RESEARCH ARTICLE

Can the lower rate of CT- or MRI-related adverse drug reactions to contrast media due to stricter limitations on patients undergoing contrast-enhanced CT or MRI?

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Objective: The aim of this study was to examine whether a decreased occurrence rate of adverse drug reactions (ADRs) to contrast media in contrast-enhanced CT and MRI was attributable to appropriate criteria for patients with some diseases. A secondary aim was to elucidate safety profiles for contrast media and factors influencing the occurrence of ADRs.

Methods: Clinical data of patients who underwent contrast-enhanced CT (5576 cases) or MRI (3357 cases) were retrospectively analyzed to evaluate rates of ADRs to contrast media, symptoms of ADRs, treatments for ADRs, and differences in medical history, blood test results, and other factors between patients with and without ADRs in a dental hospital.

Results: The rate of ADRs to contrast media was 0.54% for CT and 0.09% for MRI. The most frequent ADRs in contrast-enhanced CT or MRI were nausea and vomiting as physiologic reactions. Two serious reactions were seen for CT, but none for MRI. Significant differences between patients with and without ADRs were seen in liver function according to blood tests for CT, and in digestive disorders elicited from medical interviews for MRI.

Conclusion: The lower occurrence rate of ADRs to contrast media in dental hospitals could be due to the adoption of appropriate criteria for patients with some diseases undergoing enhanced CT or MRI. Complete suppression of ADRs to contrast media for CT or MRI is unrealistic, so attention is warranted for patients with decreased liver function when performing enhanced CT, and for patients with digestive disorders when performing enhanced MRI.

Dentomaxillofacial Radiology (2020) 49, 20190214. doi: [10.1259/dmfr.20190214](https://doi.org/10.1259/dmfr.20190214)

Cite this article as: Maeda T, Oda M, Kito S, Tanaka T, Wakasugi-Sato N, Matsumoto-Takeda S, et al. Can the lower rate of CT- or MRI-related adverse drug reactions to contrast media due to stricter limitations on patients undergoing contrast-enhanced CT or MRI?. *Dentomaxillofac Radiol* 2020; 49: 20190214.

Keywords: Contrast Media; Hospital Dental Service; X-Ray Computed Tomography; Magnetic Resonance Imaging; Adverse Drug Reaction

Introduction

MRI and CT have been usefully performed in dental hospitals for cases involving expanded inflammation, tumors, and cysts in the oral and maxillofacial regions.¹⁻³ Contrast media have been frequently used

for more exact qualitative diagnosis of diseases from CT or MRI. Contrast-enhanced CT or MRI tend to be regarded positively by radiologists for diagnosing suspected malignant tumors, as these modalities provide more exact and more precise information regarding the presence and site of lesions and qualitative diagnosis than imaging without contrast

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Received 30 May 2019; revised 28 September 2019; accepted 02 October 2019

media.^{1,2} However, adverse drug reactions (ADRs) such as allergic reactions could be induced by the use of contrast media in CT or MRI, and serious status has resulted from anaphylaxis as a complication in rare cases.^{4–14} Of course, ADRs cannot be completely prevented even if we pay close attention to avoiding complications associated with contrast media.^{4–14} Various reports have examined rates and other issues associated with ADRs from CT or MRI using contrast media.^{4–14} In Japan, some large-scale investigations have been conducted.^{4,5,11,12} However, the majority of patients with oral-related disease in dental hospitals have tended not to present with serious status such as systemic diseases, and we hypothesized that previous data from medical hospitals on ADRs for CT or MRI with contrast media might not necessarily apply to dental hospitals. In addition, we hypothesized that the occurrence rate of ADRs to contrast media for CT or MRI in dental hospitals might be lower because of the better general condition than medical hospitals, and stricter, more appropriate criteria for some underlying diseases when performing contrast-enhanced CT or MRI propriety. However, no reports have described occurrence rates and associated data for ADRs from CT or MRI using contrast media in dental hospitals.

We therefore analyzed the occurrence rate and other data for ADRs to contrast media for CT or MRI in dental hospitals. We retrospectively evaluated and analyzed the occurrence of ADRs to contrast media for CT or MRI, symptoms of ADRs to contrast media, and treatments for ADRs from 1 July 2000 to 31 March 2017 in a dental hospital.

Methods and patients

The clinical data of patients who underwent contrast-enhanced CT (5576 cases) or contrast-enhanced MRI (3357 cases) from 1 July 2000 to 31 March 2017 were retrospectively analyzed to evaluate occurrence rates of ADRs to contrast media. We had performed contrast-enhanced examinations only for the diagnosis of malignant tumor or when such pathologies had been suspected. Before CT or MRI using contrast media, medical interviews had been conducted to elicit patient history and blood testing had also been performed. Patients for whom contrast-enhanced CT or MRI examinations have been considered inadvisable (Table 1) were excluded from imaging. The specific criteria in our dental hospital were defined in reference to drug package inserts from the Japanese pharmacopoeia, guidelines from the European Society of Urogenital Radiology and Japan Radiological Society, and other relevant literature.^{15–18} The present study was approved by the institutional review board at Kyushu Dental University (approval no. 16–15). The Human Investigations Committee of Kyushu Dental University ensures the protection of the individual rights of patients.

Contrast-enhanced CT had been performed using multidetector-row CT after the patient received an intravenous dose of 50 ml iohexol (300 mgI ml⁻¹; Omnipaque 300™, Daiichi Pharmaceutical, Tokyo, Japan) at the start of scanning and an additional 50 ml intravenous infusion during scanning to allow better visualization of the vascular structures. Scanning had been performed in the axial plane without angulation, in 5-mm-thick contiguous sections from the cavernous

Table 1 Inadvisable criteria for patients examined by contrast-enhanced CT or MRI based on check items in medical interviews before examinations in the present dental hospital

	<i>Enhanced-CT</i>	<i>Enhanced-MRI</i>
Impossible decision for using enhanced CT or MRI	General bad condition Previous history of ADRs caused by iodine contrast media Asthma except for pediatric asthma Kidney diseases (eGFR <40 ml/min/1.73m2) Hypersensitivity to iodine Hyperthyroidism Macroglobulinaemia Multiple myeloma Pheochromocytoma Tetany	General bad condition Previous history of ADRs caused by iodine or gadolinium contrast media Asthma except for pediatric asthma Kidney diseases (eGFR <40 ml/min/1.73m2)
Decision for using enhanced CT or MRI after judgments by medical doctor	Liver disease (AST > 80 or ALT > 80 or γ GTP > 100)	Liver disease (AST > 80 or ALT > 80 or γ GTP > 100)
Decision for using enhanced CT or MRI conditional decision	Diabetes mellitus taking biguanide (biguanide withdrawal before and after 48 h)	

ADR, adverse drug reaction; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ GTP, γ -glutamyltranspeptidase

sinuses to the thoracic inlet. Images have been obtained using standard algorithms and soft-tissue windows. Contrast-enhanced MRI had been performed using a 1.5 T full-body MR system (EXCELART Vantage™ Powered by Atlas; Toshiba, Tokyo, Japan) with a circular polarized neck coil to visualize the level of the maxilla and mandible after the patient received an intravenous dose of gadolinium contrast agent (0.2 ml/kg body weight). As macrocyclic chelate-type contrast media for MRI, gadoterate meglumine (MagneScope i.v. inj. 38%; Guerbet Japan, Tokyo, Japan) and gadoteridol (Prohance; Eisai, Tokyo, Japan) in gadolinium-based contrast agents were used as linear chelate types, and meglumine gadopentetate (Magnevist; Bayer Yakuhin, Osaka, Japan) and gadodiamide hydrate (Omniscan; Daiichi Pharmaceutical, Tokyo, Japan) were used after 2014.

We retrospectively evaluated the kinds of diseases patients presented with and rates of ADRs to contrast media for contrast-enhanced CT or MRI. Symptoms and treatments for ADRs to contrast media were also analyzed. At the same time, our data were compared with ADR-related references obtained from search engines. In concrete terms, the present data on ADRs to contrast-enhanced CT were compared with results from the biggest Japanese study (3.14%) by Katayama *et al.*⁴ the lowest reported ADR rate (0.83%) as described by Fujiwara *et al.*⁵ and the lowest rate reported from around the world (0.40%) by Li *et al.*⁹ In terms of the occurrence of ADRs to contrast-enhanced MRI, the present data were compared with results from the biggest Japanese study¹² (1.21%) and the biggest study conducted globally (0.4%) by Herborn *et al.*¹³ The contrast medium used in reports by Katayama *et al.* was not stated.⁴ The contrast medium used in reports by Fujiwara *et al.* was iopamidol 300/370 (Bracco, Milen, Italy) or Iohexolum 350 (GE Healthcare, Chicago, IL).⁵ The contrast medium used in reports by Li *et al.* was Iopromide 370 (Bayer Healthcare, Leverkusen, Germany), Iodixanol 320 (GE Healthcare, Chicago, IL), or Iohexolum 350 (GE Healthcare, Chicago, IL), Iopamidol 350 (Bracco, Milen, Italy) and Ioversol 300/320/350 (Covidien, St Louis, MI).⁹ The contrast medium used in the biggest Japanese study was gadopentetate dimeglumine (Magnevist; Berlex, Montville, NJ).¹² The contrast medium used in reports by Herborn *et al.* was gadoterate meglumine (MagneScope; Guerbet, Roissy CdG Cedex, France).¹³

We divided patients into two groups of enhanced CT or enhanced MRI at first and follow-up examinations in this dental hospital. The “first examination” by enhanced CT or MRI refers to the first image from enhanced CT or MRI acquired in this dental hospital, and not necessarily the real first examination by enhanced CT or MRI for the patient.

Next, differences in medical history, blood test results, and demographic factors were compared between

patients with and without ADRs to contrast media. To compare distributions of medical histories and blood data between patients with and without ADRs, we also analyzed medical histories and blood data in 60 patients without ADRs to contrast media in contrast-enhanced CT or MRI examinations by random sampling.

All statistical analyses, such as Student's *t*-test, Fisher's exact test, and the χ^2 test were performed using SPSS v. 11 software (SPSS, Chicago, IL). Probability values of $p < 0.05$ were considered significant.

Results

Distributions of contrast-enhanced CT and MRI examinations

Contrast-enhanced CT was performed for 5576 cases and contrast-enhanced MRI was performed for 3357 cases from 1 July 2000 to 31 March 2017 in our dental hospital. Among the 5576 patients who underwent contrast-enhanced CT, 1468 patients were receiving a first examination at this dental hospital, and 4108 were receiving a follow-up examination at this dental hospital. First examinations included 753 male patients and 715 female patients (Table 2). Of the 3357 patients who underwent contrast-enhanced MRI, 1124 were receiving a first examination, and 2233 were undergoing follow-up examinations. The 1124 first examinations included 580 male patients and 544 female patients (Table 2).

The distribution of ages in patients with contrast-enhanced CT or MRI is shown in Table 2. Mean age of male and female patients at first contrast-enhanced CT was 64.1 ± 14.2 and 67.1 ± 15.9 years, respectively. Mean age of male and female patients at first contrast-enhanced MRI was 63.5 ± 13.9 and 66.9 ± 14.6 years, respectively. Most patients were over 60 years old. Few younger patients and children underwent contrast-enhanced imaging.

Occurrence of ADRs in contrast-enhanced CT

The occurrence rate of ADRs to contrast media in contrast-enhanced CT was 0.54% (30 of 5576 patients) (Table 3), including 10 males (mean age, 63.3 ± 22.2 years) and 20 females (mean age, 65.3 ± 22.2 years). This rate was significantly lower than that reported by Katayama *et al.*⁴ (χ^2 test, $p < 0.0001$), and also lower than the lowest ADR rate previously reported by Fujiwara *et al.*⁵ (χ^2 test, $p = 0.026$). In addition, no significant difference was found between the present data and the lowest rate reported by Li *et al.* (χ^2 test, $p = 0.131$).⁹

The distribution of symptoms of ADRs to contrast media in CT is shown in Table 3. The most frequent symptoms were nausea and vomiting as physiologic reactions, followed by dizziness and headache (Table 3). Hypersensitivity reactions were less frequent than physiologic reactions (Table 3). Two serious reactions were seen among the 30 cases of ADR to contrast media in contrast-enhanced CT. Both patients showed lowered

Table 2 Distributions of sex and age in patients with first and follow-up examinations of contrast-enhanced CT or MRI in this dental hospital

Age	Enhanced CT (N=5576)						Enhanced MRI (N=3357)					
	First examination			Follow-up examination			First examination			Follow-up examination		
	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
10–19	6	2	8	7	1	8	4	1	5	3	1	4
20–29	12	18	30	11	43	54	10	11	21	11	23	34
30–39	32	32	64	66	32	98	28	18	46	50	40	90
40–49	62	40	102	172	134	306	50	30	80	121	48	169
50–59	119	102	221	329	307	636	95	84	179	213	178	391
60–69	210	154	364	631	502	1133	170	126	296	366	263	629
70–79	228	202	430	653	669	1322	170	167	337	386	331	717
80–89	80	143	223	145	366	511	51	94	145	61	113	174
>90	4	22	26	1	39	40	2	13	15	1	24	25
Total	753	715	1468	2015	2093	4108	580	544	1124	1212	1021	2233

blood pressure due to allergic reaction. One patient was a 70-year-old female with nausea, vomiting, and lowered blood pressure as an immediate allergic reaction. In the other case, the 56-year-old male patient reported nausea and vomiting 6 h after contrast-enhanced CT, followed by a sudden decrease in blood pressure and loss of consciousness due to delayed allergic reaction. Frequent ADRs included nausea, vomiting, and local urticaria (Table 3).

The frequency of ADRs in response to contrast media in contrast-enhanced CT at the first examination in this dental hospital was 0.89% (13 of 1468 patients) (Table 3), including 4 males (mean age, 48.5 ± 25.2 years) and 9 females (mean age, 74.3 ± 11.1 years). The occurrence rate of ADRs to contrast media in contrast-enhanced CT on follow-up examinations at this dental hospital was 0.41% (17 of 4108 patients) (Table 3), including 6 males (mean age, 72.5 ± 11.6 years) and 11

Table 3 Distribution of symptoms for ADRs to contrast media in contrast-enhanced CT or MRI

	Enhanced CT				Enhanced MRI (N = 3357)			
	First examination (N = 1468)	Follow-up examination (N = 4108)	Total (N = 5576)	p-value (Fisher's exact test)	First examination (N = 1124)	Follow-up examination (N = 2233)	Total (N = 3357)	P-value (Fisher's exact test)
Hypersensitivity reaction								
Local urticaria	1 (0.068%)	3 (0.073%)	4 (0.072%)	1.000	-	1 (0.045%)	1 (0.030%)	1.000
Itching	2 (0.136%)	1 (0.024%)	3 (0.054%)	0.171	-	-	0 (0%)	1.000
Generalized urticaria	2 (0.136%)	1 (0.024%)	3 (0.054%)	0.171	-	-	0 (0%)	1.000
Dyspnea	-	1 (0.024%)	1 (0.018%)	1.000	-	-	0 (0%)	1.000
Anaphylactic shock reaction with loss of consciousness	-	1 (0.024%)	1 (0.018%)	1.000	-	-	0 (0%)	1.000
Anaphylactic shock reaction with convulsions	-	1 (0.024%)	1 (0.018%)	1.000	-	-	0 (0%)	1.000
Total of hypersensitivity reaction	5 (0.341%)	8 (0.195%)	13 (0.233%)	0.346	-	1 (0.045%)	1 (0.030%)	1.000
Physiologic reaction								
Nausea, vomiting	4 (0.272%)	4 (0.097%)	8 (0.143%)	0.220	1 (0.089%)	1 (0.045%)	2 (0.060%)	1.000
Dazzling, fluttering	2 (0.136%)	2 (0.049%)	4 (0.072%)	0.284	-	-	0 (0%)	1.000
Headache	2 (0.136%)	1 (0.024%)	3 (0.054%)	0.171	-	-	0 (0%)	1.000
Sneezing	-	1 (0.024%)	1 (0.018%)	1.000	-	-	0 (0%)	1.000
Coughing	-	1 (0.024%)	1 (0.018%)	1.000	-	-	0 (0%)	1.000
Total physiologic reaction	8 (0.545%)	9 (0.219%)	17 (0.305%)	0.092	1 (0.089%)	1 (0.045%)	2 (0.060%)	1.000
Total of ADRs	13 (0.886%)	17 (0.414%)	30 (0.538%)	0.058	1 (0.089%)	2 (0.090%)	3 (0.089%)	1.000

ADR, adverse drug reaction

females (mean age, 56.1 ± 16.3 years). No significant difference in occurrence rate of ADRs to enhanced CT was found between first and follow-up patients (Fisher's exact test, $p = 0.058$).

Occurrences of ADRs in contrast-enhanced MRI

The rate of ADRs to contrast media in contrast-enhanced MRI was 0.09% (3 of 2801 patients) (Table 3). This rate was again significantly lower than that described by the biggest Japanese study (1.21%) (χ^2 test, $p < 0.0001$).¹² In addition, this rate was significantly lower than that reported by Herborn et al (χ^2 test, $p = 0.0189$).¹³ Patients with ADRs to contrast media in enhanced MRI included two males (age, 54 and 68 years), and one female (age, 75 years). The distribution of symptoms of ADRs to contrast media in enhanced MRI is shown in Table 3. Two cases involved nausea and vomiting and one involved local urticaria (Table 3). No serious reactions were seen for MRI. Likewise, no cases of nephrogenic systemic fibrosis due to contrast for MRI were seen.

The occurrence rate of ADRs to contrast media in contrast-enhanced MRI at the first examination of this dental hospital was 0.09% (1 of 1124 patients) (Table 3), including one male (age, 54 years). The occurrence rate of ADRs to contrast media in contrast-enhanced MRI at follow-up examinations in this dental hospital was 0.18% (2 of 2233 patients) (Table 3), including one male (age, 68 years), and one female (age, 75 years). No significant difference in occurrence rate of ADRs on enhanced MRI was found between initial and follow-up patients (Fisher's exact test, $p = 1.00$).

Treatments for patients with ADRs to contrast media in contrast-enhanced CT or MRI

Treatments for various ADRs were clinically appropriate, including emergency treatments in two serious cases of allergy. The majority of patients experienced non-serious ADRs such as nausea and headache, and had almost completely recovered by follow-up on the examination day. Patients with skin rash such as itching and urticaria were treated with intravenous injections of a glycyrrhizin, glycine, and cysteine combination drug, and their symptoms resolved within several hours.

In the case of severe immediate allergy during contrast-enhanced CT, emergency treatment was performed in our dental hospital. Nausea, vomiting, and low blood pressure were treated according to standard therapy for allergy, such as infusion of epinephrine and intravenous injection of steroid hormone. As a result, the patient recovered relatively early. In the case of delayed allergy to enhanced CT, the patient had tongue cancer and leukemia as a medical history, and was followed-up in a general medical hospital. After contrast-enhanced CT, the patient showed no symptoms of ADR. After 6h, the patient reported feeling nausea, then vomited. Blood pressure suddenly decreased and the patient lost consciousness. Luckily, the patient had

visited the doctor treating the leukemia due to worry about continuing nausea and vomiting after contrast-enhanced CT, and that doctor treated the lowered blood pressure and loss of consciousness.

With contrast-enhanced MRI, the two patients with nausea recovered fully and symptoms had resolved by follow-up on the examination day. The patient with itching was treated with intravenous injections of a glycyrrhizin, glycine, and cysteine combination drug, and the patient's symptoms resolved within several days.

Medical history and blood data characteristics of patients with ADRs

Differences in medical history, blood data, and other characteristics in patients with and without ADRs in contrast-enhanced CT or MRI are shown in Table 4. A significant difference was seen in liver function results from blood tests between 30 patients with ADRs and 60 patients without ADRs in CT (Fisher's exact test, $p = 0.041$) (Table 4). However, no significant differences were seen in other medical histories or blood data between patients with and without ADRs (Table 4). In MRI, a significant difference was seen in digestive disorders elicited from medical interviews between the two groups (Fisher's exact test, $p = 0.040$) (Table 4). No other significant differences in medical history, blood tests, or other characteristics were found between patients with and without ADRs in MRI (Table 4).

Discussion

One of the most interesting results in the present study was that the occurrence rate of ADRs to contrast media was 0.54% in CT, and 0.09% in MRI performed under specific exclusion criteria for various pathologies in patients undergoing contrast-enhanced imaging in dental hospitals. The present occurrence rate for enhanced CT was significantly lower than that reported in the biggest study from Japan.⁴ In addition, no significant difference was found between the present data and the lowest rate reported globally.⁹ Regarding enhanced-MRI, the present occurrence rate was significantly lower than those in the biggest studies from Japan and around the world.^{10–14} Therefore, the present results suggest that occurrence rates of ADRs to contrast media could be decreased by imposing appropriate criteria for patients with various diseases undergoing contrast-enhanced imaging.

ADRs caused by contrast agent have been considered to involve both allergic and non-allergic reactions.¹⁹ Fujiwara et al reported cumulative occurrence rates of ADRs increased as the number of examinations increased.⁵ We therefore hypothesized that the ratio of ADRs would be higher for follow-up examinations than for first examinations. Counter to our expectations, no significant difference in occurrence rate of ADRs to enhanced CT or MRI was found between first and follow-up examinations.

Table 4 Differences in medical history, blood data, and other characteristics in patients with and without ADRs to contrast media in contrast-enhanced CT or MRI

	Enhanced CT			Enhanced MRI		
	ADR group (n = 30)	Control group (n = 60)	p value (Fisher's exact test)	ADR group (n = 3)	Control group (n = 60)	p value (Fisher's exact test)
Medical history, blood data, and other characteristics (some overlap)						
Allergy-like rashes or urticaria	5	7	0.525	0	6	1
History of drug hypersensitivity	0	1	1	0	2	1
Dehydration	0	0	-	0	0	-
Hypertension	11	23	1	1	25	1
Arteriosclerosis	0	0	-	0	1	1
Diabetes mellitus	5	10	1	0	10	1
Disease of thyroid gland	2	5	1	0	1	1
Decreased liver function	4	1	0.041*	0	9	1
Decreased renal function	1	1	1	0	3	1
Acute pancreatitis	0	0	-	0	0	-
Elderly people (≥ 65 years old)	16	34	0.824	2	35	1
Young children (< 15 years old)	1	0	0.333	0	0	-
Nervous system disease (dizziness)	1	0	0.333	1	2	0.138
Digestive disturbance (abdominalgia)	2	5	1	2	6	0.040*
Number of patients with ≥ 1 risk factor	24	48		3	46	
Percentage of patients with ≥ 1 risk factor (%)	80	80		100	76.7	

ADR, adverse drug reactions.

One possible explanation is that ADRs found in this study contained many non-allergic cases. In addition, the “first” enhanced CT or MRI in the present study did not necessarily mean that enhanced CT or MRI had not been performed prior to imaging at this dental hospital. Patients in this study might thus have undergone the actual first enhanced CT or MRI elsewhere.

In terms of the kinds and rates of ADRs, the most frequent symptoms were nausea and vomiting as physiologic reactions, followed by dizziness and headache (Table 3). Hypersensitivity reactions were much less frequent than physiologic reactions (Table 3). These rates largely matched the results of previous findings.^{4–14} One possible explanation was that the exclusion criteria for patients who could undergo contrast-enhanced CT or MRI at our dental hospital were relatively strict and thus might have been more appropriate than those at most medical hospitals. In concrete terms, patients with only slight asthma (besides pediatric asthma) were strictly excluded. At the same time, relatively high standards were provided for kidney, liver, and thyroid diseases based on blood tests criteria (Table 1). In addition, all of the present patients, who could appropriately undergo CT or MRI enhanced using contrast media in our dental hospital, had either confirmed or suspected oral cancers. Therefore, enhanced CT or MRI was not applied for patients with various kinds of disease in the present study, such as cellulitis with systemic symptoms, and this likely means that subjects were strictly limited. Basically, if patients do not have suspected or confirmed oral

and/or salivary cancers, non-enhanced CT or MRI is applied for patients in our dental hospital.

One of the most important differences between the present study and previous reports was the presence or absence of diseases involving other regions. For example, use of contrast media for diagnosing liver disease involves a dilemma. Despite such patients experiencing liver dysfunction, contrast-enhanced CT is an effective modality for diagnosing liver disease.^{20,21} No such dilemma is seen for the oral and maxillofacial region. At a mental and emotional level, patients with cancers involving the oral cavity generally recognize the need for imaging, and active cooperation and participation in imaging examinations using contrast media was thus able to be obtained. We speculated that such positive cooperation might be related to the decreased rate of ADRs.

Moreover, the majority of subjects were in their sixties or seventies, with few children. The complex synergistic effects mentioned above might have contributed to the low rate of ADRs to contrast media in patients undergoing contrast-enhanced CT or MRI.

Another possible explanation was that patients with oral cancers in our dental hospital tended to have a relatively good general condition. In other words, relatively many patients in general medical hospitals need treatments under general management, but this is not the case in dental hospitals. Of course, the very small sample size for this study cannot be ruled out as a cause of this result.

An additional possible explanatory factor for the significant improvement of ADR frequencies compared to the findings of Katayama et al and Herborn et al was the

quality of contrast media.^{4,13} Historically, high-osmolality iodinated contrast media have replaced low-osmolality agents, as the former show less frequent associations with adverse reactions.²² Contrast media for enhanced CT and MRI have improved over time and frequencies of ADRs to contrast media could be decreasing with the use of newer products. However, Kim *et al* reported that the frequency of ADRs to iopamidol and iohexol were almost the same (0.67 and 0.64%, respectively).²³ We thus consider the difference in contrast media for enhanced CT as unlikely to have markedly affected the present results. Regarding contrast-enhanced MRI, the frequency of ADRs to linear chelate gadodiamide has been reported as significantly lower than that to macrocyclic agents.²⁴ The present study included cases using linear chelate-type contrast media in addition to macrocyclic types. The report by Herborn *et al* only included contrast media for macrocyclic agents.¹³ This difference might have affected the results. However, only three ADRs related to enhanced MRI were seen in the present study, so we consider that differences between types of contrast medium were unlikely to have significantly affected the results.

As mentioned for the present results, however, perfect suppression of ADRs to contrast media is not a realistic goal. In other words, application of strict limitations on contrast media for subjects would not eliminate ADRs to contrast media. The present results for the distribution of ADR rates largely coincided with previous data, and the study design of the present examination thus seems appropriate.⁴⁻¹⁴ This suggests that the low ADR rate in the present study was not attributable to bias, and was very significant. Conversely, we found that patients with decreased liver functions according to blood tests in patients undergoing enhanced CT required attention, as did patients with digestive disorders elicited from medical interviews in patients undergoing enhanced MRI. In particular, even liver-related values for our criteria for blood tests might be lenient. We should therefore reconsider the criteria for liver-related values used to allow contrast-enhanced CT.

Treatments for ADRs applied in the present study largely coincided with previous reports.⁹ Most patients with mild ADRs such as nausea and vomiting had almost completely recovered by follow-up on the examination day. Patients with skin rash such as itching and urticaria were treated by intravenous injections of a glycyrrhizin, glycine, and cysteine combination drug, and their symptoms resolved within several days. For the two serious ADRs in the present study, both patients showed lowered blood pressure due to immediate or delayed allergy. One patient was treated in our dental hospital, and the other in a medical hospital. The two patients recovered without problems. In one patient, the nausea, vomiting, and lowered blood pressure occurred immediately after performing contrast-enhanced CT, and common treatments for representative allergy were provided such as infusion of epinephrine and intravenous injection of steroid hormone. As a result, the patient recovered relatively early

as mentioned above. Conversely, the other case involved a very particular pattern. The patient with tongue cancer had a medical history of leukemia, and had been followed-up in a general medical hospital. The patient reported feeling nausea and vomited about 6 h after contrast-enhanced CT. The patient visited the doctor treating his leukemia due to worries about the nausea and vomiting, and that doctor appropriately treated the subsequent lower blood pressure and loss of consciousness. Neither patient met any of our exclusion criteria for administration of contrast media, and both had more than one experience of CT using contrast media. We clearly cannot perfectly suppress these ADRs, and we instruct patients after CT or MRI using contrast media to pay close attention to their condition for at least several days.

Several potential limitations need to be considered in our present study. First, because the sample size in our present study was much smaller than in previous reports, our data might not necessarily be representative or accurate.⁴⁻⁹ Data on the variables of sex and age might not necessarily be accurately reflected in our study sample. In the next trial, we are planning to include a larger sample size to provide more accurate results in a multicenter study of dental hospitals.

Another possible limitation was that the rates of ADRs in this study were limited to our dental hospital. The techniques for contrast-enhanced CT or MRI would be uniform, but patient ages and diseases would also be limited. Therefore, if some aspect of the techniques for CT or MRI using contrast media were incorrect, the present data would have included clear bias. However, the distribution of ADRs in the present study basically coincided with data from previous reports, despite the very small sample size, and the present study design was thus considered appropriate.⁴⁻¹⁴ The present data thus seem likely to be characteristic and significant for the occurrence of ADRs among relatively older patients with oral cancers and relatively good conditions under uniform techniques for contrast-enhanced CT or MRI.

Conclusion

We analyzed ADRs to contrast media for enhanced CT or MRI in a dental hospital, not a general medical hospital, and examined improvements in safety using contrast media and factors influencing the occurrence of ADRs. The methods involved retrospective analysis of clinical data from patients who underwent contrast-enhanced CT or MRI to evaluate rates and symptoms of ADRs to contrast media, symptoms and differences in medical history, blood tests, and other characteristics between patients with and without ADRs in dental hospitals. As a result, the rate of ADRs to contrast media was 0.54% in enhanced CT, and 0.09% in enhanced MRI. Distribution rates largely coincided with previous data. A significant difference was seen in liver function from blood tests between patients with

and without ADRs in contrast-enhanced CT. A significant difference was also seen in digestive disorders elicited from medical interviews between patients with and without ADRs in contrast-enhanced MRI. The present results suggest that the rate of ADRs to contrast media could be low due to relatively strict limitations on patients undergoing contrast-enhanced CT or MRI. While complete suppression of ADRs to contrast media is unrealistic, we should pay attention to patients with decreased liver functions in blood tests for enhanced CT, and to patients with digestive disorders elicited from medical interviews for enhanced MRI.

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Acknowledgment

We wish to thank Mr Ryo Yoshimatsu and Miss Hatsumi Uehara for their data analysis and advice.

Funding

This study was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Science, Sports and Technology of Japan to YM.