Safety and feasibility of contrast-enhanced computed tomography with a nanoparticle contrast agent for evaluation of diethylnitrosamine-induced liver tumors in a rat model

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Rationale and Objectives: Safety and feasibility of contrast-enhanced computed tomography (CECT) with a nanoparticulate contrast agent, ExiTron nano 12000, was evaluated in a rat liver tumor model.

Materials and Methods: This study employed eighteen 8-week-old male F344 rats. Six rats given tap water for 8 weeks further divided into two: Control group and Normal Liver with CECT group. Six rats each were given tap water containing diethylnitrosamine (DEN) at 100 ppm for 8 or 14 weeks; Adenoma group and Hepatocellular carcinoma (HCC) group, respectively. Biochemical marker values and adverse events were evaluated after CT imaging. ExiTron nano 12000 was evaluated for the hepatic contrast enhancement, and the detection and measurement of liver nodules by CECT after 8- and 14-weeks administration of DEN. Post-mortem liver specimens were evaluated by hematoxylin-eosin (HE) staining, and the number and size of liver nodules were measured. The HCC group was evaluated for diagnostic concordance between HE-stained and CECT-detected nodules.

Results: The contrast agent enhanced liver and was tolerated after CECT in 15 rats. Biochemical parameter values did not differ significantly between the Control and Normal Liver groups. The numbers of CECT-detected nodules in the Adenoma and HCC groups were 14.8 ± 5.1, and 32.4 ± 8.1, respectively. The HCC group had 3.6 ± 2.7 of pathological HCCs, which were identified by CECT. The size of CECT-detected HCCs correlated significantly with that of pathological HCCs (r = 0.966, p < 0.0001).

Conclusion: CECT with ExiTron nano 12000 is a safe and feasible method to measure tumors in a rat liver tumor model.

Key Words: Contrast Media; Diethylnitrosamine; Hepatocellular Carcinoma; Rats; X-Ray Computed Tomography.

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INTRODUCTION

The importance and choice of treatment for liver cancer is expanding due to development in the past two decades of molecular targeted drugs, immune checkpoint inhibitors, and new local thermal therapies (1-7). In the cancer research field focusing on liver tumors, small-animal imaging, targeting to mice and rats, also has been an essential tool for evaluating tumor progression or regression in animal experiments (8). Small-animal models offer multiple advantages, including low procurement and maintenance costs, ease of handling, and the need for less-extensive anesthesia during procedures (9). Among such models, experimental rats are medium-sized rodents that are about ten-fold heavier than mice. Rats can be used for invasive experiments such as hepatectomy and catheterization (10-12) as well as for chemotherapy or immunotherapy. However, there is no established method that can diagnose liver tumors in rats in a minimally invasive manner.
Recently, nanoparticulate contrast agents have been developed for use in computed tomography (CT) imaging in mice. However, to our knowledge, no studies have been conducted to clarify the safety and feasibility of contrast-enhanced CT (CECT) imaging using nanoparticulate contrast agents in a rat model. Diethylnitrosamine (DEN) has been used as a carcinogen in many small animal studies (13-16). DEN was adopted in the study based on this compound’s advantageous property of creating multiple liver tumors following oral administration. In this study, we aimed to use micro-CT to detect tumors in a rat model of liver tumors induced by DEN exposure (13). The purpose of the present study was to evaluate the safety and feasibility of CECT using ExiTron nano 12000 in this rat liver tumor model.

MATERIALS AND METHODS

Animals

These experiments were performed according to the “Guidelines of the Public Health Service Policy on the Humane Use and Care of Laboratory Animals.” The animal experimental protocol was approved by the Institutional Animal Care and Use Committee of our facility (Approval No. 18059, 2018). Male Fischer 344 rats (F344), 8 weeks old, body weight 155 ± 10 g (mean ± standard deviation (SD)) were purchased from Japan SLC (Hamamatsu, Japan). During the in-life period, rats were maintained on a 12 hours light and/or dark cycle and were supplied with ad libitum access to autoclaved food (Oriental CE-2 pellet diet; Oriental Yeast, Tokyo, Japan). Depending on the group, rats were provided with ad libitum access to either normal tap water or tap water containing 100 ppm diethylnitrosamine (DEN; Sigma-Aldrich, St. Louis, MO, USA) to initiate hepatocarcinogenesis.

Rats were anesthetized with 1.5% isoflurane vaporized in 3.0 L/min of oxygen gas for animal preparation and micro-CT imaging. The rats were euthanized by intraperitoneal injection of xylazine and ketamine at 24 hours after micro-CT imaging.

CT imaging

Liver tissues and liver tumors in the rats were visualized by contrast-enhanced micro-CT using a contrast agent, ExiTron nano 12000 (Viscover ExiTron nano; Miltenyi Biotec, Bergisch-Gladbach, Germany). This compound is an alkaline earth-based nanoparticulate contrast agent specifically formulated for pre-clinical CT imaging (17). The contrast agent was administered to the rats via a tail vein by a bolus injection of 250 μL of ExiTron nano 12000. Rats were imaged 4 hours after injection.

CT imaging was performed using a micro-CT scanner (Latheta LCT-200; Hitachi Aloka Medical, Tokyo, Japan). The X-ray tube was operated using a tube voltage of 50 kV, a tube current of 0.5 mA, and a slice interval of 240 μm. The CT scan time was 7-12 minutes. The nodule was defined as a non-enhanced lesion of greater than 1 mm in diameter in the liver. Using approximately 150-200 CT images of samples, the number and maximum diameter of the nodules were measured by two interventional radiologists using a DICOM viewer (OsiriX 12.0; Pixmeo, Bernex, Switzerland).

Pathological analysis

Following euthanasia of the animals, the livers were excised and fixed in 10% phosphate-buffered formalin. The left and right lobes then were sliced longitudinally at 4 mm thicknesses, and the slices were dehydrated and embedded in paraffin. The liver specimens were stained with hematoxylin and eosin (HE) and the number of the lesions histologically diagnosed as HCC was measured. The HCC diagnosis was performed by an expert in rat liver pathology. The maximum diameter of each tumor pathologically diagnosed as HCC was measured on the HE-stained slides.

Immunohistochemical analysis of glutathione S-transferase pi (GST-P) was performed using paraffin-embedded sections to detect the GST-P foci, which are considered the precancerous lesions in rat hepatocarcinogenesis (14,18). In general, normal hepatocytes are negative for GST-P, while bile duct epithelial cells are positive for this marker (19). Quantitative analysis was performed in each group, and the percentage of normal liver parenchyma and HCC area stained with GST-P was calculated for each section using ImageJ software (20,21).

Experimental design

The study workflow is shown schematically in Figure 1. A total of eighteen F344 rats were divided into four groups. Six rats were provided with normal tap water for 8 weeks, and...
then further divided into two subgroups of three rats each: a group subjected to CT without the contrast agent was designated as the Control group, and a group of subjected to CT with the contrast agent (i.e., CECT) was designated as the Normal Liver group. Separate groups of six rats each were provided with tap water containing 100 ppm DEN for 8 weeks or 14 weeks; these groups were designated as the Adenoma group and the HCC group, respectively. CECT with the contrast agent was performed in 15 rats, that is, all except for those of Control group. General condition was observed by measuring body weight and water and food consumption throughout the in-life period.

To examine the safety of the contrast agent and procedure, the rats were awakened and allowed to recover in their laboratory cages for one day following CT imaging. All 15 rats that received contrast medium were observed in their cages for at least one day following the CT imaging procedure. We further evaluated the potential side-effects caused by the contrast agent injection by determining the liver function and renal function in the Control group with non-CECT and the Normal Liver group with CECT. Specifically, blood samples were collected from the three animals on the day after administration of ExiTron nano 12000 in the Normal Liver group. They were also collected from the three animals on the day after CT without contrast agent in the Control group. Serum levels of blood urea nitrogen (BUN), creatinine (Cre), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (T-Bil), and albumin (ALB) were measured and used to evaluate possible differences in liver and renal function between the Control group and the Normal Liver with CECT group.

To examine the feasibility of liver tumor imaging by CECT, the contrast agent was evaluated for its ability to enhance liver contrast, to detect liver nodules, and to measure nodule size on CECT in animals administered DEN for 8 and 14 weeks. One day after CECT, the rats were euthanized and livers were collected for pathological analysis. Liver specimens from these rats were evaluated following HE staining, and the number and size of liver nodules were measured. The diagnostic concordance between HE staining and CECT-detected nodules was evaluated in animals of the HCC group.

### Statistical analysis

All statistical analyses were performed using Prism 7 (GraphPad, La Jolla, CA, USA). All parametric values are reported as mean ± SD. The differences in biochemical parameters between the rats in the Control group and the rats in the Normal Liver group with CECT were analyzed using a two-tailed non-paired Student's t test. The differences between pathological and CT tumor diameters were analyzed using a two-tailed paired Student’s t test. Furthermore, Pearson’s correlation coefficient was used to elucidate the correlation between pathological and CT tumor diameters. For these analyses, a p-value <0.05 was considered statistically significant. Statistical comparison of percentages of GST-P-positive areas among hepatic parenchyma in the Control group and the HCC and non-HCC areas in the HCC group was performed using a two-tailed non-paired Student’s t test with Bonferroni correction. For these analyses, a p-value <0.0167 was considered statistically significant.

### RESULTS

#### Safety of DEN in rats

All 18 rats, including the 12 with DEN exposure and the 15 subjected to CECT, survived until the scheduled euthanasia. Mean body weight gain and mean total DEN intake per rat in each group are shown in Supplementary Table 1. Rats in the HCC group exhibited attenuation of weight gain compared to rats in the other groups.

#### Safety of CT imaging with ExiTron nano 12000

Fifteen rats were successfully injected with contrast agent via their tail vein. CECT images were obtained for each of these 15 rats at the end of the experimental interval. The other three rats in the Control group underwent CT without the use of a contrast agent. All rats appeared to remain healthy at 24 hours after CT imaging. No adverse events, immobility, or death was observed in any of the 18 rats studied. The contrast agent successfully enhanced imaging of the liver and spleen in each of the 15 rats subjected to CE compared to those subjected to non-contrast-enhanced CT (Fig 2).
Notably, the blood chemistry parameters did not differ significantly between the Control and the Normal Liver groups (Table 1).

Feasibility of nodule detection using CECT with ExiTron nano 12000

CECT detected nodules as non-enhancing lesions in the rat liver in both groups with DEN exposure (Figs 3a-c). The numbers (mean ± SD) of liver nodules per rat detected by CECT were 0, 14.8 ± 5.1, and 32.4 ± 8.1 in the Normal Liver, Adenoma, and HCC groups, respectively (Table 2). The largest nodules detected by CECT in the Adenoma and HCC groups had diameters of 4.6 and 13.9 mm, respectively (Table 2).

Pathological correlation of CECT-detected nodules

Macroscopically, multiple nodules were observed on the liver surface in the livers of animals from the two DEN-exposed groups (Figs 3d-f). Microscopically, nodules also were observed in the HE-stained slides of liver sections from animals of these same groups (Figs 3g-i). Most nodules were diagnosed as adenomas (Figs 3h, j). The other microscopically-detected lesions included hepatic cysts and vacuolated foci. No nodules diagnosed as HCC were observed in the HE-stained slides of liver sections from the Adenoma group. Several nodules in livers from the HCC group were diagnosed as HCC (Figs 3i, k). The number of the nodules diagnosed as HCC per rat in the HCC group was 3.6 ± 2.7 (Table 2). The diameters of tumors diagnosed as HCC on HE-stained slides were compared with those of HCC tumors identified by CECT (Fig 4a). The diameters of HCC tumors identified by CECT were larger than those of HCC tumors identified by pathology (6.55 ± 3.28 mm vs. 6.02 ± 2.75 mm, respectively; p = 0.0264). There was a positive correlation between the two variables, fitting a curve with the formula \( y = 0.811x + 0.716 \), \( r = 0.966 \), with an \( r^2 \) value of 0.933 and \( p < 0.0001 \) (Fig 4b).

GST-P staining

In the Normal Liver group, hepatocytes were GST-P negative, while bile duct epithelial cells were positive for GST-P (Figs 5a, c). GST-P-positive areas were observed within non-HCC areas; representative images are provided in Figures 5b and d. The percentages of GST-P-positive area within the non-HCC area in the livers of the HCC group were statistically significantly larger than those in the normal liver parenchyma of the Normal Liver group and in the HCC area of livers of the HCC group (Fig 6).

DISCUSSION

This study represents the first report that CECT with a nanoparticle contrast agent, ExiTron nano 12000, is safe and useful for the detection of liver tumors in a rat model.
Figure 3. Contrast-enhanced computed tomography (CECT) images, macroscopic images, and hematoxylin-eosin (HE)-stained slides. (a, d, g) Normal Liver indicates the group subjected to CECT after 8-week administration of normal tap water. (b, e, h, j) Adenoma indicates the group subjected to CECT after 8-week administration of tap water containing 100 ppm diethylnitrosamine (DEN). (c, f, i, k) Hepatocellular carcinoma (HCC) indicates the group subjected to CECT after 14-week administration of tap water containing 100 ppm DEN. (a) An axial CECT image in the Normal Liver group. (b) An axial CECT image in the Adenoma group. Non-enhancing nodules are detected due to the positive liver contrast (black arrows). (c) An axial CECT image in the HCC group. Non-enhancing nodules are detected due to the positive liver contrast (black arrows). A large (12-mm-diameter) nodule was found in the right hepatic lobe (white arrowhead). (d) The gross morphology of excised liver from rats in the Normal Liver group. No nodules were found on the liver surface. (e) The gross morphology of excised liver from rats in the Adenoma group. Numerous nodules were found on the liver surface (black arrows). (f) The gross morphology of excised liver from rats in the HCC group. Numerous nodules were found on the liver surface (black arrows). A large nodule was found on the right hepatic lobe (white arrowhead). (g) HE-stained slide of longitudinal section of the left hepatic lobe in the Normal Liver group. (h) HE-stained slide of longitudinal section of the right hepatic lobe in the Adenoma group. Hepatic nodules were found (black arrows), which were diagnosed as adenomas. (i) HE-stained slide of longitudinal section of the right hepatic lobe in the HCC group. The large nodule was diagnosed as HCC (white arrowhead). (j) Microscopic image of HE-stained slide at 400-fold magnification showing an adenoma in the Adenoma group. (k) Microscopic image of HE-stained slide at 400-fold magnification showing HCC in the HCC group.
Notably, our results demonstrated that the contrast agent was well-tolerated in rat. Previous studies proved the safety of ExiTron nano 12000 in comparison with other contrast agents in mouse CT imaging. Nebuloni et al. reported that a bolus injection of ExiTron nano 12000 is well-tolerated in mice (22). That study also demonstrated that most mice died of respiratory failure immediately after a bolus injection of eXIA160XL (Binitio Biomedical Inc., Ottawa, Canada), a commercial blood-pool agent (22). Generally, mice have a total blood volume of 1200-1500 mL; therefore, mice might die when the injection volume exceeds 200 mL per mouse (23). Boll et al. reported that a volume of only 100 mL of ExiTron nano 12000 provides stronger contrast enhancement of the liver tissue in mice than does 400 mL of Fenestra LC (Advanced Research Technologies Inc, Montreal, Canada), an iodinated oil-in-water lipid emulsion (23). That study showed that cumulative contrast enhancement in the liver was observed with a single injection of ExiTron nano 12000 as well as with repeated injections of Fenestra LC (23). We believe that ExiTron nano 12000 is a safe contrast agent, given that this agent provides a long-lasting contrast enhancement of the liver tissue with a small injection volume and a single dose, resulting in less stress on experimental animals. ExiTron nano 12000 is a nanoparticle-based, non-iodinated contrast agent that provides both liver and spleen CT contrast (17). Previous reports revealed that mouse liver tumors can be identified by CT using ExiTron nano 12000 in pre-clinical translational research (17,24-26). ExiTron nano 12000 subsequently has been used for CECT imaging of lymph node metastasis in a lung cancer model in rat (27). However, to our knowledge, no study has been conducted to clarify the safety of CECT imaging using ExiTron nano 12000 in a rat model. In the present work, ExiTron nano 12000 was administered to rats for CT imaging at a dose per body weight equivalent to the amount of contrast agent used in mice, and examinations were performed without any apparent adverse events. Therefore, we infer that ExiTron nano 12000 is safe for CECT imaging in rat models.

ExiTron nano 12000 is more amenable for contrast-enhanced liver imaging in rat compared to the conventional iodine contrast agent. The conventional water-soluble iodine contrast agent is known not to be appropriate for use as a contrast agent in CECT for the evaluation of the liver and other parenchymal organs in small animals (28). Specifically,
the conventional iodine contrast agent remains in the blood vessels in mice for a shorter time than in humans and is excreted via the kidneys of mice within seconds (29,30). In contrast, the time required for a micro-CT scan typically ranges from 5-8 minutes, depending on experimental conditions (31). In the present work, CT scans of the rats typically took 7-12 minutes. Thus, a water-soluble iodine contrast agent is not suitable for small-animal research. Recently, various contrast agents based on metal nanoparticles have gained wide use for preclinical imaging in mouse models (23,31). ExiTron nano 12000 is one such metal-containing nanoparticle contrast agent and kupffer macrophages take up the nanoparticle contrast agent two minutes after injection (17). This contrast agent was shown to be imported by the reticular system of the liver and spleen, via a process similar to that seen with superparamagnetic iron oxide (SPIO), resulting in accumulation in the body for at least 6 months (17). Nanoparticle contrast agents provide stronger and longer lasting contrast enhancement of healthy liver parenchyma compared to iodine-based contrast media in mouse models. For instance, CECT imaging using the nanoparticle contrast agent was employed to evaluate a time course of changes in tumor size (17,32). The present study demonstrated that ExiTron nano 12000 provided contrast for liver imaging in all of the tested rats. Therefore, this nanoparticle contrast agent is expected to be of use for contrast-enhanced liver imaging in the rat.

In the present study, histologically diagnosed cases of HCC were identified as liver nodules using CECT. Indeed, there was significant positive correlation regarding the size of HCC when comparing between HCC in slide specimens and as detected by CT imaging in alive animals. The maximum diameters of the lesions diagnosed as HCC based on HE staining were smaller than those of the nodules identified by CECT. This difference reflects the nature of the specimen preparation process. Specifically, given that liver specimens were cut arbitrarily to 4 mm thicknesses, the stained slides may not have captured the maximum diameter of the tumor. Nonetheless, there was a strong correlation ($r = 0.966, r^2 = 0.933, p < 0.0001$) between the diameter of CT-detected HCC and that of pathologically diagnosed HCC. A previous report in mouse demonstrated that there is a fair correlation for liver tumors between CT-based volumetry and

![Figure 5. Immunohistochemical staining for glutathione S-transferase pi (GST-P) in the rat liver. Normal Liver indicates the group of rats subjected to contrast-enhanced computed tomography (CECT) after 8 week administration of normal tap water. Hepatocellular carcinoma (HCC) indicates the group of rats subjected to CECT after 14 week administration of tap water containing 100 ppm diethylnitrosamine (DEN). (a, b) Microscopic images of GST-P-stained slides at 40-fold magnification. (c, d) The respective black and white images adjusted to threshold using ImageJ. The GST-P positive cells are seen as black spots. (a, c) Hepatic parenchyma in the Normal Liver group, expressing GST-P in the bile duct cells. (b, d) Hepatocellular carcinoma (HCC) area and non-HCC area in the HCC group.](image-url)
paired Student small as 300 nanoparticle contrast agent detected mouse liver metastases as parenchyma and HCC area. In the HCC group. The percentage of GST-P-positive area for the HCC area means the hepatic parenchyma outside of the HCC area of tap water containing 100 ppm diethylnitrosamine (DEN)). Non-the HCC group (rats subjected to CECT after 14 week administration of normal tap water). Hepatocellular carcinoma (HCC) area indicates the area of HCC in the HCC group (rats subjected to CECT after 14 week administration of tap water containing 100 ppm diethylnitrosamine (DEN)). Non-HCC area means the hepatic parenchyma outside of the HCC area in the HCC group. The percentage of GST-P-positive area for the non-HCC area is statistically larger than that in the normal hepatic parenchyma and HCC area. *p-value < 0.0167 (a two-tailed non-paired Student’s t test with Bonferroni correction).

Figure 6. Percentages of glutathione S-transferase pi (GST-P)-positive areas. Normal Liver indicates hepatic parenchyma in the Normal Liver group (rats subjected to contrast-enhanced computed tomography (CECT) after 8 week administration of normal tap water). Hepatocellular carcinoma (HCC) area indicates the area of HCC in the HCC group (rats subjected to CECT after 14 week administration of tap water containing 100 ppm diethylnitrosamine (DEN)). Non-HCC area means the hepatic parenchyma outside of the HCC area in the HCC group. The percentage of GST-P-positive area for the non-HCC area is statistically larger than that in the normal hepatic parenchyma and HCC area. *p-value < 0.0167 (a two-tailed non-paired Student’s t test with Bonferroni correction).

histology (33). In other work, micro-CT imaging using a nanoparticle contrast agent detected mouse liver metastases as small as 300 μm in diameter (17,23). Our study also detected small nodules, with diameters as small as 1 mm, in a rat liver tumor model. Thus, the present work demonstrated the utility of CECT in rats using a non-invasive imaging method augmented by a nanoparticle contrast agent. Invasive interventions usually can be performed for experimental rats (10-12). Therefore, the CECT imaging technique tested here is expected to be of use for evaluating treatment efficacy in a small-animal model during the follow-up after invasive interventions such as surgery and catheterization.

In this experiment, DEN-induced HCC was visualized by CECT, and this diagnosis then was validated histopathologically. DEN has been used in many rat studies as a chemical initiator of hepatocarcinogenesis (13-16, 34). In previous reports, DEN-induced HCC was created by feeding 100 ppm orally for 12-15 weeks (9,11,35). Oral intake of DEN represents a less-invasive method of administration and so was employed in our study. Jagan et al. reported finding an average of 102 nodules in six rats administered 100 ppm DEN for 15 weeks (34). However, few studies have confirmed that DEN-induced lesions were indeed HCC, as assessed by experts (14,36). Kakehashi et al. reported that 6.65 ± 2.64 HCCs per rat were observed after 36 weeks of intraperitoneal administration of 100 mg/kg b.w. of DEN (14). The same laboratory also showed that GST-P-positive foci are precursors for the later formation of HCCs in a rat model of HCC (57). HCCs were relatively negative for GST-P, while hepatocellular adenoma was positive. In the present study, approximately 30 liver nodules were observed by CECT after treatment with 100 ppm DEN in drinking water for 14 weeks. We observed 3.6 ± 2.7 HCCs per rat in histological specimens; these HCCs were negative for GST-P staining. Approximately 10%-15% of nodules were identified as HCCs in the present HCC model after the DEN initiation. It is still important to keep in mind that not all lesions observed here are HCCs, and hepatocellular adenomas are also present, to use this model in cancer experiments.

As this study was successful in a rat model, CECT with the nanoparticle contrast agent can be expected in larger animals, perhaps even in humans, in the near future. This contrast agent is iodine-free and can be used for animals with impaired renal function (38). The agent exhibits extended retention in the systemic circulation (17,22). However, an appropriate imaging protocol has not yet been established. The nanoparticle contrast agent has been shown to successfully visualize vessels in a mouse model (39). Given that this technique has been employed in dynamic CT scanning, dynamic studies should be able to detect hypervascular tumors in the liver. While ExiTron nano 12000 has a function similar to that of SPIO, dynamic CECT with ExiTron nano 12000 has the potential to generate images similar to gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOBDTPA) dynamic contrast-enhanced magnetic resonance imaging (MRI). Furthermore, recent reports have shown that dual-energy CT images can detect intrahepatic lesions and can be employed for the quantitative measurement of liver content. Lenga et al. reported that low-KeV virtual monoenergetic images improved sizing and diagnostic accuracy compared to standard linearly-blended images in portal-venous phase dual-energy CT examination for colorectal liver metastases in humans (40). Cao et al. used the material decomposition technique in rapid kVp switching dual-energy CT to quantify liver fat content in rats with non-alcoholic fatty liver (41). The combination of CECT with nanoparticle contrast agent and these dual-energy CT technique is expected to be feasible for rat liver imaging to quantify tumor components and to determine accurate tumor size.

This study has several limitations. First, this study had a small-sample size and used a single rat liver tumor model. While a large sample size would have been preferable from a statistical point of view, a small sample size was employed in the interest of animal welfare. Secondarily, regarding safety evaluation of ExiTron nano 12000, biochemical tests were not performed before and after contrast medium administration in the same animal. Thirdly, the number of nodules smaller than 1 mm in CECT images was not counted in this study, although it has been reported that nodules with a diameter of 300 μm also can be identified in the mouse liver tumors (17,30). Lastly, histopathologically diagnosed HCC and hepatocellular adenoma were difficult to differentiate in the CECT images as well as in the images of hepatobiliary
phase of Gd-EOB-DTPA enhanced MRI. However, dynamic studies like those mentioned above may help in qualitative diagnosis in the near future.

CONCLUSION

CECT with ExiTron nano 12000 is a safe and feasible method for identifying DEN-induced liver tumors in a rat model.

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REFERENCES


SUPPLEMENTARY MATERIALS

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