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Renal cortical retention on delayed CT and nephropathy following transcatheter arterial chemoembolisation

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Abstract. The aim of this study was to examine the relationship between renal cortical retention on delayed CT and contrast medium-associated and/or transarterial chemoembolisation (TACE)-associated nephropathy following TACE. The authors reviewed the findings on 180 treatments in 121 patients with normal serum creatinine levels who underwent TACE for liver tumours. Nephropathy was defined as an increase in the creatinine level of greater than 0.5 mg dl^{-1} (44 μmol l^{-1}) and greater than 25% on days 1, 3, 7 or 14 post TACE. Renal cortical retention was recognized when CT values for the renal cortex showed either mild renal cortical retention (CT value >50) or severe renal cortical retention (CT value >100). There was evidence of renal cortical retention in 81 (45%) cases and of nephropathy in 11 (6%) cases. Only 2% of patients without renal cortical retention showed nephropathy, whereas 11% of those with renal cortical retention showed nephropathy ($p=0.02$). Stepwise selection using a multivariate logistic regression model showed renal cortical retention and gender to be significant factors for nephropathy following TACE. In conclusion, renal cortical retention is a useful predicator for nephropathy following TACE. Delayed CT could be used not only for assessment of lipiodol retention but also for predicting nephropathy.

Contrast media may sometimes induce an adverse reaction, known as contrast-associated nephropathy [1–4]. Although serious contrast-associated nephropathy requiring dialysis is rare, it has been reported in 5–20% of patients as a mild but potentially lethal decrease in renal function. On the other hand, renal cortical retention (RCR) of contrast medium is regarded as a sign of renal deficiency [5, 6]. We have previously reported a high incidence of RCR on CT examination without any sign of nephropathy [7, 8], and have named this phenomenon "incidental RCR" after angiography. Although quantitative assessment of renal function is possible using CT after injection of contrast medium [9, 10], radiation exposure and financial consideration limit its applicability.

Few studies have reported post-transarterial chemoembolisation (TACE) renal dysfunction, despite the fact that TACE plays an important role in the treatment of liver tumours and may enhance nephropathy. We encountered one patient who had undergone TACE for advanced (stage 4) hepatocellular carcinoma who suffered hepatic failure 1 week later as well as subsequent renal failure requiring haemodialysis. His serum creatinine level was elevated from 0.8 mg dl^{-1} on day 7 to 5.5 mg dl^{-1} on day 14. If we had determined serum creatinine levels only on day 7, we could not have applied the previously established criteria for contrast-associated nephropathy (assessed serum creatinine level days 1, 3 or 7 after the procedure) because this patient did not show any signs of renal failure at 7 days. His death due to hepatorenal failure demonstrates that TACE-related nephropathy may occur later than contrast-associated nephropathy after angiography. Although it is likely that the renal failure resulted from the patient's hepatic failure rather than from contrast-induced nephropathy, this case prompted us to examine contrast- and/or chemoembolisation-associated nephropathy after TACE, as early detection of nephropathy may be

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effective for such patients. In addition, as we had already performed delayed CT to detect lipiodol deposition [11], we could obtain the delayed CT images simultaneously without additional cost and with little more radiation exposure. Under these circumstances, the aim of this study was to clarify the role of RCR in the detection of contrast- and/or chemoembolisation-associated nephropathy after TACE.

Materials and methods

Between 1989 and 1996, abdominal CT was performed 16–21 h (median 19 h) after TACE on 180 treatments in 121 patients (108 males and 13 females). Three patients underwent TACE for metastatic liver tumour from carcinoma of colon, kidney and breast; the others underwent TACE for primary hepatocellular carcinoma. The patients' ages ranged from 33–80 years (median 58 years). The injected volume of contrast medium per body weight ranged from 1.1 ml kg^{-1} to 7.8 ml kg^{-1} (mean $\pm$ standard deviation 4.4 ± 1.3 ml kg^{-1}). Diatrizoate (76%) (Urografin; Schering, Berlin, Germany) was administered in 31 cases, iopamidol (Iopamiron 370; Bracco, Milan, Italy) in 62 cases, iohexol (Omnipaque 350; Winthrop-Breon, New York, NY) in 33 cases and ioxaglate (Hexabrix 320; Guerbet, Aulnay-sous-Bois, France) in 54 cases. Details of TACE have been described elsewhere [11, 12]. In brief, a catheter was selectively introduced, using the Seldinger technique, into the targeted arterial branch of the liver. Doxorubicin-in-oil emulsion was used as a chemoembolic material. This was prepared by dissolving doxorubicin hydrochloride in 50% diluted diatrizoate sodium meglumine (Urografin) and emulsifying that solution in a 2:3 volume of iodized oil (lipiodol; Guerbet). A gelatine sponge particle 1–3 mm in diameter was added to reduce blood flow in the target segment. The mean dosages of iodized oil and doxorubicin were 12 ml (2–35 ml) and 41 mg (0–100 mg), respectively; 19 patients received epiadriamycine (30–80 mg, median 40 mg) with lipiodol instead of adriamycin. Cisplatinum was administered to 57 patients (50–200 mg, median 102 mg). The mean weight of the gelatin sponge particle was 0.04 g (0.01–0.16 g). The area of treated liver was classified into three groups: total (total liver treated); lobar (right or left lobe treated); and segment (two or less segments treated). Patients with urological disease detected by previous CT as well as data from their medical records, such as renal stones and renal tumours, were excluded. Cases of congestive heart failure and severe hypertension and/or diabetes mellitus not controlled by medication were also excluded. Informed written consent was obtained from all patients. RCR was recognized when CT images showed a high density area in the renal cortex, as described elsewhere [8]. Whenever possible, the CT images of RCR following TACE were compared with those before angiography and were evaluated by at least two radiologists. The following graded classification was used: RCR (−), normal appearance; RCR (+), mild RCR indicated by apparently higher density in the renal cortex (CT value >50); and RCR (++), severe opacification (CT value >100) (Figure 1). CT was performed with a slice thickness of 10 mm at 120 kV (210 mA) using a CT/T 8800 (General Electric, USA) and a Somatome plus (Siemens AG, Germany). Delayed time from TACE to CT was 16–21 h (median 19 h). Serum creatinine was measured 1, 3, 7 and 14 days after TACE, and nephropathy was defined as an increase in the creatinine level of more than 0.5 mg dl^{-1} (44 μmol l^{-1}) and more than 25% on day 1, 3, 7 or 14.

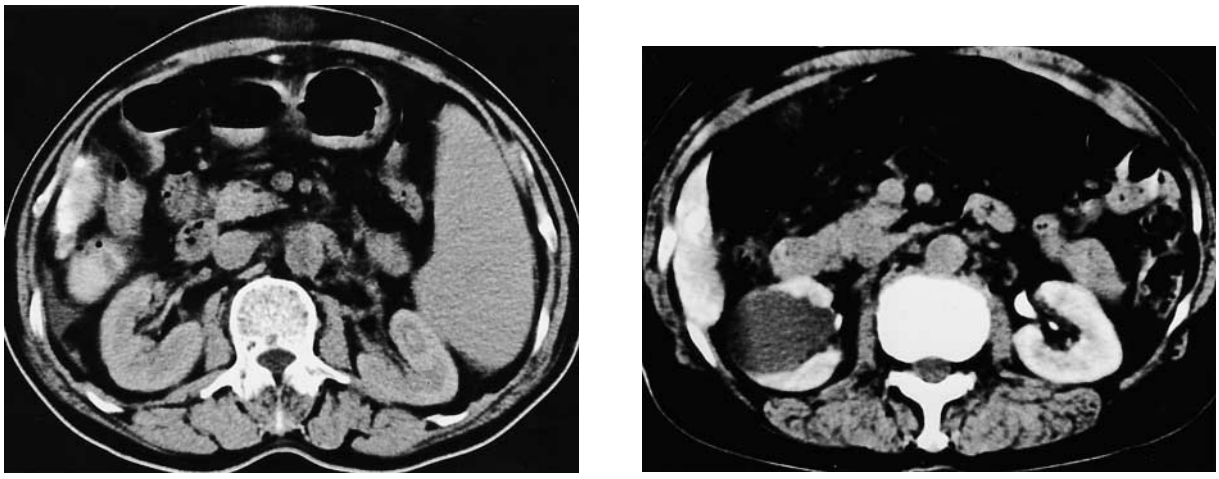
The following predisposing factors were examined for their contribution to nephropathy: (1) patient factors: age, gender and presence of diabetes mellitus; (2) treatment factors: dosage of contrast medium per body weight, type of contrast medium, treated area of liver and chemotherapeutic agents; and (3) laboratory factors: serum creatinine level for renal function, obtained from venous blood samples in the morning of the day of the procedure.

Statistical analysis

χ^2 analysis was used for data sets. A multivariate logistic regression model was applied to the variables using the SAS program package. To use multivariate analysis, some variables were divided into two groups by mean or median values. All analyses used the conventional 0.05 level of significance.

Results

Nephropathy was demonstrated in 11 (6%) of the 180 studies and RCR in 81 (45%). Table 1 shows patient characteristics for nephropathy. Female gender, age, type of contrast medium, dose of contrast medium administered and renal function were identified as predisposing factors. Iohexol (15%) and diatrizoate (10%) showed higher nephropathy ratios than the other two contrast media, iopamidol (3%) and ioxaglate (2%). The type of chemotherapeutic agent, the liver area treated, the frequency of TACE and the T category were not related to nephropathy; however, RCR showed a significant relationship with nephropathy ($p=0.008$). Patients with severe RCR registered a higher nephropathy rate (18%) than patients with mild RCR (6%) or those



(a) (b)

Figure 1. (a) Renal cortical retention (RCR) grade 1. A 75-year-old male who underwent transcatheter arterial chemoembolisation (TACE) (cisplatinum 150 mg and gelatin sponge) for hepatocellular carcinoma (T4, vp3), using 5.2 ml kg^{-1} diatrizoate. His serum creatinine level before the procedure was 0.9 mg dl^{-1} (79 μmol l^{-1}) and he did not show nephropathy. (b) RCR grade 2. A 70-year-old female who underwent TACE (cisplatinum 50 mg, adriamycin 20 mg, lipiodol 6 ml and gelatin sponge) for hepatocellular carcinoma (T4), using 5.1 ml kg^{-1} diatrizoate. She showed severe RCR with nephropathy. Her serum creatinine level raised to 1.9 mg ml^{-1} (167 μmol l^{-1}) 1 day following TACE (from 1.3 mg ml^{-1} (114 μmol l^{-1}) before the procedure) and recovered to normal value 3 weeks later without haemodialysis.

without RCR (2%). Results of multivariate analysis using a logistic regression model are shown in Table 2. Table 2a shows the results of analysis of maximum likelihood estimates using six variables with a significant value in Table 1. The type of contrast medium was a determinant of nephropathy: ioxaglate and iopamidol had a relative ratio of 5.15 compared with diatrizoate and iohexol ($p=0.03$). Gender and RCR were identified as significant predicators for post-TACE nephropathy using a stepwise procedure (Table 2b). Patients with RCR has a higher nephropathy rate, with a relative risk of 11.5 ($p=0.02$). The nephropathy rate for females was considerably higher than that for males, with a relative risk of 5.00 ($p=0.04$).

We encountered one patient with renal failure who required haemodialysis. A 63-year-old male without diabetes mellitus or pre-existing renal failure suffered renal failure with concurrent liver failure requiring haemodialysis after TACE for a stage 4 hepatocellular carcinoma using 30 mg adriamycin in 9 ml lipiodol and 50 mg cisplatinum. His serum creatinine level increased from 1.2 mg dl^{-1} (106 μmol l^{-1}) to 2.4 mg dl^{-1} (212 μmol l^{-1}) and his serum K was elevated to 6.3 meq l^{-1}. He recovered from renal dysfunction following haemodialysis.

Discussion

Risk factors for contrast-associated nephropathy include diabetic nephropathy, myeloma, osmolarity, dose of contrast medium and intravascular volume depletion. The highest risk is associated with pre-existing renal impairment for patients with a baseline serum creatinine concentration averaging 220 μmol l^{-1}; while nephropathy, defined as a 25% increase in serum creatinine concentration, occurs in 30–50% [2, 3] of patients with poor renal function. Several authors have reported the detection of RCR by delayed CT [9, 10, 13, 14] and its correlation with renal function. Jakobsen et al [14] reported that the increase in renal cortical attenuation in patients with severe renal failure (serum creatinine level 451–860 μmol l^{-1}) peaked at 24 h, *i.e.* later than when the highest plasma and urinary concentrations of iodine were noted, and that it was always higher than the attenuation in the aorta. Increased attenuation in the renal cortex, measured by CT and probably reflecting intracellular retention of contrast medium, peaked at 24 h. They concluded that although transient and minor changes in glomerular filtration rate were noted, both iodixanol and iohexol were safe for use in angiography for non-diabetic patients with severe chronic failure when the patients were well hydrated.

A previous study of ours showed that RCR is not a rare phenomenon, even for patients with normal renal function after angiography [8]. The 48% of RCR cases in this study was no more than that reported for patients who had undergone angiography (47%) [8]. Although the average contrast load to the patients (60 kg) was relatively high at 264 ml, with nephrotoxicity in part being dose dependent, renal failure was low. One reason

Table 1. Characteristics of patients[a] with or without nephropathy after transcatheter arterial chemoembolisation

Variable	Strata		Nephropathy (+) (n=11)	Nephropathy (−) (n=169)	% with nephropathy	p-value
Gender	Male		7	158	4	
	Female		4	11	27	<0.01
RCR[b]		−	2	97	2	
		+	3	45	6	
		++	6	27	18	<0.01
Age (years)		⩽59	1	92	1	
		⩾60	10	77	11	<0.01
Dose of contrast medium per kg body weight	ml kg^{-1}	<4.0	1	72	1	
		⩾4.0	10	81	11	=0.01
Renal function (serum creatinine level)	mg ml^{-1}	<1.0 (88)	6	107	5	
	(μmol l^{-1})	⩾1.0 (88)	5	62	7	<0.01
Type of contrast medium	ioxaglate		1	53	2	
	iopamidol		2	60	3	
	diatrizoate		3	28	10	
	iohexol		5	28	15	=0.046
Chemotherapeutic agent	adrimaycin	−	1	54	2	
		+	10	115	8	ns
	epirubicin	−	10	151	6	
		+	1	18	5	ns
	cisplatinum	−	9	121	7	
		+	2	48	4	ns
Area of liver treated	total		4	97	4	
	lobar		3	51	6	
	segmental		4	21	16	ns
Diabetes mellitus		−	7	131	5	
		+	4	38	10	ns
T category		1	2	5	29	
		2	1	34	3	
		3	2	24	8	
		4	6	104	5	ns

ns, not significant.
[a]Total No. of patients is not always 180 owing to missing data.
[b]RCR, renal cortical retention; ++, severe RCR; +, mild RCR.

for this result may be the use of a larger volume of fluid for hydration and the frequent use of diuretics both before and during TACE.

One of the problems taken into account was the use of serum creatinine level as the indicator of renal damage. Many, if not most, of the RCR patients had a reduction in their glomerular filtration rate (GFR). This would not be identified using serum creatinine determination until the GFR fell below 60 ml min^{-1}. If the patient had normal renal function (120 ml min^{-1}) prior to TACE, a 50% reduction in renal function could be missed. Thus, although we do not wish to exaggerate the significance of this study for assessing the frequency of nephropathy, it is considered as a rough but sufficient indication of

Table 2. Results of multivariate logistic regression model

Variable	Strata	Odds ratio	95% CI	p-value
(a) Analysis of significant factors in univariate analysis				
Type of contrast medium	iopamidol and ioxaglate *vs* diatrizoate and iohexol	5.15	1.13–23.3	0.03
Age (years)	⩽59 *vs* ⩾60	6.74	0.73–61.7	0.09
RCR	− *vs* +	3.19	0.50–20.2	0.23
Serum creatinine level	<1.0 mg ml^{-1} (88 μmol l^{-1}) *vs* ⩾1.0 mg ml^{-1}	3.24	0.29–5.92	0.71
Gender	male *vs* female	4.61	0.93–22.7	0.06
Dose of contrast medium per kg body weight	<4.0 mg kg^{-1} *vs* ⩾4.0 mg kg^{-1}	1.32	0.43–44.2	0.21
(b) Results of stepwise procedure				
Gender	male *vs* female	5.00	1.02–24.5	0.04
RCR	− *vs* +	11.5	1.40–94.9	0.02

CI, confidence interval.
RCR, renal cortical retention.

the presence of RCR in correlation with nephropathy after TACE.

TACE may cause damage not only to the liver but also to renal function. We reported 13 cases of acute hepatic failure in 623 patients with hepatocellular carcinoma following TACE administered between 1984 and 1993. 7 cases of acute renal failure out of 623 patients (1%) were noted simultaneously [11]. Several other investigators have also reported renal failure after interventional procedures [15, 16]. Allison et al [15] reported two cases of renal failure in 75 patients without chronic liver disease after TACE for metastatic liver tumour. We have experienced several cases of hepatorenal syndrome (renal failure following hepatic dysfunction). Accumulation of fluid in the peritoneal or pleural cavity caused by renal dysfunction after hepatic resection is still the most common post-operative complication and often diminishes the patient's quality of life [17, 18]. Liver dysfunction thus appears to have an effect on renal function. In cases of TACE for hepatocellular carcinoma, liver injury may have been caused by TACE but it may also be enhanced by a pre-existing chronic liver disease such as liver cirrhosis. Use of chemotherapeutic agents and contrast material also tends to increase the risk of renal dysfunction. The frequency of nephropathy (6%) seen in this study was higher than that reported for angiography (3%) [8]. In addition, although no patient required haemodialysis after angiography, one patient in this study required haemodialysis after TACE. Therefore, TACE was seen to elevate the risk of nephropathy not only in cases of irreversible and transient elevation of serum creatinine levels but also in cases of critical renal failure requiring haemodialysis.

Several risk factors for nephropathy were identified in our analysis. In addition to the factors reported in other studies for contrast-associated nephropathy, elderly patients are at risk for nephropathy, which may correlate with diminished renal function due to aging. Although gender is suspected to be a factor for nephropathy, the number of females in this study was too small to determine the actual effect of gender on renal function. It is also possible that the type of contrast medium is a significant factor for nephropathy, but the number of patients is not large enough to clarify the difference. This aspect should be obtained from data dealing with a larger population.

Since higher nephropathy rates were found to be associated with higher grades of RCR, RCR is considered to be an important sign of nephropathy. However, RCR does not relate to nephropathy in most cases. In other words, most instances of RCR are incidental phenomena that do not imply renal failure. For financial reasons and because of the risk of unnecessary radiation exposure, we are therefore not in a position to recommend a delayed CT only to detect early signs of nephropathy in patients with normal renal function. In case of TACE, however, RCR could be assessed with delayed CT 1–2 days after the procedure during the detection of lipiodol deposition to assess the efficacy of TACE. Delayed CT may thus have potential as an early detector of nephropathy.

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