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Risk factors associated with the administering of Gadolinium in cancer patients with some type of renal impairment, detected by nurses: case studies.

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KEY WORDS: Risk factors, Gadolinium, Cancer patients, Magnetic resonance imaging, Renal function.

ABSTRACT

Goal: To describe the risk factors of the administration of Gadolinium for magnetic resonance imaging (MRI) in cancer patients with some type of renal alteration, detected in the interview held with nurses.

Method. Retrospective descriptive observational case study. The sample consisted of 218 subjects admitted to the Fundación Instituto Valenciano de Oncología hospital (FIVO in Spanish) in Valencia, Spain. Subjects with an estimated glomerular filtration rate (eGFR) >30ml/min/1,73m^2 were selected, divided into two subgroups: stable patients (maintained or improved) and non-stable patients (worsening). The study period was from March to May 2020. The modified European Society of Urogenital Radiology (ESUR) questionnaire was used. Data was coded in a Microsoft Excel Redmond® database and analysed with R v3.4.0® software via the Rstudio® integrated development environment. 95% CI for p-value <0.05.

Results. In the sample analysed, the administration of Gadolinium for MRI in cancer patients did not lead to the relevant deterioration of the renal function. There was evidence of a relationship between the worsening of eGFR with increasing age and blood pressure. The female sex was found to be protective.

Conclusions. The administration of gadolinium-based contrast media for MRI in cancer patients was not associated with increased renal damage. Questionnaires applied by nurses can obtain relevant information for detecting risk factors not necessarily associated with cancer. Questionnaires applied by nurses can obtain relevant information for detecting risk factors not necessarily associated with cancer. The risk factors associated with eGFR were age, high blood pressure and sex.

INTRODUCTION

Magnetic Resonance Imaging (MRI) is an essential technique for diagnostic imaging and is used in clinical practice, especially in oncology (Kuhl et al. 2019) (Petralia et al. 2020). In the diagnosis of cancer patients by means of MRI, and with the aim of detecting biomarkers, it is necessary to avoid contrast-associated nephropathy (Li et al. 2022), using gadolinium-based contrasts (Supawat et al. 2020) (Weinred et al. 2021). Some authors have shown that these types of contrasts do not produce significant adverse effects in patients, although others describe alterations such as renal insufficiency that can trigger nephrogenic systemic fibrosis (NSF) (Alfano et al. 2020) (Lim et al. 2021) (Benzon et al. 2021).

Nurses should be familiar with the indications, mechanisms of action, dosage, contraindications and the effects, among others, of the contrasts used in MRI. With the administration of contrasts, a change in tissue attenuation is achieved; apart from this change, any manifestation that may be immediate or delayed is considered an adverse effect. These effects are also classified as mild, severe or very severe (Umakoshi et al. 2020).

It is important to highlight that renal failure in cancer patients is not always caused by contrast; there are other factors that can cause it. Hence the European Society of Urogenital Radiology (ESUR) recommends previously assessing patients who are going to undergo MRI with gadolinium-based contrasts; this task is carried out by nurses by means of specific questionnaires (Gijón et al. 2021) (González et al. 2021).

More research based on clinical practice is therefore needed (Roberts et al. 2019) (Jeon et al. 2019).

The goal of this study was to describe the risk factors of the administration of Gadolinium in MRI in cancer patients with some type of renal alteration, detected during the interview with nurses.

METHOD

Retrospective observational case series study. Subjects were patients undergoing MRI with pre- and post-measuring eGFR monitoring. Participants were from primary care, emergency and inpatient departments. Data was collected by nurses from the computerised clinical record in an ad hoc questionnaire (Annex 1) and the ESUR questionnaire (Gijón et al. 2021) which was completed with socio-demographic and socio-health variables of clinical interest such as age, sex, type of contrast, type of tumour, presence or absence of metastasis, chemotherapy treatment, presence of arterial hypertension (AHT) and diabetes, among others. The information was collected from March to May 2020.

The population consisted of 1000 subjects who had been administered gadolinium (Gd) as a contrast medium. Data collection by nurses was conducted over four months (March to June 2019). The data collection centre was the Fundación Instituto Valenciano de Oncología (FIVO) in Valencia, Spain. The sample selection criteria were: subjects over the age of 18 diagnosed with some type of cancer, with an eGFR of 30 ml/min/1.73 m2 and who did not present cognitive impairment that would prevent them from answering the questions in the questionnaire. After the selection filters, the sample consisted of 218 participants who were followed up for 18 months.

To proceed with the statistical analysis, the first step was the estimation of the glomerular filtration rate (eGFR) of the subjects. This led to two different groups: eGFR>60 ml/min/1.73 m2 and eGFR<60 ml/min/1.73 m2. Secondly, the sample was divided up into three groups: firstly, patients who worsen the value, those who maintain it and those who improve the value with respect to the baseline. This classification was used for bivariate analysis and logistic regression. For continuous variables, measures of dispersion and centralisation were used, and given that the statistical criteria were met, ANOVA: binary logistic regression models were performed according to their applicability. Firstly, the data obtained was made anonymous, coded in a Microsoft Excel Redmond® database and analysed with R v3.4.0® software via the Rstudio® integrated development environment. 95% CI for p-value <0.05.

RESULTS

The sample consisted of 218 people with an age of 61.39 ± 11.99; 45.40% were men as compared to 54.60% women (table 1), where the type of contrast, origin of the patient, allergies, other diseases, renal filtration, type of tumour, chemotherapy, metastasis and exits in three groups (worsens, maintains and/or improves) are described.

In relation to the renal function after the administration of gadolinium, it was observed that of those with baseline eGFR values > 60 ml/min/1.73m2, 4.5% worsened and 95.5% remained the same. In contrast, of those with baseline eGFR < 60 ml/min/1.73 m2, 27.8% subsequently improved while 72.2% remained the same.

Statistical significance was obtained for the eGFR construct against age, sex, renal failure, hypertension, baseline glomerular filtration rate, tumour type and metastasis (table 1). A statistically significant relationship was found between age and eGFR<60 ml/min/1.73 m2 as well as renal impairment (table 2). Finally, in the logistic regression analysis (table 3), associated with eGFR deterioration, arterial hypertension obtained an OR of 3.77 (p=0.055).

DISCUSSION

The questionnaires carried out by nurses provide extremely valuable clinical information for detecting possible side effects in cancer patients undergoing magnetic resonance imaging (MRI) with contrasts.

We can affirm that this research provides evidence that the administration of Gadolinium-based contrast media in cancer patients does not produce a clinically relevant deterioration of the renal function; however, although the short- and medium-term effects are well known, it is necessary to discover the long-term biological and clinical effects (Abu-Alfa et al. 2020) (McDonald et al. 2020) (Woolen et al. 2020).

The association between age, sex and hypertension in patients with impaired eGFR after contrast administration was evident, especially in those with baseline eGFR > 60 ml/min/1.73 m2. It was also shown that patients with baseline eGFR>60 ml/min/1.73 m2 maintained the values and even improved after the administration of Gadolinium: this result is in line with authors such as Layne et al. who state that it is not necessary to measure eGFR in patients undergoing GCBM (Layne et al. 2020).

Logistic regression analysis shows that patients with eGFR>60 ml/min/1.73 m2 did not manifest nephrogenic systemic fibrosis (NSF) after frequent administration of gadolinium-based contrast agents for MRI. In this context, authors such as Gonzalez et al. have already stated that NSF is a disease with a low prevalence, estimated at a maximum of 18% in the at-risk population (Gonzalez et al. 2021).

Regarding the questionnaires used in this study to assess the state of renal function and which provided relevant information, other authors have already demonstrated this fact: Snaith et al. in a similar study, in this case with a sample of 1086 patients, were able to show this efficacy, in which they assessed the risk of NSF in MRI with gadolinium: in this case they used a double screening questionnaire. The first questionnaire was not carried out by nurses as it was in our research, but rather was filled in by the doctors requesting the radiological test, and the second was filled in by the patients (Snaith et al. 2016). Thanks to these questionnaires, patients with eGFR<30 ml/min/1.73m2 could be detected earlier, thereby avoiding additional tests, and saving both time and money. It would be interesting to standardise these questionnaires and determine which questions they should contain, as there is clearly no agreement in the literature. Schreuder et al. drew up a questionnaire with a sensitivity of 76% for patients with eGFR<60 ml/min/1.73 m2, which included questions such as heart failure (HF) and previous history of urological and renal disease, among others (Schereuder et al. 2017).

We can affirm that, despite the pros and cons, the questionnaire identifies comorbidities that may be associated with contrast-induced nephropathy (CIN), as occurred in our research with HTN, and which other authors corroborate as a variable linked to cancer patients (Fowler et al. 2020).

As for gadolinium deposits in brain tissue, no cases have been detected, perhaps due to the short follow-up of patients, as Fujita and colleagues state in a recent study (Fujita et al. 2020). Other authors attribute this to the direction of follow-up, often retrospective (Lyapustina et al. 2019). It is also related to the time of administration, as stated by Chazot et al., who specifically relate it to cases in which gadolinium has been administered in the last eight years (Chazot et al. 2020).

It is therefore necessary to assess the impact of contrast, not only in terms of the patients to whom it has been administered, but also in terms of the possibility of environmental contamination (Brisset et al. 2020). Fujita and colleagues advocate the use of synthetic MRI to reduce the dose of gadolinium administered (Fujita et al. 2020).

ETHICAL CONSIDERATIONS

The research project was approved by the Clinical Research Ethics Committee (CEIC). The participants signed an express written informed consent (IC) form. Committee that approved the study: CEIC Ethics Committee Instituto Valenciano de Oncología (FIVO) Valencia, Spain. Secretariat EDITORIAL. Quality Oncology Practice Initiative (QOPI) certification programme. Ethics approval number REDACTED 2017-14.

CONCLUSIONS

The administration of gadolinium-based contrast media for MRI in cancer patients, in our sample, was not associated with greater renal damage in either the short or the medium term. Questionnaires applied by nurses can obtain relevant information for detecting risk factors not necessarily associated with cancer. The risk factors ─ not clinically significant ─ associated with eGFR deterioration were age, sex and HTN.

INFORMED CONSENT STATEMENT

Express and written informed consent was obtained from everybody involved in the study.

DATA AVAILABILITY STATEMENT

The data supporting the conclusions of this study is available from the principal researcher upon request.

CONFLICTS OF INTERESTS

The authors declare that they have no conflicts of interest.

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There was no funding for this study.

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***Table** 1: Diferences in eGFR with respect to all variables.*

Variable	Total	Worsens	Maintains	Improves	P-value
	218 (100%)	9 (4.13 %)	204 (93.58%)	5 (2.29%)	
Age					0,033
Mean (SD)	61.39 (11.99)	70.55 (7.41)	60.88 (12.02)	65.57 (11.42)	
Median (IR)	63.11 (53.91-69.96)	70.96 (65.54-72.12)	62.02 (53.32-69.64)	71.06 (66.32-72.03)	
Exploration					NA
RM	218 (100.00%)	9 (100.00%)	204 (100.00%)	5 (100.00%)	
Contrast					0,938
Primovist	5 (2.30%)	0 (0.00%)	5 (2.45%)	0 (0.00%)	
Gadovist	192 (88.10%)	8 (88.89%)	180 (88.24%)	4 (80.00%)	
Prohance	17 (7.80%)	1 (11.11%)	15 (7.35%)	1 (20.00%)	
Multihance	4 (1.80%)	0 (0.00%)	4 (1.96%)	0 (0.00%)	
Contrast before the test					0,234
No	56 (25.70%)	1 (11.11%)	55 (26.96%)	0 (0.00%)	
Yes	162 (74.30%)	8 (88.89%)	149 (73.04%)	5 (100.00%)	
Source					0,017
Hospitalisation	19 (8.70%)	3 (33.33%)	15 (7.35%)	1 (20.00%)	
Outpatient clinics	199 (91.30%)	6 (66.67%)	189 (92.65%)	4 (80.00%)	
Sex					0,652
Man	99 (45.40%)	5 (55.56%)	91 (44.61%)	3 (60.00%)	
Woman	119 (54.60%)	4 (44.44%)	113 (55.39%)	2 (40.00%)	
Allergies contrast					0,698
No	208 (95.40%)	9 (100.00%)	194 (95.10%)	5 (100.00%)	
Yes	10 (4.60%)	0 (0.00%)	10 (4.90%)	0 (0.00%)	
Drug allergies					0,026
No	159 (72.90%)	7 (77.78%)	151 (74.02%)	1 (20.00%)	
Yes	59 (27.10%)	2 (22.22%)	53 (25.98%)	4 (80.00%)	
Asthma					0,442
No	210 (96.30%)	8 (88.89%)	197 (96.57%)	5 (100.00%)	
Yes	8 (3.70%)	1 (11.11%)	7 (3.43%)	0 (0.00%)	
Thyroid					0,363

No	192 (88.10%)	9 (100.00%)	178 (87.25%)	5 (100.00%)	
Yes	26 (11.90%)	0 (0.00%)	26 (12.75%)	0 (0.00%)	
Heart disease					0,003
No	203 (93.10%)	6 (66.67%)	193 (94.61%)	4 (80.00%)	
Yes	15 (6.90%)	3 (33.33%)	11 (5.39%)	1 (20.00%)	
Diabetes					0,007
No	192 (88.10%)	5 (55.56%)	182 (89.22%)	5 (100.00%)	
Yes	26 (11.90%)	4 (44.44%)	22 (10.78%)	0 (0.00%)	
Renal insufficiency					0,725
No	209 (95.90%)	9 (100.00%)	195 (95.59%)	5 (100.00%)	
Yes	9 (4.10%)	0 (0.00%)	9 (4.41%)	0 (0.00%)	
BP problems					0,118
No	161 (73.90%)	4 (44.44%)	153 (75.00%)	4 (80.00%)	
Yes	57 (26.10%)	5 (55.56%)	51 (25.00%)	1 (20.00%)	
Pre-filtered value					<0.001
<60	18 (8.30%)	0 (0.00%)	13 (6.37%)	5 (100.00%)	
>60	200 (91.70%)	9 (100.00%)	191 (93.63%)	0 (0.00%)	
Time between filtering					0,106
Mean (SD)	4.50 (4.84)	4.17 (3.38)	4.60 (4.93)	0.95 (0.82)	
Median (IR)	2.78 (0.87-6.70)	3.53 (0.67-6.57)	2.82 (0.98-6.78)	0.73 (0.53-1.03)	
Tumour type					0,475
Ca Mama	45 (20.60%)	1 (11.11%)	43 (21.08%)	1 (20.00%)	
Ca Lung	7 (3.20%)	1 (11.11%)	6 (2.94%)	0 (0.00%)	
Ca Prostata	36 (16.50%)	0 (0.00%)	36 (17.65%)	0 (0.00%)	
Gynaecological Ca	9 (4.10%)	0 (0.00%)	9 (4.41%)	0 (0.00%)	
Digestive Ca	17 (7.80%)	0 (0.00%)	17 (8.33%)	0 (0.00%)	
Rest	104 (47.70%)	7 (77.78%)	93 (45.59%)	4 (80.00%)	
Gammopathy/myeloma					0,901
No	215 (98.60%)	9 (100.00%)	201 (98.53%)	5 (100.00%)	
Yes	3 (1.40%)	0 (0.00%)	3 (1.47%)	0 (0.00%)	
Chemotherapy					0,381
NO QT	166 (76.10%)	7 (77.78%)	156 (76.47%)	3 (60.00%)	
QT Oral	6 (2.80%)	0 (0.00%)	5 (2.45%)	1 (20.00%)	

QT IV	40 (18.30%)	2 (22.22%)	37 (18.14%)	1 (20.00%)	
Combined QT	6 (2.80%)	0 (0.00%)	6 (2.94%)	0 (0.00%)	
Chemotherapy					0.69
No	166 (76.10%)	7 (77.78%)	156 (76.47%)	3 (60.00%)	
Yes	52 (23.90%)	2 (22.22%)	48 (23.53%)	2 (40.00%)	
Vascular problems					0,312
No	205 (94.00%)	9 (100.00%)	192 (94.12%)	4 (80.00%)	
Yes	13 (6.00%)	0 (0.00%)	12 (5.88%)	1 (20.00%)	
Metastasis					0,463
No	194 (89.00%)	9 (100.00%)	181 (88.73%)	4 (80.00%)	
Yes	24 (11.00%)	0 (0.00%)	23 (11.27%)	1 (20.00%)	
Exitus					0.08
No	185 (84.90%)	6 (66.67%)	176 (86.27%)	3 (60.00%)	
Yes	33 (15.10%)	3 (33.33%)	28 (13.73%)	2 (40.00%)	
Emergency assistance					0,966
No	217 (99.50%)	9 (100.00%)	203 (99.51%)	5 (100.00%)	
Yes	1 (0.50%)	0 (0.00%)	1 (0.49%)	0 (0.00%)	

Percentage by groups for entire population

***Table 2**: Main risk factors according to baseline eGFR*

Variable	Total	<60	>60	P-value
	218 (100%)	18 (8.26 %)	200 (91.74%)	
Age				<0.001
Mean (SD)	61.39 (11.99)	71.09 (9.48)	60.52 (11.82)	
Median (IR)	63.11 (53.91-69.96)	71.61 (69.64-77.08)	61.93 (53.16-68.72)	
Heart disease				0,002
No	203 (93.10%)	13 (72.22%)	190 (95.00%)	
Yes	15 (6.90%)	5 (27.78%)	10 (5.00%)	
Diabetes				1
No	192 (88.10%)	16 (88.89%)	176 (88.00%)	
Yes	26 (11.90%)	2 (11.11%)	24 (12.00%)	
Renal insufficiency				<0.001
No	209 (95.90%)	12 (66.67%)	197 (98.50%)	
Yes	9 (4.10%)	6 (33.33%)	3 (1.50%)	
HTA				0,657
No	161 (73.90%)	12 (66.67%)	149 (74.50%)	
Yes	57 (26.10%)	6 (33.33%)	51 (25.50%)	

***Table 3**: Binary logistic regression with worsening outcome*

Variable	Total	It does not get worse	If it gets worse	OR	IC:	95%	P-value
	218 (100%)	209 (95.87%)	9 (4.13%)	1,088	1,018	1,179	
Age							0,023
Mean (SD)	61.39 (11.99)	61.00 (12.00)	70.55 (7.41)				
Median (IR)	63.11 (53.91-69.96)	62.12 (53.33-69.75)	70.96 (65.54-72.12)				
Sex							0,534
Man	99 (45.40%)	94 (94.95%)	5 (5.05%)	(baseline)			
Woman	119 (54.60%)	115 (96.64%)	4 (3.36%)	0,65	0,20	2,54	0,535
Diabetes							0,012
No	192 (88.10%)	187 (97.40%)	5 (2.60%)	(baseline)			
Yes	26 (11.90%)	22 (84.62%)	4 (15.38%)	6,80	1,60	27,60	0,007
Renal insufficiency							0,379
No	209 (95.90%)	200 (95.69%)	9 (4.31%)	(baseline)			
Yes	9 (4.10%)	9 (100.00%)	0 (0.00%)	0,00	NA	2.189639e+31	0,991
BP problems							0,056
No	161 (73.90%)	157 (97.52%)	4 (2.48%)	(baseline)			
Yes	57 (26.10%)	52 (91.23%)	5 (8.77%)	3,77	1,00	15,75	0,054
Metastasis							0,143
No	194 (89.00%)	185 (95.36%)	9 (4.64%)	(baseline)			
Yes	24 (11.00%)	24 (100.00%)	0 (0.00%)	0,00	NA	1.905867e+42	0,991

APPENDIX 1. Variables

Questionnaire. MRI EXAMINATION

CLINICAL HISTORY _____

1. REFERRED FROM: ☐HOSPITAL ☐OUTPATIENTS ☐EMERGENCY
2. Date of Birth _____
3. Gender ☐MALE ☐FEMALE
4. Are you allergic to any medication? ☐NO ☐YES _____
5. Are you allergic to any contrast agent? ☐NO ☐YES _____
6. Have you been given contrast prior to this scan? ☐NO ☐YES _____
7. Do you have a history of diabetes? ☐NO ☐YES

   If so, were you treated with insulin or with medication _____
8. Do you have asthma? ☐NO ☐YES
9. Do you have any thyroid problems? ☐NO ☐YES _____
10. Do you suffer from high blood pressure? ☐NO ☐YES _____
11. Do you have kidney failure or kidney problems? ☐NO ☐YES _____
12. Have you had any heart disease? ☐NO ☐YES _____
13. Have you suffered from brain, vascular, ICTUS or bleeding problems? ☐NO ☐YES _____
14. What tumour are you being treated for? _____
15. Do you have or have you had monoclonal gammopathy or myeloma? ☐NO ☐YES _____
16. Are you receiving chemotherapy? ☐ORAL ☐NO ☐YES

    INTRAVENOUS ☐NO ☐YES
17. When was intravenous chemotherapy last given? _____