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Nephrogenic systemic fibrosis: A survey of the use of gadolinium-based contrast agents in Ghana

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ABSTRACT

Introduction: The aim of this study is to identify current practice of administration of gadolinium-based contrast agents (GBCAs) in Ghana.
Method: A total of 13 MRI (magnetic resonance imaging) facilities were sent a survey questionnaire to request information on their current practice with the use of GBCAs.
Results: Gadodiamide, a high risk GBCA accounted for 67% of first line agents. 5 (42%) had a departmental protocol on the administration of GBCAs with regards to its association with nephrogenic systemic fibrosis (NSF). Of the 8 that use gadodiamide, 3 check kidney function in all patients, 2 check in selected patients, and 3 do not check at all. All 3 that screen all patients do not use contrast if the patient has an eGFR (estimated glomerular filtration rate) of 30–59 ml/min, 1 considers other modality; and if the patient has an eGFR of <30 ml/min, 2 do not use contrast but consider other modality, however 1 continues with the high risk agent.
Conclusion: Gadodiamide is widely used, with varied practice in screening for renal function, and risk factors associated with NSF. Current evidence shows that it is advisable to administer macrocyclic agents in patients with compromised renal function. It is also imperative to establish local guidelines in line with international guidelines in order to minimize the incidence of NSF.

Introduction

Nephrogenic systemic fibrosis (NSF), identified in 1997 with the first report of 14 cases published in 2000[1] is a rare but potentially fatal acquired systemic disease. NSF is not only associated with great morbidity, but also increased mortality in the most severe cases.[2] Primarily it involves the skin and subcutaneous tissues, but other organs are also involved.[3] Gadolinium-based contrast agents (GBCAs), the most commonly used magnetic resonance imaging (MRI) agents, have been associated with the development of NSF in patients with end-stage chronic kidney disease (CKD).[4] The pathophysiology of NSF is not yet fully understood.[5] However, a consistent body of knowledge from laboratory studies supports the idea that an important factor in the pathogenesis of NSF is the slow excretion of GBCAs in patients with severe renal impairment, allowing the lower stability gadolinium chelates to dissociate, releasing gadolinium.[5] Although many theories have been postulated regarding factors such as renal dysfunction, high dose gadolinium administration, tissue injury, proinflammatory conditions and hypercoagulable states to confer susceptibility to NSF, it is however important to note that no proven cause–effect relationship currently exists.[4] However, it is clear that NSF occurs exclusively in patients with severe to end-stage CKD (eGFR < 30 ml/min/1.73 m^2), and so exposure to GBCAs in this patient population should be avoided if at all possible.[6]

All GBCAs consist of gadolinium (Gd^{3+}) a paramagnetic element of the lanthanide series with atomic number 64, and atomic weight 157.25 g/mol. It is highly paramagnetic in its ionized state (Gd^{3+}) due to seven unpaired electrons in the four orbital shell, making it an effective T1-shortening agent for hydrogen protons. They reduce the T1 relaxation times of hydrogen protons to differing extents, as a function both of their relaxivity and of their local tissue Gd concentration.[7–9] However, free Gd^{3+} ion is toxic, therefore to reduce its toxicity, it is surrounded by a chelating ligand.[10] The term chelate is derived from the Greek word for "claw" (Gd^{3+} ion is held by ligands as if in the claw of a lobster).[11]

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The difference in the structure of the GBCAs is as a result of the type of their chelating ligand (macrocyclic vs. linear) and their charge (ionic vs. non-ionic).[12] Whereas with linear chelates the ligand wraps around the Gd^{3+}, but does not enclose it, with macrocyclic chelates, a rigid cage-like ligand is noted around the Gd^{3+}.[13] These properties are responsible for determining the ease with which the highly toxic free gadolinium ion (Gd^{3+}) dissociates from the gadolinium–chelate complex.[12,14] Whereas ionic and macrocyclic agents have the highest affinity for gadolinium, the risk of gadolinium dissociating from its chelate increases for non-ionic and linear agents.[15] So far, nine GBCAs have been approved by the United States Food and Drugs Administration,[16] namely Gadodiamide (Omniscan® – GE Healthcare), Gadopentetate dimeglumine (Magnevist® – Bayer HealthCare Pharmaceuticals), Gadoversetamide (OptiMARK® – Covidien), Gadobenate dimeglumine (MultiHance® – Bracco Diagnostics), Gadobutrol (Gadavist® – Bayer HealthCare Pharmaceuticals), Gadoterate meglumine (Dotarem® – Guerbet), Gadoteridol (ProHance® – Bracco Diagnostics), Gadofosveset trisodium (Ablavar® – Lantheus Medical Imaging), and Gadoxetate disodium (Eovis – Bayer HealthCare Pharmaceuticals). While some of these GBCAs have been associated with few, if any, confirmed cases of NSF, most unconfounded cases have been reported after exposure to gadodiamide, gadopentetate dimeglumine, and/or gadoversetamide,[17] all classified as high risk agents.[18] Thus to ensure the safe use of GBCAs in view of NSF, several international organisations i.e. the American College of Radiology (ACR),[17] the European Society of Urogenital Radiology (ESUR),[18] the Royal College of Radiologists (RCR)[19] have provided guidelines to be adopted for use in clinical MRI practice.

In Ghana, since the operationalization of the first MRI scanner, there has been increasing growth of MRI facilities parallelled by a rapid rise in the indications for, and application of GBCAs. Although NSF has received much attention in the USA and Europe in the past, its occurrence in many developing countries i.e. Ghana is not documented in the medical literature. In addition, no study has been conducted in Ghana to evaluate the administration of GBCAs in MRI facilities. Therefore the aim of this national survey is to identify current practice of administration of GBCAs in Ghana with respect to international guidelines on NSF.

Materials and methods

In Ghana, a total number of thirteen MRI suites were identified to participate in the survey. These included tertiary hospitals, private hospitals, and private diagnostic centres. They were contacted via email with a questionnaire with some of the questions adopted from the study conducted by Rees and Agarwal,[20] and addressed to the MRI radiographer-in-charge for completion. Follow-ups were done via the social media 'whatsapp' and phone calls for the completion of the questionnaires. The questionnaires were sent out in September, 2016 and were finally collected in November, 2016. The aim of the survey was to evaluate current practice of administration of GBCAs in Ghana awareness of the association between GBCAs and NSF, the types of GBCAs used, awareness of international guidelines on NSF, and departmental policy on screening renal function prior to the administration of GBCAs.

Results

Out of the 13 facilities identified, 12 (92%) responded to the questionnaire. In all, 9(75%) facilities affirmed their awareness of the association of NSF with exposure to GBCAs. Two types of GBCAs namely gadodiamide (Omniscan) and gadoteridol (ProHance) are currently used in Ghana. However, Omniscan a high risk agent associated with the greatest number of NSF cases was the most common, accounting for 67% of first line agents (Fig. 1). Only 42% facilities indicated that their choice of GBCA was influenced by their known association of certain GBCAs with NSF. None of the facilities use any other GBCAs as a second-line agent in case of any other indication. Only 5(42%) had a departmental protocol on the administration of GBCAs with regards to its association with NSF (Fig. 2). In finding out if facilities that use either Omiscan or Magnevist check kidney function prior to administration, it was noted that of the 8 facilities that use the high risk agent Omniscan, 3 check kidney function in all patients, 2 check in selected patients, and 3 do not check at all (Fig. 3). All 3 facilities that screen all patients

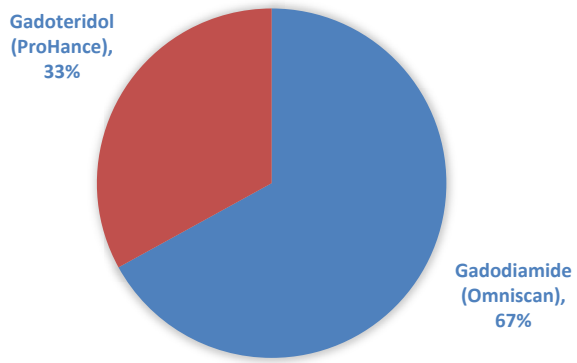

Figure 1. Summary of the two main types of GBCAs in use nationwide.

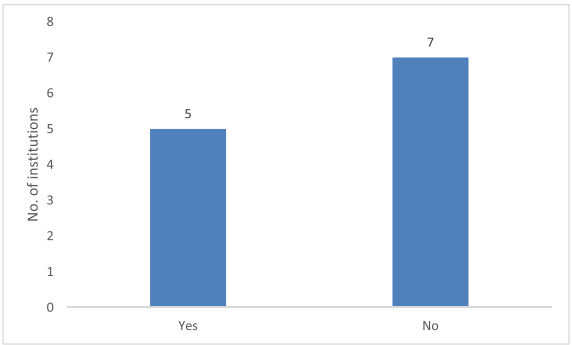

Figure 2. Summary of how many institutions have a departmental protocol on the administration of GBCAs with regards to its association with NSF.

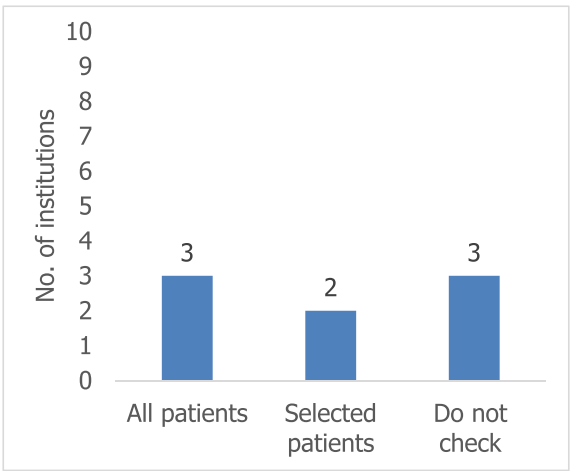

Figure 3. Summary of how many out of 8 institutions that use Omniscan, a high risk GBCA associated with NSF that subject their patients to renal function before administration.

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indicated that they do not use contrast if the patient has an estimated glomerular filtration rate (eGFR) of 30–59 ml/min, but only 1 consider other modality as an additional alternative; and if the patient has an eGFR of <30 ml/min, only 2 do not use contrast but consider other modality, however 1 continue with the contrast agent (Omniscan). Of the 2 facilities that check kidney function in selected patients, both screen patients with known renal disease, however only 1 indicated checking in patients with history of diabetes, hypertension, etc.

It was also revealed that 9 (seventy-five percent) respondents were aware that patients are at a higher risk of NSF following a liver transplant with reduced kidney function, again 9 (75%) indicated they were aware that patients awaiting a liver transplant with reduced kidney function are at a higher risk, 11 (92%) were aware that patients on dialysis are at higher risk, however only 4 (33%) were aware that patients with proinflammatory events are at a higher risk (Fig. 4).

Discussion

In 1996 the first article was published stating that, unlike iodine-based contrast media, GBCAs were not nephrotoxic.[21] However with the first report of 14 cases of NSF in 2000[1] which was noted to occur mostly in patients with end-stage chronic kidney disease, particularly in those on dialysis,[17] and with its occurrence noted to be strongly associated with GBCAs,[23,24] this link quickly gained a widespread attention within the medical community. It is now generally accepted that GBCA exposure is a necessary factor in the development of NSF.[17] The most important patient-related risk factor for NSF is markedly reduced renal function as almost all reported cases of NSF have been on haemodialysis or peritoneal dialysis.[2,4,5,12] In patients on haemodialysis, the GBCA clearance is 65% in a single session of haemodialysis, with a substantial removal (>95%) only after three dialysis sessions, while the clearance with peritoneal dialysis is poor (69% after 22 days of continuous dialysis.[25] Therefore, patients with severe renal impairment have increased risk of developing NSF due to delayed clearance and prolonged exposure to GBCA.[14,26] However, it has been noted that the difference in the molecular structure of the GBCAs i.e. the type of their chelating ligand (macrocyclic vs. linear) and their charge (ionic vs. non-ionic)[5,12] play a crucial role in the development of NSF. The molecular structure affects the stability of the molecules, i.e. how tightly the gadolinium is held within them.[5] In general macrocyclic chelates bind Gd^{3+} more tightly than linear chelates, therefore are more stable both in vitro and in vivo and have lower kinetic dissociation rates.[22] In less stable linear chelates, gadolinium is not as tightly bound as in macrocyclic chelates and therefore transmetallation reactions may take place. In vitro measurements of the chemical stability of GBCAs have shown that the macrocyclic chelates are the most stable and that the non-ionic linear chelates are the least stable.[27] Importantly, most unconfounded cases of NSF have been reported after exposure to gadodiamide, gadopentetate dimeglumine, and/or gadoversetamide,[17] all which are non-ionic linear GBCAs. The survey revealed that the main types of GBCAs used for MRI examinations in Ghana are Gadodiamide (Omniscan® – GE Healthcare) and Gadoteridol (ProHance® – Bracco Diagnostics). The study revealed that Omniscan accounted for 67% of the first line agents, thus it has the largest market shares in Ghana. Although NSF cases have been reported for all GBCAs,[6] the majority of NSF cases involve the linear GBCAs—the most commonly reported agent being gadodiamide.[16,22,28,29] Gadodiamide, a high risk GBCA is the least stable open-chain gadolinium compound.[22] Its substantially lower thermodynamic stability by a factor of 1000 or more compared with ProHance[30] might explain why it more readily dissociates and undergoes to transmetallation.[22] Transmetallation, the release of free gadolinium from chelate and the subsequent binding to endogenous ions, occurs more readily in chelates having a weaker affinity for gadolinium such as those that demonstrate non-ionic linear bonding.[4] Compared to gadoteridol, a macrocyclic chelate and a low risk agent, gadodiamide yields two-to-four times more Gd^{3+} ions in the bone tissue of patients with normal kidney function.[31] In spite of the generally accepted notion that GBCA exposure is a necessary factor in the development of NSF,[17] the study revealed that only 42% respondents indicated that their choice of GBCA was influenced by their known association of certain GBCAs with NSF. It is important to note that the choice of GBCAs should be tailored to individual patients based on their susceptible risk factors to NSF. Furthermore, the study demonstrated that only 42% have a departmental protocol on the administration of GBCAs with regards to its association with NSF. Departmental protocols are important guidelines that serves as standards for safe and

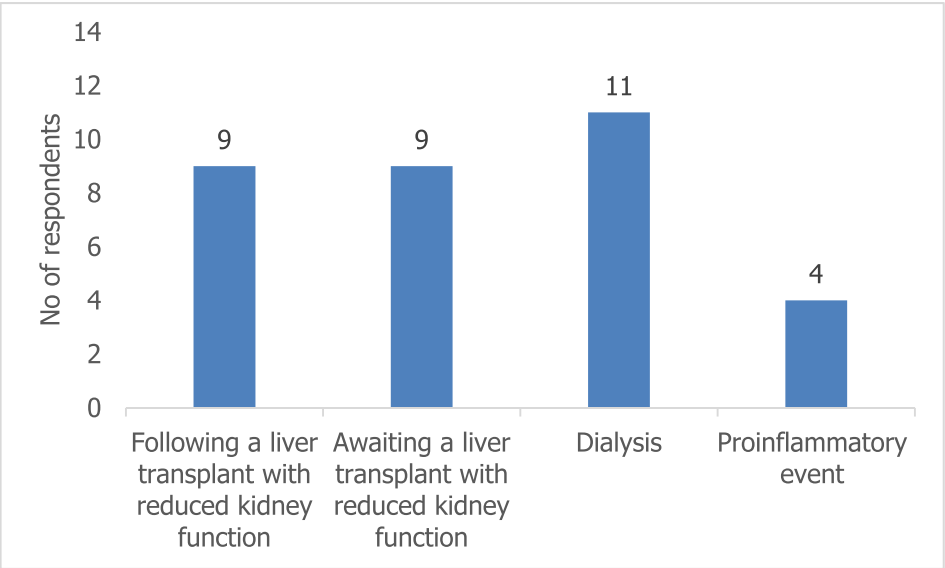

Figure 4. Summary of awareness of factors associated with NSF.

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responsible practices in the clinical settings. By establishing a departmental protocol on the administration of GBCAs in the wake of its association with NSF, safety practices can be enhanced, and GBCAs can be effectively used when deem fit. This protocol will also help in identifying patients at risk for NSF before the administration of any GBCA, consideration for alternative diagnostic examinations that do not employ a GBCA, and what decision to take in the event of emergent or urgent cases.

In finding out if facilities that use either Omniscan or Magnevist check kidney function prior to administration, it was noted that of the 8 facilities that use the high risk agent Omniscan, 3 check kidney function in all patients, 2 check in selected patients, and 3 do not check at all. It is important to estimate eGFR rather than depend on serum creatinine alone to judge the presence or severity of renal disease because it is a better indicator of baseline renal function.[2,32,33] The positions of the ACR[17] and the ESUR[18] although somewhat similar, vary with regards to measuring eGFR in patients prior to administration of GBCAs. For instance, the ACR[17] did not specifically indicate measuring eGFR before administration of any GBCA, but rather recommend pre-administration of eGFR calculation in individuals scheduled to receive any GBCA with the following risk factors – more than 60 years of age, history of renal disease (i.e. dialysis, kidney transplant, single kidney, kidney surgery, and history of known cancer involving the kidney[s]), history of hypertension requiring medical therapy, and history of diabetes mellitus. On the other hand, although the ESUR[18] did not support the measurement of eGFR in all patients receiving GBCA; it however recommends mandatory measurement of eGFR prior to the administration of GBCAs which have been associated with subsequent development of NSF, particularly the high risk agents (Omniscan, OptiMark, and Magnevist) (see Table 1).

In finding out the options considered by facilities that screen all patients for renal function, it was shown that all three facilities do not use contrast if the patient has an eGFR of 30–59 ml/min, but only 1 considers other modality as an additional alternative; and if the patient has an eGFR of <30 ml/min, only 2 do not use contrast but consider other modality, however 1 continue with the contrast agent (Omniscan). Furthermore, of the 2 facilities that check kidney function in selected patients, both screen patients with known renal disease, however only 1 indicated checking in patients with history of diabetes, hypertension, etc. According to the ACR,[17] patients at risk for NSF include those with any of the following conditions – on dialysis (of any form), severe or end-stage CKD (CKD 4 or 5, eGFR < 30 ml/min/1.73 m^2) without dialysis, eGFR 30–40 ml/min/1.73 m^2 without dialysis, and acute kidney injury (AKI). On this note, it is recommended that high risk agents i.e. gadodiamide is contraindicated by the FDA in these group of patients. Other options include considering alternative diagnostic examinations that do not employ a GBCA, or if non-emergent and the potential benefit of administering GBCAs outweigh the risk of NSF in an individual patient and there is no suitable alternative, administration of GBCA may be considered after and established agreement with the referring physician and patient. A summary is provided in (see Table 1) comparing recommendations from international organisations.

When first described in 2000, NSF was noted to occur predominantly in patients with end-stage CKD, particularly in patients on dialysis who received GBCA.[17] Thus apart from GBCA exposure being a necessary factor in the development of NSF,[17] it is important to note that end-stage CKD is a complementary factor. Furthermore, it was suggested that there must be predisposing factors other than exposure to one of the less stable gadolinium-based contrast media, because not all patients with poor renal function who had received one of these agents developed NSF.[5] Possible factors which were suggested included inflammatory conditions, recent vascular surgery, use of high dose erythropoietin (EPO), increased serum concentration of ionised calcium and phosphate, acidosis and the effect of iron (i.e. iron status and therapy).[34,35] In the present survey, it was determined that 9 (75%) respondents were aware that patients are at a higher risk of NSF following a liver transplant with reduced kidney function, again 9 (75%) indicated they were aware that patients awaiting a liver transplant with reduced kidney function are at a higher risk, 11 (92%) were aware that patients on dialysis are at higher risk, however only 4 (33%) were aware that patients with proinflammatory events are at a higher risk (Fig. 2). Some of the early reported cases of NSF were patients with severe

Table 1
Renal function of patients and recommendations on the use of GBCAs.

eGFR	ACR	ESUR	RCR
<30 (CKD 4 or 5)	It is recommended that any GBCA be avoided in this patient group. However if GBCA enhanced MRI is deemed essential, use of the lowest possible dose needed to obtain a diagnostic study is recommended (note: for many MRI examinations, the lowest diagnostic dose has not been determined, and care should be taken not to lower the dose below diagnostic levels). Although there is no absolute proof that any GBCA is completely safe in this patient group, group I agents (see Table 2) have been contraindicated by the FDA. Further, it may be prudent to avoid readministration of GBCA for several days to a week (with the precise duration of delay balanced with the severity of renal disease and medical urgency in a particular patient).	High risk GBCAs (Omniscan, OptiMark, and Magnevist) are contraindicated	- High risk GBCAs (Omniscan, OptiMark, and Magnevist) are contraindicated. - Administer the smallest amount of GBCA to achieve an adequate diagnostic examination. - Avoid administering GBCA for radiography, computed tomography, or angiography as a method of avoiding nephropathy associated with iodinated contrast media.
30–59 (CKD 3)	Precautions described above for CKD4 and CKD5 patients are also recommended for in patients with an eGFR < 40 ml min/1.73 m^2. In comparison, no special precautions are required in patients with an eGFR of 40–59 ml/min/1.73 m^2	High risk GBCAs should be administered cautiously.	High risk GBCAs should be administered cautiously.
60–119 (CKD 1 or 2)	There is no evidence that patients in these groups are at increased risk of developing NSF. Current consensus is that any GBCA can be administered safely to these patients.	High risk GBCAS should be administered cautiously in only patients with eGFR of 60.	High risk GBCAS should be administered cautiously in only patients with eGFR of 60.

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Table 2
Classification of GBCAs in different risk groups and according to the risk of developing NSF, and determination of eGFR prior to injecting GBCA.

Brand name	Generic name	Molecular structure	Classification		Measurement of eGFR before injecting GBCA	
			ACR	ESUR	ACR	ESUR
Gadodiamide	Omniscan	Linear, non-ionic	Group I	High risk	NI	M
Gadopentetate digmeglumine	Magnevist	Linear, ionic	Group I	High risk	NI	M
Gadoversetamide	OptiMark	Linear, non-ionic	Group I	High risk	NI	M
Gadobenate dimeglumine	MultiHance	Linear, ionic	Group II	Medium risk	NI	NM
Gadobutrol	Gadavist	Macrocyclic, non-ionic	Group II	Low risk	NI	NM
Gadoterate meglumine	Dotarem	Macrocyclic, ionic	Group II	Low risk	NI	NM
Gadoteridol	ProHance	Macrocyclic, non-ionic	Group II	Low risk	NI	NM
Gadofosveset trisodium	Ablavar	Linear, ionic	Group III	–	NI	NM
Gadoxetate disodium	Eovis	Linear, ionic	Group III	–	NI	NM

According to the ACR[17] classification, Group I agents are associated with the greatest number of NSF cases; Group II agents are associated with few, if any, unconfounded cases of NSF; and Group III are agents that have only recently appeared on the market.
Unconfounded: In 'unconfounded' cases only one GBCA had been given before NSF developed.
Confounded: If two GBCAs had been administered within eight weeks of each other (may be longer), it is impossible to determine with certainty which agent triggered the development of NSF and the situation is described as 'confounded'. However, the agent that is most likely responsible is the one which has triggered NSF in other uncounfounded situations.[19]

liver dysfunction who were awaiting liver transplantation and who also had impaired renal function.[36] On this premise the initial FDA warning was against the use of GBCAs in patients with "… acute renal insufficiency of any severity due to the hepatorenal syndrome or in the perioperative liver transplantation period".[37] However, this was not supported by most data.[17] For instance, in a literature review, Mazhar et al.[38] found that only 34 (12%) out of 291 NSF patients, had concomitant liver disease; however, all but one of these patients also had known severe renal insufficiency (eGFR of <30 ml/min/1.73 m^2) prior to GBCA administration. Therefore, hepatic disease in and of itself, in the absence of AKI or severe CKD, is no longer considered a risk factor for NSF.[17] Although proinflammatory events have been postulated as one of many possible co-factors to play a role in the development of NSF, it is not consistently confirmed as a true co-factor.[17] Therefore it is recommended that routine screening in such cases is not mandatory, but may be done on an optional basis.[17]

Conclusion

With the rapid proliferation of MRI in Ghana, parallelled by an increasing indications for, and applications of GBCAs, it is imperative that local guidelines be established in line with international guidelines with regards to the administration of GBCAs in order to minimize the incidence of NSF. In view of this study which revealed that more than half of the respondents administer gadodiamide, a high risk agent, it is important that mandatory screening of renal function using eGFR in patients at risk of NSF is undertaken, as well as in those that will receive gadodiamide. Macrocyclic agents are currently advised for use in those with compromised renal impairment. Patients should be evaluated on an individual basis by weighing the benefits and risks of an MRI study that may warrant the administration of GBCA.

Conflict of interest statement

None.

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