymph nodes, and the primary tumor itself will often enhance and this will also aid in optimal contouring.

Thoracic

For patients with lymph node involvement (mediastinal or hilar), IV contrast is vital in being able to distinguish hilar vessels from lymph nodes. In patients for whom there is no planned radiation to lymph node regions (early stage NSCLC for example) IV contrast can be withheld.

Gastrointestinal Tract

IV contrast is very helpful in defining vessels as landmarks for contouring. Both in nonoperative and post-operative pancreatic cancer patients it is important to accurately contour portal vein, celiac axis, and superior mesenteric artery. These anatomical relationships may be significantly altered in the postoperative patient.

Adverse effects of IV contrast

There are two general categories of adverse reactions to iodinated contrast for CT: chemotoxic (contrast induced nephropathy), and acute idiosyncratic systemic (also referred to as anaphylactoid and allergic-like). Contrast allergy, most often mild, can potentially result in life-threatening anaphylaxis, circulatory collapse, and death. These events are rare but have been estimated to occur in 1 case per 200,000 administrations of contrast [2-5]. Contrast-medium induced nephropathy (CIN) is a condition in which renal function acutely declines following contrast exposure, with no other attributable etiology than the IV contrast.

Incidence of CIN

CIN is the third leading cause of acute renal failure in hospitalized patients and can be associated with prolonged hospitalization and even death [6,7]. CIN is thought to be caused by direct tubular toxicity and also by renal ischemia [8,9]. Interestingly, there is no consensus on the definition of CIN. Most clinical studies [10-12] have used a definition of 25% increase in serum creatinine or absolute increase of 0.5 mg within 2 to 7 days of the procedure. The lack of a consensus definition for CIN is one of the factors that leads to difficulties in estimating the true incidence of CIN. Most of the data regarding incidence of CIN is derived from retrospective studies looking at IV contrast for cardiac procedures where there is an overall incidence between 1.6 to 2.3% [13]. This likely leads to an overestimation of CIN in non-cardiac diagnostic scans, and there are certainly pitfalls in extrapolation. Intraarterial contrast administration (such as that used in cardiac procedures) is thought to pose a greater risk of CIN than intravenous administration [14]. Some authors have postulated that IV contrast in diagnostic radiology may not cause CIN at all; a large retrospective study looked at 53,439 patients and 157,140 diagnostic CT scans and did not find any difference in CIN rate between patients receiving contrast versus those without contrast [15], leading the authors to question if CIN was causal or simply coincident.

Certain patient subsets undergoing coronary angiography are at a higher risk of CIN, but it should once again be noted that these risk factors may not be relevant for non-cardiac patients. Further complicating this is that studies deriving risk factors are heterogeneous, retrospective, and often not validated. Several of the proposed risk factors include diabetes [16,17], age [18,19], chronic kidney disease (including multiple myeloma) [17,18,20], use of metformin containing medications [21], and hypertension [22,23]. Different studies have determined different risk factors and when consensus guidelines rely upon the disparate data, they too lose uniformity. This can be highlighted by using the example of metformin containing medications. There is limited evidence linking metformin to CIN in patients taking metformin. While often cited as a risk factor for CIN, the data for this is primarily from case reviews and case series [21], and there is no evidence that CIN occurs in patients with otherwise normal renal function and there is no evidence that withholding metformin prevents CIN [24]. Given the limited quality data regarding CIN risk factors it should not be a surprise that there is not uniformity among contrast guidelines.

Screening for at Risk Patients for CIN

The major concern with CIN is that the resulting decreased renal function will not be sufficient to support fluid and toxin elimination which is the primary role of the kidneys. Patients with already low renal function are the subset at greatest risk from CIN. Thus, the most important information to know prior to IV contrast is pre-contrast renal function. The single most important quantitative marker for renal function is the glomerular filtration rate (GFR) which is the rate at which the kidneys are able to filter volume, and therefore the higher number the better. GFR is approximated by the estimated glomerular filtration rate (eGFR) which can be calculated via the Cockcroft-Gault or similar equations [16]. Medical laboratory reports will routinely list the eGFR. For patients with an eGFR greater than 60 ml/min the renal function is fully adequate and IV contrast can be safely given.

As discussed above, there are several proposed risk factors for CIN (Table 2). Especially in the oncology setting, it is important to recognize that many chemotherapy agents can be nephrotoxic, and patients receiving such chemotherapy should always have close follow-up of their renal function while on chemotherapy [25] (of course most often the medical oncologist will be ordering and tracking serum creatinine for these patients). Not all patients need a serum creatinine prior to proceeding with IV contrast; young and otherwise healthy patients are at low enough risk for CIN that creatinine screening is not indicated [26-27]. In a large study of 2034 outpatients for whom contrast-enhanced CT scans were ordered, serum creatinine was checked in all patients, and 66 patients had serum creatinine greater than 2.0 and 64 of these patients had some risk factor that would have prompted screening. Thus, only 2 of 2034 patients (0.1%) would have been missed with selective creatinine screening. While serum creatinine should always be looked for if available, for young patients (< 60 years) without risk factors (Table 2) contrast can be given without obtaining serum creatinine [28]. For patients who have any of the risk factors in Table 2 a serum creatinine should be obtained within 7 days of contrast administration. A simple algorithm (Figure 1) outlines the screening process.

Table 2 Proposed risk factors for CIN

Age greater than 60
Hypertension
Chronic kidney disease
Diabetes
Recent nephrotoxic chemotherapy
When to require serum creatinine prior to CT scan

Contrast Administration in Patients with Elevated Creatinine

Patients with a low eGFR are at increased risk of CIN. However, it is unclear what the low-limit cutoff should be. While nearly all consensus guidelines are in agreement that eGFR > 60 is safe, there is a paucity of data regarding CIN in patients with lower eGFR rates, specifically those with rates of 45 to 60. While some authors have retrospectively found that eGFR < 60 to be a risk factor for patients undergoing percutaneous coronary intervention [16] others have not. In a study of 1826 consecutive coronary intervention patients there was no case of CIN requiring dialysis in patients with eGFR greater than 47. Based on the predictive model, the estimates for CIN requiring dialysis with a eGFR of 50 is 0.2% for diabetics and 0.04% for non-diabetics and with a eGFR of 40 is 2% for diabetics and 0.3% for non-diabetics. This rate thereafter starts to significantly increase with a rate of 84% for diabetic patients with an eGFR of 10 [20]. Thus, while a cut-off of 60 is commonly cited, there is no data to clearly support this. Because CIN rates do increase with lower eGFR it stands to reason that caution is used for patients with eGFR between 45 and 60 and that consultation with nephrology is used for patients with an eGFR below 45.

Concerns of CIN should not dissuade use of IV contrast if it is believed that better anatomy visualization would improve the treatment planning. Even when CIN does occur it is almost always transient. Typically serum creatinine increases 48 to 72 hours, peaks at 3 to 5 days, and returns to baseline in another 5 to 9 days [29-30]. Short of CIN to the extent that dialysis is required, it is unclear if there are any long-term health consequences for transient CIN. While several reports have noted overall worse outcomes for patients who had CIN [31-33] it is impossible to determine if it was actually the CIN that drives this poor long term survival or if patients with renal function susceptible to CIN would have poor long term survival independent of CIN. A systematic review and meta-analysis looked at patients with CIN after a contrast CT compared to patients without contrast CT scans, 25,950 patients were included in this analysis and there was no difference in incidence of dialysis or death between the two patient groups [34].

Another situation that commonly arises is repeat use of IV contrast within a short period of time. This situation can occur if a patient needs both a diagnostic and radiation planning CT scan. A study of 100 consecutive patients receiving two administrations of IV contrast within 32 hours did not show any elevation in CIN rates when compared to a control group [35]. This small study offers some reassurance of the safety of repeat CT contrast administration if medically indicated.

Treatment and Prevention of CIN

Multiple methods have been tested to prevent CIN or treat CIN once it has occurred. However, the majority have either been negative or not reproduced. A large review [36] of prophylaxis strategies did not find any evidence to clearly support any agent to prevent CIN (including hydration). Even so, several authors have concluded that available data suggests that hydration either before or after contrast may be beneficial [29, 36]. N-acetylcysteine is the most commonly examined pharmacologic agent used to prevent CIN. The available data including multiple meta-analyses have not been conclusive [36]. We feel that for patients deemed to be at risk for CIN, extra hydration (oral or IV) before and after the contrast is a reasonable approach, even if the evidence for benefit is not conclusive, since there is little risk involved.

Management of Acute Contrast Reactions

Acute contrast reactions are an allergic-like reaction to the contrast medium. Most major and minor reactions occur in patients without any known risk factor. Virtually all life-threatening reactions occur immediately or within 20 minutes of contrast injection. For these reasons, it is recommended that a physician is present within the department whenever IV contrast is used. Also, all areas where contrast is given need to be equipped with an emergency anaphylaxis box.

Most acute contrast reactions occur in people with no known risk factor and occur shortly after the administration of the IV contrast; 70% of reactions occur in the first 5 minutes [37]. Thus, diligence is important. The most benign of the acute reactions is hives (urticaria) this is not life-threatening, and generally only patient reassurance is indicated. If symptomatic, a single dose of diphenhydramine (Benadryl) can be given orally or intravenously. For more severe reactions (edema, bronchospasm, hypotension) supplemental oxygen should be provided for all patients, rapid response team should be alerted, and consideration may be given to subcutaneous epinephrine (1:1000, 0.1 to 0.3 ml). It should be noted that warmth or flushing, albeit unpleasant, is physiologic and not considered an adverse event and not indicative of a future adverse event. **Table 3** outlines acute contrast reactions and appropriate treatment.

Table 3 Acute Contrast Reactions

Reaction	Action
Warmth, flushing	• No action (patient reassurance only that this is physiologic and not harmful)
Hives (urticaria)	• Discontinue injection. • Can consider diphenhydramine (Benadryl)
Edema	• Epinephrine SC • Oxygen
Bronchospasm	• Oxygen • Beta-agonist (albuteral) • Epinephrine if not improved
Hypotension	• Oxygen • Elevate legs • IV fluids if needed

Table 4 Risk factors for Contrast Allergic Reaction

Previous reaction to IV contrast
Severe allergies to food or medicine

In a Japanese nationwide study looking at 337,647 patients the incidence of severe and very severe reactions with low osmolar contrast were 0.04% and 0.004% respectively [38]. In several studies looking at risk factors for predicting allergic reactions, the most commonly found risk factors include history of previous reaction, and any allergy (drug or food) requiring medical treatment [38, 39] (Table 4). Several reports have found asthma to be a risk factor [38-39] but other studies have not [40] and it is felt that patients with well controlled asthma are not at risk for reactions [41]. While allergy to shellfish is often cited as a contraindication to IV contrast this has been dispelled as a myth (albeit a rather well entrenched myth). While shellfish do contain iodine, the iodine in shellfish is not the source of allergy (the major allergen is in the shellfish muscle), nor is iodine in contrast the allergic agent (it is the contrast molecule) [42]. That being said, allergy to shellfish needs to be regarded in the context of multiple additional allergies which is a known contrast reaction risk factor.

Prevention of Contrast Reactions

There is some data that the incidence of contrast reactions can be reduced using premedications, but this data is limited and their conclusions are controversial [38,43,44]. In a randomized study 1,155 patients were randomized between 32 mg methylprednisolone 6-24 and 2 hours versus placebo prior to IV contrast and found that the prophylactic measure protected against mild contrast reactions (4.9% without prednisone reduced to 1.7%). Secondary to a limited number of events it was not possible to conclude that moderate and severe reactions were also reduced [43]. The American College of Radiology guidelines for prophylaxis are seen in Table 5 [45]. Although the evidence for prevention of serious reactions is not convincing we feel that the prophylaxis regimen is well tolerated with low risk and remains recommended for patients at elevated risk for reactions (Table 4).

Table 5 prophylaxis medication in high risk patients (American College of Radiology)

50 mg prednisone	13 , 7, 1 hours before contrast
50 mg diphenhydramine (Benadryl)	1 hour before contrast

Discussion

The use of CT contrast is an important adjunct to obtaining the best possible CT images and thus optimal contouring and target definition in radiation oncology. The two issues of concern when using CT contrast are CIN and acute contrast reaction. There is a paucity of data regarding CIN on several levels; definition, incidence, patients at risk, long-term effects of CIN, and prevention. CIN is an uncommon event and almost always self-resolving, and by using some simple screening and algorithm (**Table 2, Figure 2**) patients can safely receive CT contrast. Allergic-like reactions are rare events, most often seen in patients without any risk factors, but do occur disproportionately in patients with history of previous contrast reaction and severe allergies. For these high-risk patients we recommend prophylactic medication (**Table 5**). Most allergic reactions occur in patients without any risk factors and occur shortly after contrast administration and thus we recommend that the physician be present in the department whenever CT contrast is given.

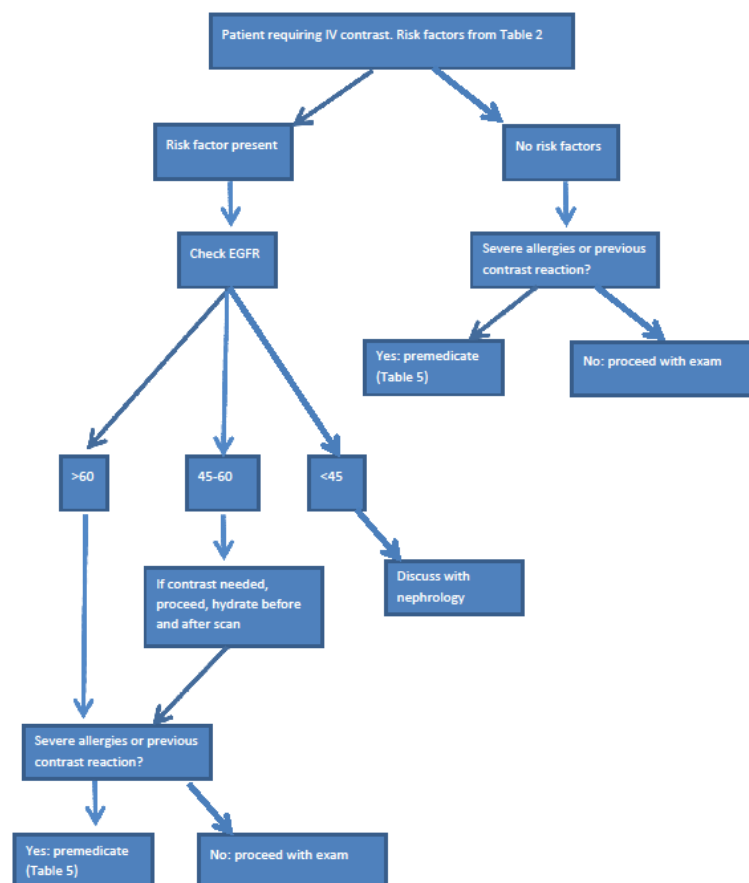
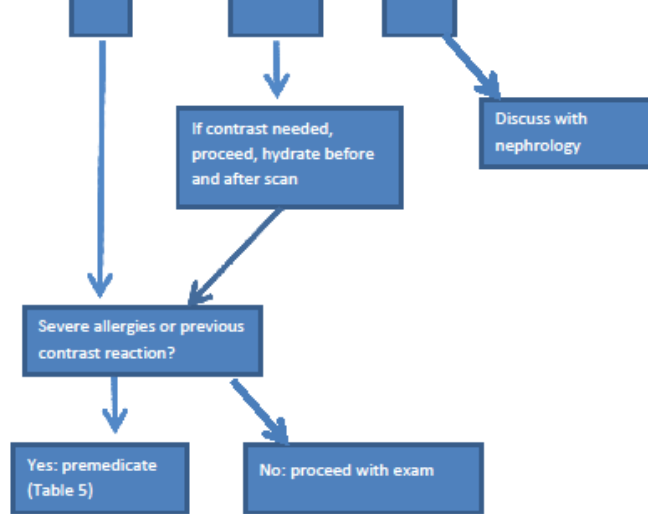


Figure 2 Algorithm for delivering IV contrast

References

1. Kim S, Russell W, Price P, et al. Suboptimal use of intravenous contrast during radiotherapy planning in the UK. *Br J Radiol*. 2008, 81(972):963-969
2. Morcos S K. Acute serious and fatal reactions to contrast media: our current understanding. *British Journal of Radiology*. 2005, 78, 686-693
3. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media. *Radiology*. 1990, 175:621-628
4. Lasser EC, Lyon SG, Berry CC. Reports on contrast media reactions: analysis of data from reports to the U.S. Food and Drug Administration. *Radiology*. 1997,203:605-610
5. Goss JE. Systemic anaphylactoid reactions to iodinated contrast media during cardiac catheterization procedures: Guidelines for prevention, diagnosis, and treatment. *Catheterization and Cardiovascular Diagnosis*. 1995, 34:99-104
6. Asif A, et al. Current trials of interventions to prevent radiocontrast-induced nephropathy. *Am J Ther*. 2005, 12(2): 127-1321.
7. Pannu N, et al. Prophylaxis strategies for contrast-induced nephropathy. *JAMA*. 2006, 295(23):2765-2779
8. Waybill MM, Waybill PN. Contrast media-induced nephrotoxicity: identification of patients at risk and algorithms for prevention. *J Vasc Interv Radiol*. 2001, 12(1):3-9
9. Gerlach AT, Pickworth KK. Contrast medium-induced nephrotoxicity: pathophysiology and prevention. *Pharmacotherapy*. 2000, 20(5):540-548
10. Levy EM, Viscoli CM, Horwitz RI. The effect of acute renal failure on mortality: a cohort analysis. *JAMA*. 1996, 275:1489-1494
11. McCullough PA, Sandberg KR. Epidemiology of contrast-induced nephropathy. *Rev Cardiovasc Med*. 2003, 4 (Suppl 5):S3-S9
12. Barrett BJ, Parfrey PS, Vavasour HM, et al. Contrast nephropathy in patients with impaired renal function: high versus low osmolar media. *Kidney Int*. 1992, 41:1274-1279
13. Lasser EC, Lyon SG, Berry CC. Reports on contrast media reactions: analysis of data from reports to the US Food and Drug Administration. *Radiology*. 1997, 203:605-610
14. Moore RD, Steinberg EP, Powe NR, et al. Nephrotoxicity of high-osmolality versus low-osmolality contrast media: randomized clinical trial. *Radiology*. 1992, 182:649-655
15. McDonald RJ, McDonald JS, Bida JP, et al. Intravenous contrast material-induced nephropathy: causal or coincident phenomenon? *Radiology*. 2013, 267(1):106-118
16. Lin J, Bonventre JV (2005) Prevention of radiocontrast nephropathy. *Curr Opin Nephrol Hypertens*. 14:105-110
17. Bartholomew BA, Harjai KJ, Dukkipati S et al (2004) Impact of nephropathy after percutaneous coronary intervention and a method for risk stratification. *Am J Cardiol*. 93:1515-1519
18. Mehran R, Aymong ED, Nikolsky E, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol*. 2004, 44:1393-1399
19. Barrett BJ, Parfrey PS. Clinical practice. Preventing nephropathy induced by contrast medium. *N Engl J Med*. 2006, 354(4):379-386
20. McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *Am J Med*. 1997, 103 (5): 368-375
21. Jackson N . Metformin associated lactic acidosis following administration of intravenous contrast media. Centre for Clinical Effectiveness . Evidence Centre Evidence report, 2002. Health Technology Assessment (HTA)

- database. York, England: Centre for Reviews and Dissemination, University of York, 2002. www.crd.york.ac.uk. Published August 11, 2003
22. Iakovou I, Dangas G, Mehran R, et al. Impact of gender on the incidence and outcome of contrast-induced nephropathy after percutaneous coronary intervention. *J Invasive Cardiol.* 2003;15:18-22
 23. Nikolsky E, Aymong ED, Dangas G, Mehran R. Radiocontrast nephropathy: identifying the high-risk patient and the implications of exacerbating renal function. *Rev Cardiovasc Med.* 2003;4(suppl 1):S7- S14
 24. Goergen SK, Rumbold G, Compton G, et al. Systematic review of current guidelines, and their evidence base, on risk of lactic acidosis after administration of contrast medium for patients receiving metformin. *Radiology.* 2010, 254(1):261-269
 25. Kintzel, PE. Anticancer Drug-Induced Kidney Disorders. *Drug Safety* 2001; 24:19-38.
 26. Tippins RB, Torres WE, Baumgartner BR, Baumgarten DA. Are screening serum creatinine levels necessary prior to outpatient CT examinations? *Radiology.* 2000, 216: 481-484
 27. Manual on Contrast Media, Edition 5.0, 2004. American College of Radiology Kintzel, PE. Anticancer Drug-Induced Kidney Disorders. *Drug Safety.* 2001, 24:19-38
 28. Olsen JC, Salomon B (1996) Utility of the creatinine prior to intravenous contrast studies in the emergency department. *J Emerg Med.* 14:543-546
 29. Gleeson TG, Bulugahapitiya S. Contrast-induced nephropathy. *AJR AmJ Roentgenol.* 2004, 183:1673- 1689
 30. Rudnick MR, Berns JS, Cohen RM, Goldfarb S. Nephrotoxic risks of renal angiography: contrast media-associated nephrotoxicity and atheroembolism— a critical review. *Am J Kidney Dis.* 1994, 24:713- 727
 31. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. *Am J Kidney Dis.* 2002, 39:930- 936
 32. Levy EM, Viscoli CM, Horwitz RI. The effect of acute renal failure on mortality: a cohort analysis. *JAMA.* 1996, 275:1489-1494
 33. Rihal CS, Textor SC, Grill DE, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation.* 2002, 105:2259-2264
 34. McDonald JS, McDonald RJ, Comin J, et al. Frequency of acute kidney injury following intravenous contrast medium administration: a systematic review and meta-analysis. *Radiology.* 2013 , 267(1):119-128
 35. Langner S, Stumpe S, Kirsch M, et al. No increased risk for contrast-induced nephropathy after multiple CT perfusion studies of the brain with a nonionic, dimeric, iso-osmolal contrast medium. *AJNR Am J Neuroradiol.* 2008, 29(8):1525-1529
 36. Pannu N, Wiebe N, Tonelli M; et al. Prophylaxis strategies for contrast-induced nephropathy. *JAMA.* 2006;295(23):2765-79
 37. Schopp JG, Iyer RS, Wang CL, et al. Allergic reactions to iodinated contrast media: premedication considerations for patients at risk. *Emerg Radiol.* 2013, 20(4):299-306
 38. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. *Radiology.* 1990, 175: 621-628
 39. Morcos SK Acute serious and fatal reactions to contrast media: our current understanding. *Br J Radiol* (2005) 686-693
 40. Kobayashi et al.: Risk factors for adverse reactions from contrast agents for computed tomography. *BMC Medical Informatics and Decision Making.* 2013 13:18
 41. Bettmann MA, Heeren T, Greenfield A, Goudey C: Adverse events with radiographic contrast agents: results of the SCVIR Contrast Agent Registry. *Radiology.* 1997, 203:611-620
 42. Schabelman E, Witting M. The relationship of radiocontrast, iodine, and seafood allergies: a medical myth exposed. *J EmergMed.* 2012, 39(5):701-707



Page 12 of 12

t adverse reactions to

eased risk of adverse

Version 7, p 5-6, 20-21