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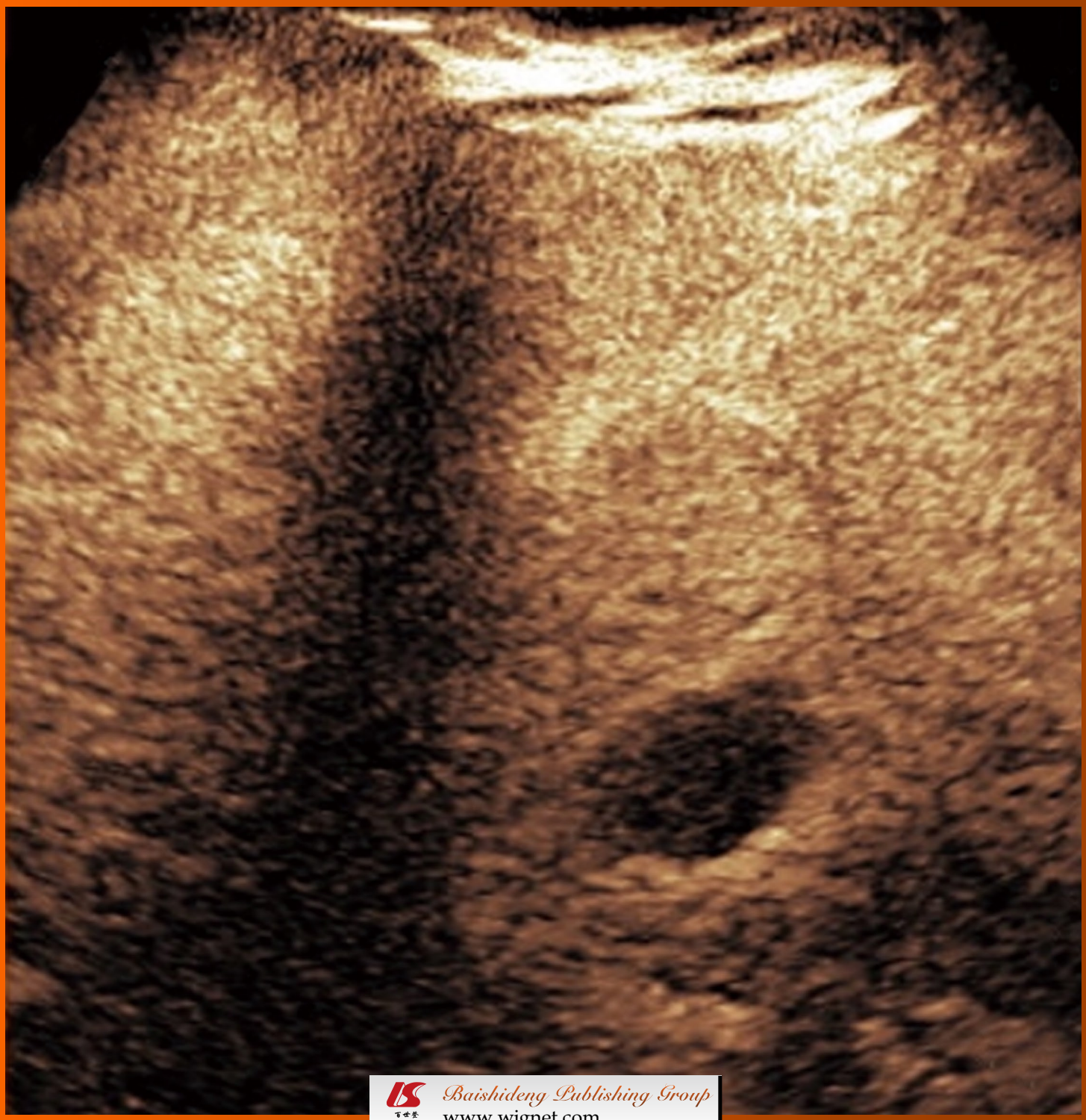

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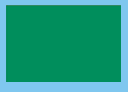

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EDITORIAL

Contrast-enhanced ultrasound in diagnosis and characterization of focal hepatic lesions

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Abstract

The extensive use of imaging techniques in differential diagnosis of abdominal conditions and screening of hepatocellular carcinoma in patients with chronic hepatic diseases, has led to an important increase in identification of focal liver lesions. The development of contrast-enhanced ultrasound (CEUS) opens a new window in the diagnosis and follow-up of these lesions. This technique offers obvious advantages over the computed tomography and magnetic resonance, without a decrease in its sensitivity and specificity. The new second generation contrast agents, due to their intravascular distribution, allow a continuous evaluation of the enhancement pattern, which is crucial in characterization of liver lesions. The dual blood supply in the liver shows three different phases, namely arterial, portal and late phases. The enhancement during portal and late phases can give important information about the lesion's behavior. Each liver lesion has a different enhancement pattern that makes possible an accurate approach to their diagnosis. The role of emerging techniques as a contrast-enhanced three-dimensional US is also discussed. In this article, the advantages, indications and technique employed during CEUS and the different enhancement patterns of most benign and malignant focal liver lesions are discussed.

Key words: Focal liver lesion; Ultrasound; Contrast sonography; Contrast-enhanced ultrasound; Liver mass; Hepatocellular carcinoma

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INTRODUCTION

The widespread availability of imaging modalities such as ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI), to screen for liver lesions and in the study of nonspecific abdominal complaints, has greatly increased the diagnosis of liver lesions in asymptomatic patients[1].

The precise diagnosis of liver lesions should not only

be based on imaging techniques but also must be taken into acco-unt the clinical history and laboratory data. For example, the use of oral contraception in young women, history of cirrhosis, positive serologic test for hepatitis viruses, elevation of α fetoprotein (AFP) or excessive alcohol consumption may provide important clues. Therefore, a comprehensive clinical history and physical examination are as important as the imaging technique for the characterization of liver masses. In some cases, histology is needed for the final diagnosis.

Ultrasound is usually the first line of investigation in the detection of focal liver lesions due to its relatively low cost, safety and wide availability, but the differentiation between benign and malignant lesions is difficult in many cases with this technique[2,3]. The introduction of contrast media in imaging technique can better characterize the non-invasive focal liver lesions based on their enhancement pattern than the surrounding liver parenchyma. Contrast-enhanced CT and MRI are most commonly used, but the introduction of ultrasound contrast has expanded the role of sonography in the characterization of focal liver masses[4].

CONTRAST-ENHANCED SONOGRAPHY

The ultrasound contrast agents are microbubbles with an approximate size of red blood cells that circulate into vessels but not through the vascular endothelium into the intersticium. This property helps to provide accurate information about the vascularity of the lesion[5]. There are different types of contrast but all of them consist of a gas microbubble stabilized with a phospholipid-membrane.

The contrast works as a signal enhancer. The interface between microbubble and aquatic medium reflects the ultrasonic wave improving the contrast between the blood and hepatic tissue around.

Under low mechanical index imaging, the microbubbles have a much higher nonlinear behavior than the native tissue, resulting in detectable echoes[2]. Pulse inversion imaging suppresses echoes from tissues in favor of those from bubbles. When used at a low mechanical index, pulse-inversion imaging does not cause disruption of the microbubbles, thus allowing a continuous assessment of the vessels as the contrast agent traverses the imaging field[6].

Contrast agents are safe and produce very few adverse effects. Severe anaphylactoid reactions have been described in 0.001% of abdominal explorations, similar to those described in MRI contrasts (gadolinium) and fewer than allergic reactions to CT iodized contrasts.

Before ultrasound contrast is injected, a complete sonographic study in B-mode must be performed, with or without the use of Doppler. After the lesion is identified, the transducer has to be placed in a fixed position in order to visualize the mass along the whole exploration. The mechanical index ought to be changed to a low index to prevent a fast destruction of microbubbles, thereby allowing a complete multiphase imaging. The principal vascular structures and other anatomic references like the diaphragm must remain visualized. Some sonographers have a double screen with one of them under a low index state and the other one in B-mode, which facilitates the visualization under both mode conditions at the same time. The contrast is usually administered in bolus through a peripheral vein followed by a saline flush. The chronometer must be started as the same time as the initial injection. It is recommended that the exploration be performed continuously in the first 90 s to evaluate correctly the arterial and portal phase, but can be explored discontinuously in the late phase. If a second lesion has to be studied, the previous microbubbles can be washed out sweeping with the transducer by using a high mechanical index. It is recommended to record the exploration[7].

The liver, with its dual blood supply, shows first enhancement in the arterial phase as the contrast agent fills the hepatic artery, with progressively enhancement as it arrives to the portal vein. The arterial phase (10-35 s after the injection) gives information about the amount and type of the lesion's microvascularization. The portal (30-120 s after the injection) and late phases (over 120 s after the injection) give more information about the elimination of the contrast in the lesion than about that of the rest liver parenchyma. It is believed that the contrast is uptaken by Kupffer cells or remains in the hepatic sinusoids in the late phase. There are new contrast agents that provide the additional post-vascular or Kupffer phase that allows an assumption of the degree of malignancy based on Kupffer function[8].

The portal and late phase enhancement can give important information about the lesion's behavior. The majority of malignant lesions present a lower enhancement than the rest liver parenchyma, while the majority of benign solid lesions present a higher than or the same enhancement as the rest liver parenchyma[2]. The differentiation between benign and malign tumors is possible in 95% of cases in the late phase, between 120 s and 5 min after contrast injection[9].

The use of ultrasounds provides several advantages over CT and MRI, such as lack of exposure to radiation, more availability and less expensive contrast-enhanced US (CEUS)[10]. Furthermore, the contrast media used in sonography are not nephrotoxic, do not influence the thyroidal metabolism while the microbubbles remain in the intravascular space, allowing a continuous assessment of the lesions' vascularity and enhancement with a high temporal resolution, not limited to the pre-defined time points[11,12]. In CT and MRI, the very early contrast period can be missed and the enhancement during the first seconds gives important information, especially in highly arterialized lesions. Another advantage is that contrast injection can be repeated if necessary, due to its excellent tolerance[7]. CEUS has a sensitivity of 90%, a specificity of 99% and an accuracy of 89% in diagnosis of malignant liver lesions, as shown in Von Herbay's study[13].

The limits of enhanced-sonography for detection of liver lesions are the same as conventional ultrasonography. Enhanced-sonography is an operator-dependent tech-

Table 1 Indications for the use of contrast-enhanced ultrasonography

Patients for whom the ultrasonography without contrast, computed tomography, magnetic resonance imaging or cytology is not conclusive
Evaluation of lesions before percutaneous treatment to have a first image to compare after the procedure if necessary
Guidance of the needle or the probe during percutaneous treatment
Immediate evaluation of the lesion after percutaneous treatment to detect viable areas[24]
Follow-up of patients with liver lesions treated by percutaneous ethanol injection or radiofrequency ablation
Detection of liver tumors and study of its microcirculation
Evaluation of organ perfusion
Study of macrocirculation
Improvement of sensibility and specificity during intraoperative sonography

nique, due to the evaluation of some liver segments like Ⅷ segment with difficult accessibility, cirrhotic or fatty livers which limit the ultrasound penetration, patients with low collaboration during exploration, and the need of additional injection of contrast for patients with multiple lesions.

The indications for the use of CEUS are summarized in Table 1.

CEUS is contraindicated in patients with acute cardiac failure, class Ⅲ/Ⅳ cardiac failure, cardiac rhythm disorders, recent coronary arterial intervention or factors suggestive of clinical instability, right-to-left shunts, severe pulmonary hypertension and uncontrolled systemic hypertension. Ultrasonographic contrast media have not been used in patients under the age of 18 years, pregnant or breastfeeding women. They must be used with caution in patients with severe chronic obstructive pulmonary disease[3]. It is recommended that patients stay at hospital under medical supervision for at least 30 min after contrast administration.

CHARACTERIZATION OF FOCAL LIVER LESION WITH CEUS

Benign liver lesions

Simple cyst: It is a congenital lesion surrounded by biliary-type epithelium with serous content. It is usually asymptomatic but may produce abdominal pain if it reaches large dimensions. It is anechoic with posterior enhancement in conventional sonography and hypoenhanced in all phases with contrast. Simple cysts do not need surveying or treatment, unless they accompany hemorrhage or infection (Figure 1).

Hemangioma: It is the commonest tumor in the liver with a prevalence of 0.4%-7.4%[14]. It is more frequent in women at the age of 30-50 years. This lesion consists of multiple vessels supported by fibrous interstitium. Usually asymptomatic, it may cause abdominal pain. Only in exceptional cases, it is associated with thrombopenia, consumption coagulopathy and microangiopathic anemia (Kassabach-Merritt syndrome)[15]. It may grow during pregnancy or estrogenic therapies.

Ultrasonography shows a hyperechogenic, well defined lesion. CEUS shows that hemangiomas present peripheral nodular enhancement with centripetal filling during the portal phase and remaining isoenhanced in the late phase (Figure 2).

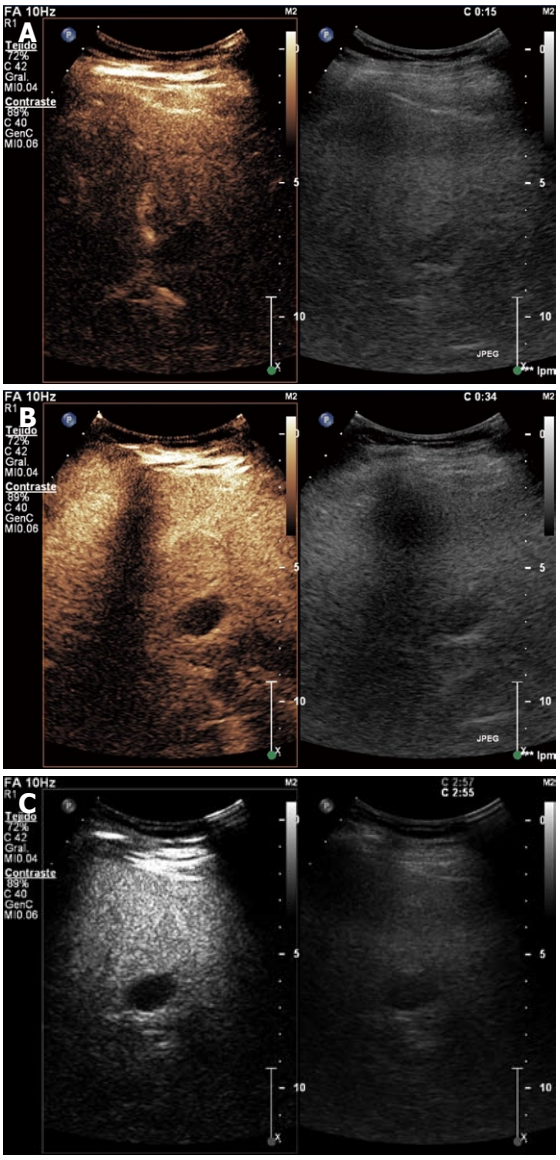

Figure 1 Simple cyst showing no enhancement in the arterial (A), portal venous (B) and late phases (C).

Labeled red blood cell scintigraphy is the best and least expensive modality for lesions over 2.5 cm in diameter and MRI for lesions under 2 cm in diameter[1].

Asymptomatic patients with hepatic hemangiomas do not need follow-up as there is no risk of malignant transformation, but when a homogeneous hyperechoic lesion is discovered in a patient with a history of cirrhosis

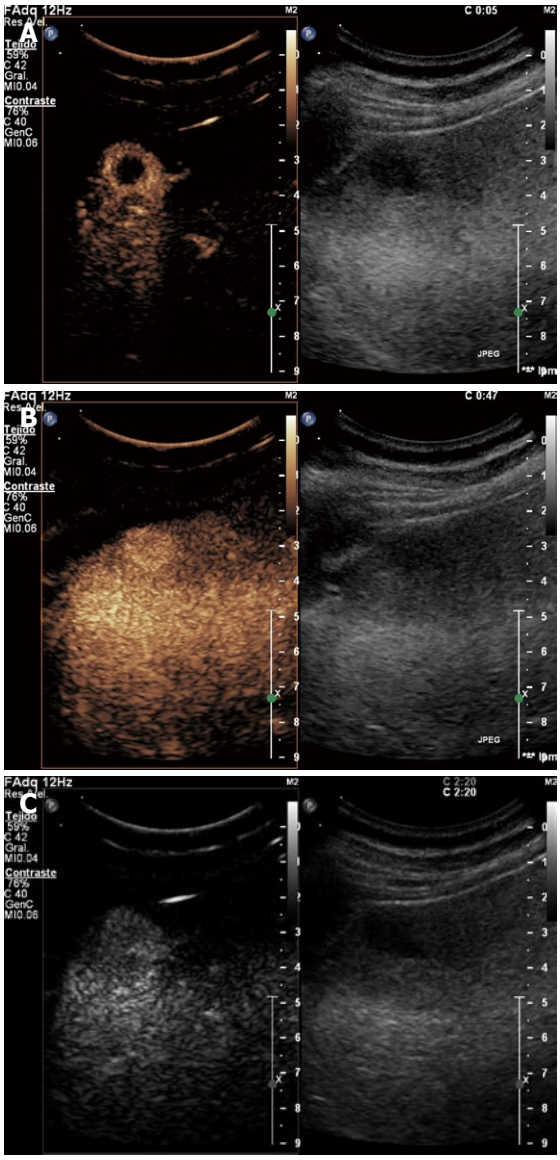

Figure 2 Hemangioma showing peripheral-nodular enhancement in arterial phase without central enhancement (A), partial centripetal filling in the portal venous phase (B), and complete enhancement in the late phase (C).

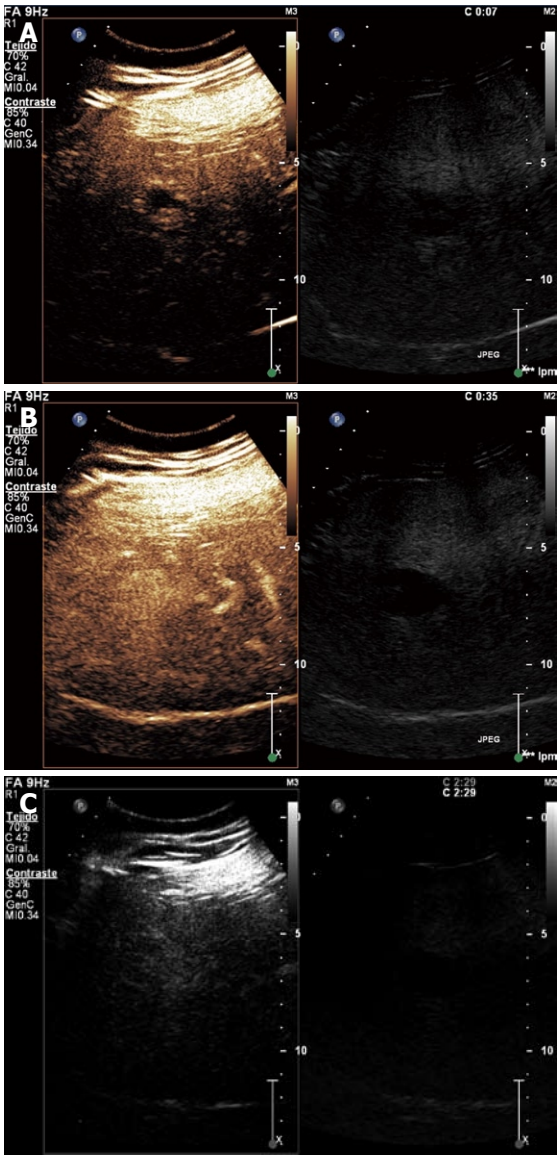

Figure 3 Focal nodular hyperplasia showing hyper-enhancement in arterial phase with complete and early centrifugal filling (A), in portal venous phase (B), and hyper/iso-enhancement in late phase (C).

or known malignancy, further characterization is recommended[4].

Focal nodular hyperplasia: It is a pseudotumor, which is considered a hyperplastic proliferation of normal liver cells in response to a preexisting arterial malformation. Large lesions commonly have a central scar made up from fibrous stroma with a supply artery and hyperplastic bile ducts[15]. It is more frequent in young women and usually asymptomatic.

Enhanced sonography demonstrates that the lesion typically presents a central enhancement in the arterial phase, with a centrifugal filling through radial vascular branches (wheel sign). This image occurs in 95% of cases if the lesion measures at least 3 cm in diameter and in 20%-30% of cases if the lesion is smaller. In the portal phase, the lesion usually remains enhanced with a non-enhancing central scar and becomes isoenhanced in the late phase (Figure 3). Nowadays, MRI is the technique of choice for the diagnosis of focal nodular hyperplasia (FNH), but the characteristic image of the wheel sign is better visualized with CEUS due to its dynamic facet[9].

No cases of malignization are reported. Such cases do not need treatment or follow-up. The interruption of oral contraception is recommended as it may reduce the size of the lesion.

Adenoma: It is related with the use of anabolic androgens, type-1 glycogenosis and oral contraceptives with an incidence of 0.03%. It is histologically made up of normal or atypical hepatocytes with none or few bile ducts and Kupffer cells. Up to 25% of liver adenomas cause abdominal pain in the right hypochondrium or in the epigastrium[16]. In very large adenomas, intratumoral hemorrhage

Table 2 Typical enhanced-ultrasound patterns in benign focal liver lesions

	Arterial phase	Portal phase	Late phase
Hemangioma	Peripheral nodular hyperenhancement with centripetal progression	Slow centripetal filling. The lesion becomes iso or hyperenhanced	Iso or hyperenhanced
Focal nodular hyperplasia	Hyperenhanced in the center of the lesion (central vessel) with fast centrifugal filling due to radial vascular branches: "wheel sign"	Iso or hyperenhanced	Iso or hyperenhanced. Sometimes the central scar can be seen
Adenoma	Highly hyperenhanced with complete filling and fast wash-out. No radial branches	Iso or hyperenhanced	Iso or hyperenhanced
Simple cist	No enhancement	No enhancement	No enhancement
Regenerative nodule	Isoenhanced	Isoenhanced	Isoenhanced
Focal fatty accumulation	Isoenhanced	Isoenhanced	Isoenhanced

is frequent, provoking hemoperitoneum in exceptional cases.

During CEUS, adenomas show a fast centripetal hyperenhancement during arterial phase, but in the majority of cases, the enhancement is irregular in the presence of necrosis or hemorrhages. In portal phase, the adenoma begins to wash out contrast becoming iso or hypoenhanced with the liver parenchyma.

The management is surgical due to its high bleeding risk and potential malignant degeneration [5% of hepatic adenomas transform to hepatocellular carcinoma (HCC)][1].

Regenerative nodule: Regenerative nodules often appear in cirrhotic livers or after a massive hepatic necrosis. These nodules are isoenhanced during the three phases of contrast sonography. Progression to HCC is possible.

Focal fat accumulation: It is present in 10% of patients with liver esteatosis. These fat accumulations are usually located next to the gallbladder, portal veins or the falciform ligament. It is isoenhanced during the arterial, portal and late phases (Figure 4).

The characteristics of hepatic benign lesions according to their vascular pattern on CEUS scan are summarized in Table 2.

Malign liver lesions

HCC: It is the most frequent primary tumor of the liver and the fifth more common malignancy worldwide. It represents the third cause of cancer-related death[17]. About 80% of HCCs appear in cirrhotic population. A liver mass in a cirrhotic patient should be considered a HCC until proven otherwise[1]. Screening of HCC is recommended in these patients through the determination of AFP and a conventional ultrasound every 6 mo. This makes possible a curative or palliative treatment in its early phases.

HCC may be silent but is usually associated with weight loss, abdominal pain, hepatomegaly or ascites. Laboratory data include elevation of serum alkaline phosphatase, persistent leukocytosis and increased ratio of serum AST/ALT.

Two thirds of HCC are hyperechoic in conventional ultrasonography and the other third of HCC are heterogeneous, showing hyper and hypoechoic areas. Small

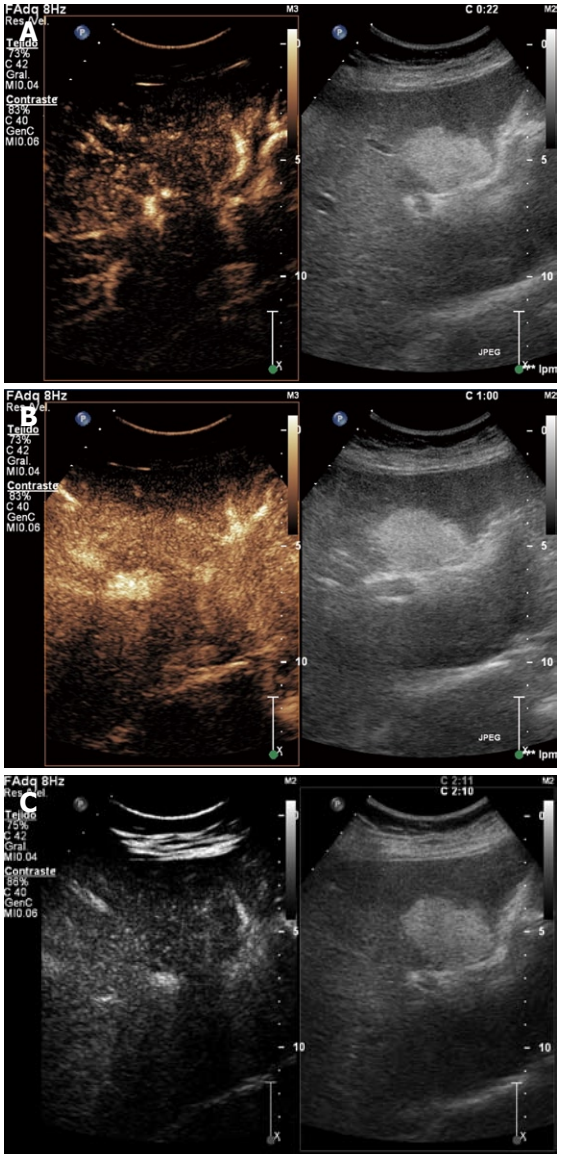

Figure 4 Focal fatty sparing demonstrating an iso-enhancement in the arterial (A), portal (B) and late phases (C).

lesions tend to be hypoechoic. Contrast-ultrasonography shows that HCC are enhanced in arterial phase, often with feeding vessels around and inside the tumor. It has a characteristic rapid wash-out in portal phase and frequently remains hypoenhanced in late phase (Figure 5).

Table 3 Typical enhanced-ultrasound pattern in malignant focal liver lesions

	Arterial phase	Portal phase	Late phase
Hepatocellular carcinoma	Hyperenhanced due to its arterial vascularization	Fast wash-out leaving an iso or hypoenhanced lesion	Hypoenhanced
Cholangiocarcinoma	Hyperenhanced in the border	Iso or hypoenhanced	Hypoenhanced
Hypervascular metastasis	Hyperenhanced, usually starting in the margin: ring sign	Iso or hypoenhanced	Hypoenhanced
Hypovascular metastasis	Hypoenhanced	Hypoenhanced	Hypoenhanced

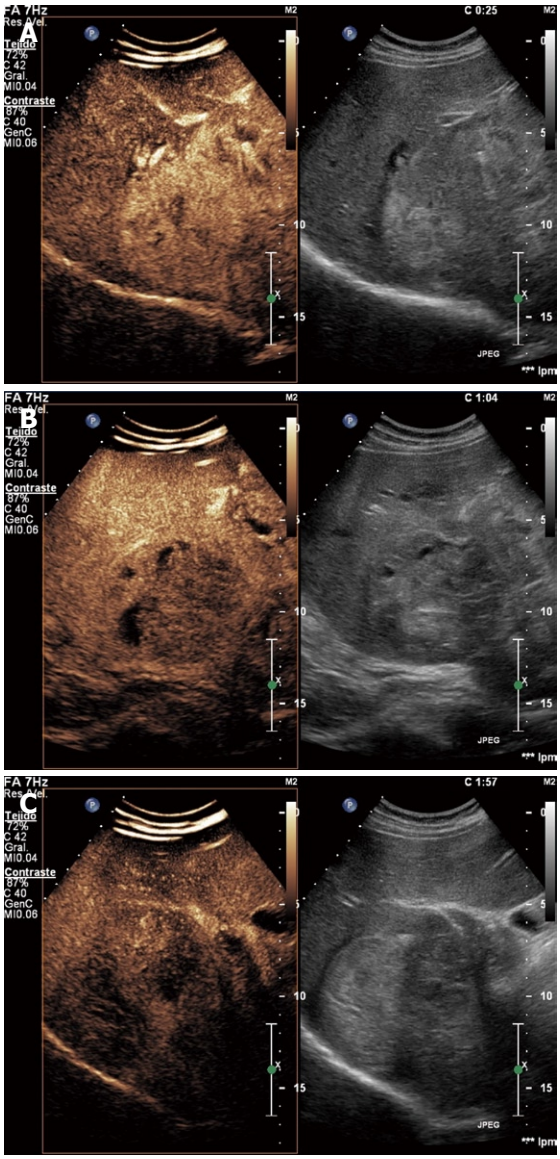

Figure 5 Hepatocellular carcinoma showing hyper-enhancing in arterial phase with necrotic non-enhancing areas (A), iso-enhancement in portal venous phase with necrotic non-enhancing areas (B), and hypo/iso-enhancing in late phase (C).

For the diagnosis of HCC in cirrhotic patients, lesions over 2 cm in diameter need just one imaging technique showing typical findings or one imaging technique showing an AFP level over 400 μg. In nodules between 1 and 2 cm in diameter, two techniques showing typical imaging criteria are needed for the diagnosis. Follow-up every 3 mo is recommended for masses less than 1 cm in diameter[1].

Intrahepatic cholangiocarcinoma: It is generally a unique mass originated in small intrahepatic bile ducts. This tumor should be considered in patients with chronic primary sclerosing cholangitis, longstanding choledochocele, intrahepatic lithiasis, parasitic disease of the bile ducts, Caroli's disease, and in patients exposed to thorotrast for radiographic procedures[1]. Jaundice is the most common clinical presentation[18] and usually associated with a high serum bilirubin level. Up to 80% of the cholangiocarcinomas present elevated values of serum CA 19-9 and 50% present elevated CEA[15].

Cholangiocarcinomas show different enhancement patterns depending on size of the lesion and different pathological components of the tumor[19]. In arterial phase, this tumor may show irregular peripheral rimlike hyperenhancement, heterogeneous hyperenhancement, homogeneous hyperenhancement or heterogeneous hypoenhancement. In portal phase, it presents complete wash out staying hypoenhanced. Even though there are many ultrasound patterns, the use of CEUS helps to differentiate between cholangiocarcinoma and HCC[20].

Metastasis

The liver is the most common site of metastasis from the gastrointestinal tract, pancreas, breast and lung. Colorectal cancer most commonly metastasizes to liver. Metastasis occurs in the most common malignant hepatic tumor. Generally, both hepatic lobes are involved[1].

Hypervascular metastases are associated to carcinoid tumors, melanomas, sarcomas, thyroid tumors and hypernephromas. They are completely enhanced in arterial phase with fast wash out and hypoenhanced in portal and late phases (Figure 6). Hepatic metastases can be classified into hypo and hypervascular.

Hypovascular metastases remain unenhanced during the three phases (Figure 7).

Intraoperative ultrasonography is the most sensitive imaging technique for diagnosing liver metastases and may be helpful in delineating the extent of disease and vascular landmarks during hepatic resection[21].

The vascular pattern characteristics of hepatic focal malignant on CEUS scan are summarized in Table 3.

CONTRAST-ENHANCEMENT THREE DIMENSIONAL IMAGES AND FOCAL HEPATIC LESSIONS

Recently, CE three-dimensional (3D) US has been incor-

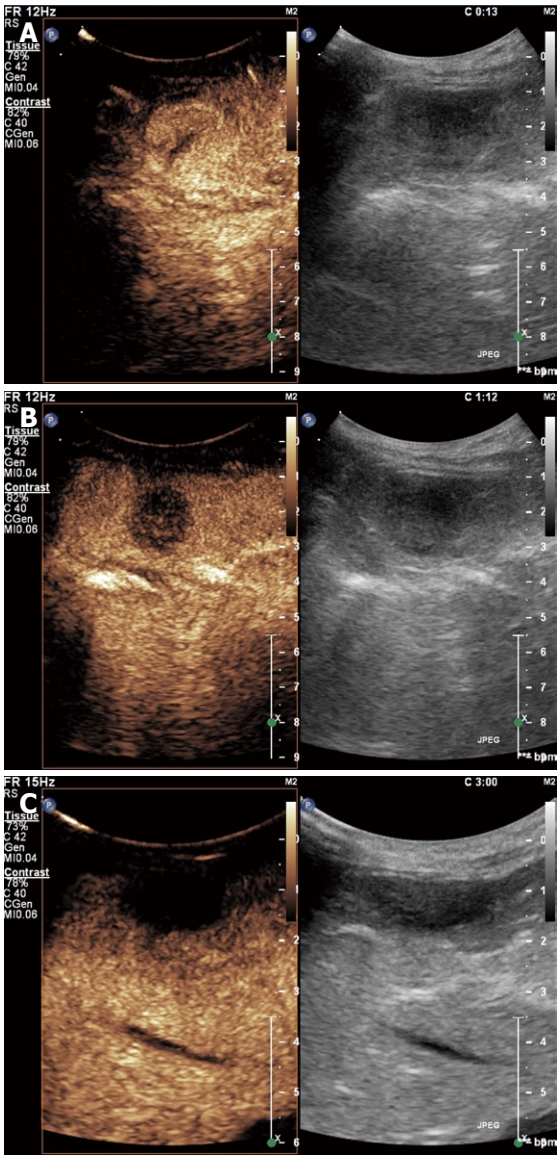

Figure 6 Hypervascular metastases showing hyper-enhancement in arterial phase (A), hypo-enhancement in portal venous phase (B), and hypo/non-enhancement in late phase (C).

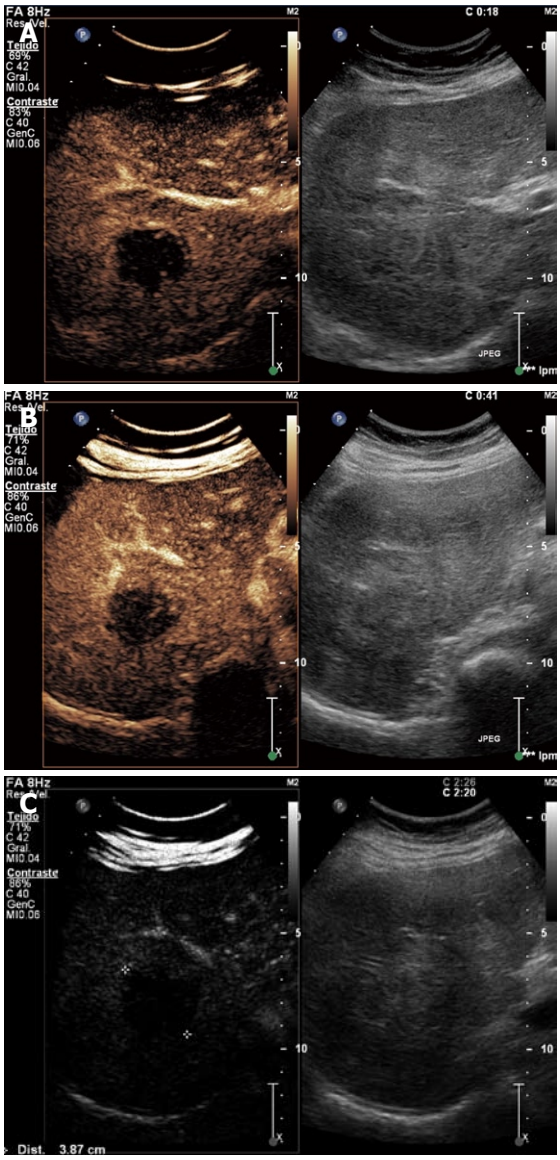

Figure 7 Hypovascular metastases showing rim enhancement with central hypo-enhancement in arterial phase (A), hypo-enhancement in portal venous phase (B), and hypo/non-enhancement in late phase (C)

porated to the diagnostic US technologies. This technique provides dynamic information for spatial volume. As compared with CEUS 2D, CEUS-3D acquires the data in a volume of interest (VOI) by scanning with a desired angle and allows reconstruction of images in three orthogonal planes and yields images similar to angiograms, with accurate visualization of the vascular characteristics of focal liver tumors[22,23]. A recent retrospective-prospective large study by Luo *et al*[5], found that dominant enhancement patterns are as diffuse enhancement or peripheral ring-like enhancement, followed by washout change in HCC or peripheral ring-like enhancement with venous washout for metastases. In the case of hemangiomas, the pattern is usually a nodular enhancement, whereas in FNH, the dominant pattern is observed in spoke-wheel arteries. Although CE 3D US shows a high sensitivity and specificity for differentiation of lesions and a good-excellent inter-observer agreement, no significant difference has been observed in prospective diagnosis accuracy of CE 3D US and CE 2D US.

However, some artifacts from the cardio-pulmonary motion, shadows of costal bones, and interference from abdominal gas might lead to reader's misinterpretation. The role of this technique in both evaluation of focal liver lesions and assessment of the effect of percutaneous or TACE therapies on HCC should be further evaluated before its routine use is recommended.

CONCLUSION

CEUS is an emerging imaging technique that offers important advantages over CT and MRI. It is becoming the procedure of choice, using a low mechanical index, for the study and detection of focal liver lesions and a valu-

able complementary tool with CT and MRI in the diagnosis and follow-up of these lesions.

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BRIEF ARTICLE

Percutaneous cecostomy in the management of organic fecal incontinence in children

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Abstract

AIM: To assess the effectiveness and safety of imaging-guided percutaneous cecostomy in the management of pediatric patients with organic fecal incontinence.

METHODS: Twenty three cecostomies were performed on 21 children with organic fecal incontinence (13 males, 8 females), aged from 5 to 16 years (mean 9.5 years). Thirteen patients had neurogenic fecal incontinence and 8 patients had anorectal anomalies. Procedures were performed under general anesthesia and fluoroscopic guidance. Effectiveness and complication data were obtained for at least 1 year after the procedure.

RESULTS: Cecostomy was successful in 20 patients (primary technical success rate 95%). Cecostomy failed in one patient due to tube breakage (secondary technical success rate 100%). The tubes were *in situ* for an average of 18 mo (range 12-23 mo). Eighteen patients (87%) expressed satisfaction with the procedures. Resolution of soiling was achieved in all patients with neurogenic fecal incontinence (100%) and in 5 of 8 patients with anorectal anomalies (62.5%). Eleven patients (52%) experienced minor problems. No major complications were noted.

CONCLUSION: Percutaneous cecostomy improves the quality of life in children with organic fecal incontinence. A satisfactory outcome is more prevalent in patients with neurogenic fecal incontinence than anorectal anomalies.

Key words: Cecostomy; Fecal incontinence; Interventional radiology; Pediatric radiology

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INTRODUCTION

Fecal incontinence refers to the inability to hold feces in the rectum. This is due to failure of voluntary control over the anal sphincters, permitting untimely passage of feces and gas. Though most children become toilet trained between 2 and 4 years of age, there are some situations in which children do not develop complete control of their stool elimination. This leads to stool leaking from the rectum at unexpected times. Fecal incontinence is a devastating disability that is not uncommon in the pediatric population. Fecal incontinence can be one of the most

psychologically and socially debilitating conditions in an otherwise healthy individual. It can lead to social isolation, loss of self-esteem and self-confidence, and depression[1].

Fecal incontinence can be associated with peristalsis, sensation, sphincter control, anatomy, or psychosocial disorders. Most cases of fecal soiling in children are functional and are usually associated with severe constipation. Organic fecal incontinence may be permanent, as in patients with myelodysplasia, self-limiting, as in patients who have fecal soiling after a pull-through operation for Hirschsprung's disease, or partial, as with many patients who have undergone repair of an anorectal malformation[2]. Recently, Di Lorenzo *et al*[3] classified pediatric fecal incontinence into four main categories according to pathophysiology. The first category is functional fecal retention due to withholding of feces because of fear of painful defecation, which results in constipation and overflow soiling. The second category is functional nonretentive fecal soiling due to antidiarrheal agents, which can increase the consistency of stools and facilitate continence. The third category is organic fecal insentience due to congenital anorectal anomalies. The last category is organic neurogenic fecal insentience, which occurs in children with spina bifida or spinal injuries.

Traditional treatments of fecal incontinence include dietary modification, laxatives, suppositories, enemas, manual disimpaction, biofeedback and electrostimulation. Despite these efforts, many patients do not achieve fecal continence. Fecal incontinence can be treated by emptying the bowels with a rectal enema. This treatment is effective, but it can also be messy, time-consuming, inconvenient, and difficult (or impossible) for some patients to do by themselves.

Surgically created cecostomies have been attempted for many years. In 1986, Casola *et al*[4] described a percutaneous approach for the placement of a cecostomy catheter for colonic decompression in adults. In1988, Ganc *et al*[5] described a technique for transcolonoscopic extraperitoneal cecostomies as an effective new therapeutic technique for the management of fecal incontinence. In 1990, Malone *et al*[6] described antegrade colonic enema (MACE) as a surgical procedure where the appendix is used to form a cutaneous cecostomy for fluid irrigation of the colon. However, these surgically created cecostomies carry risks of stomal stenosis, stomal leakage, appendiceal necrosis, general anesthesia and bowel perforation.

In 1996, Shandling *et al*[7] described a pilot study for a percutaneous image-guided approach to gain access to the cecum for the introduction of an antegrade enema. This study was later followed by other studies that showed this percutaneous procedure represents a less invasive alternative to a surgical procedure[8-12]. Percutaneous endoscopic cecostomy is a viable alternative to surgically or fluoroscopically placed cecostomy in a select group of patients with recurrent colonic pseudo-obstruction or chronic intractable constipation[13]. In general, and according to the pathophysiology of pediatric fecal incontinence, functional fecal retention is treated by dietary changes, use of drugs, anorectal biofeedback and cognitive and behavioral interventions, such as toilet training. On the other hand, patients with organic fecal incontinence benefit from techniques that teach them how to defecate, such as with cecostomy, which completely cleanses the colon, increases the child's autonomy, and decreases the chance of soiling. However, there is great variation in the postsurgical functional outcomes of these procedures[3,8-12].

The purpose of our study was to assess the effectiveness and safety of imaging-guided percutaneous cecostomy in the management of pediatric patients with organic fecal incontinence.

MATERIALS AND METHODS

From January 2005 to December 2009, 23 imaging-guided percutaneous cecostomy tube placements were performed on 21 children with organic fecal incontinence. The patients included 13 males and 8 females aged from 5 to 16 years (mean 9.5 years). Thirteen patients suffered from neurogenic fecal incontinence secondary to spinal etiology (6 patients had myelomeningocele, 2 had sacral agenesis and 5 had dorso-lumbar spinal injuries with paraplegia). The other 8 patients had fecal incontinence secondary to anorectal anomalies after failure of medical and surgical management. This study was approved by the credential and privileges committee in our hospital. Informed consents were obtained from the parents or guardians. All patients had lax anal sphincter by digital rectal examination and had marked cecal dilatation 13 ± 3.5 cm as seen in plain abdominal radiographs. Ten patients underwent a barium enema study before admission to detect the position of the cecum.

Technique of percutaneous cecostomy

Pre-procedure preparation: The patients consumed a fluid diet for 2 d before the percutaneous cecostomy procedure. Usually the patients were admitted 1-d before the procedure. Forty five milliliters sodium phosphate solution (Phospho-Soda oral laxative; Fleet, Lynchburg, Va) was administered orally the night of admission. Radiography of the abdomen was performed just prior to the procedure to assess bowel cleansing, and a repeat dose of the phosphate solution was given, if necessary. Complete blood analysis, clotting and coagulation times were checked before the procedure. Abdominal and pelvic ultrasonography (Voluson 730 Expert, GE, Austria) was performed before the procedure to identify fluid collections and the positions of major organs, including the gallbladder, liver, and urinary bladder. Glucagon hydrochloride (Eli Lilly, Scarborough, Ontario, Canada) was administered intravenously at a dose of 0.5-1.0 mg before the procedure to inhibit colonic peristalsis. A prophylactic antibiotic regimen was given to all patients before and after the procedure. The antibiotic regimen included three intravenously administered antibiotics: 2.5 mg/kg gentamicin (Gentamicin Injection USP; Sabex, Boucherville, Quebec, Canada) every 8 h, 10 mg/kg metronidazole

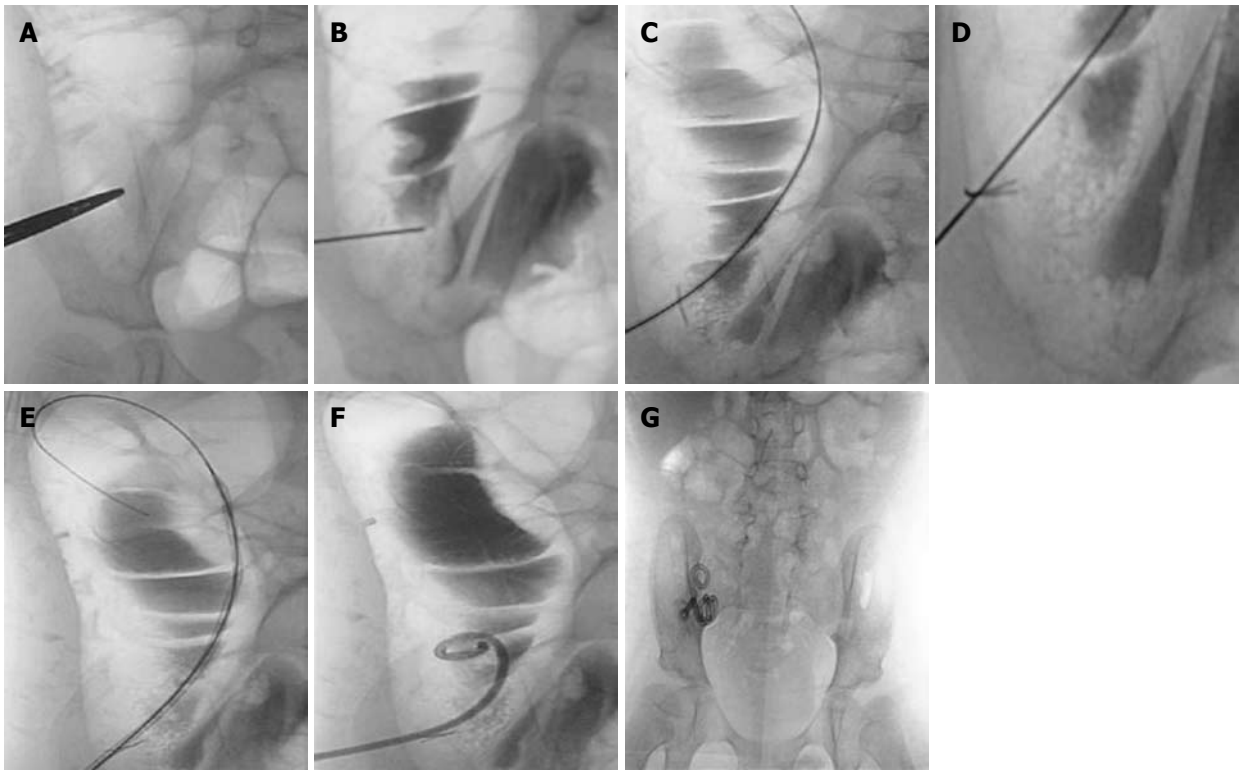

Figure 1 Procedure of percutaneous cecostomy. A: Skin entrance site is localized over the air-filled distended cecum; B: After needle insertion into the cecum, contrast is injected to confirm its location within the cecal lumen; C: Guide wire insertion into the distended right side of the colon; D: T-fastener deployed to fix the anterior wall of the cecum to the abdominal wall; E: The insertion tract is dilated before placement of the cecostomy tube; F: Locking pigtail catheter is inserted into the cecum; G; After 6 wk, the Dawson Mueller catheter is exchanged for the permanent Chait Trapdoor cecostomy catheter.

(Metronidazole Injection; Abbott, St Laurent, Quebec, Canada) every 8 h, and 20 mg/kg ampicillin (Ampicillin Sodium for Injection USP; Novofarm, Toronto, Ontario, Canada) every 6 h.

Procedure: The procedures were performed under general anesthesia in all patients. Imaging was performed on a C-arm fluoroscopic table with tilting capabilities (Siemens Neurostar, Siemens Medical Systems, Munich, Germany). We used the technique that was described in detail by Chait *et al*[14] in 2003.

Briefly, the cecum was distended with air by using a 22-F silicone (latex-free) Foley catheter (Rusch-Pilling, Kamunting, Malaysia) that was inserted through the rectum. The skin entrance site of the air-filled cecum was localized under fluoroscopic guidance (Figure 1A). A puncture was made using a Majestic 18-gauge, 7-cm, one-wall needle with a Seldinger shield (Merit Medical, South Jordan, Utah). To confirm the intraluminal position of the needle, 5 mL of water soluble contrast material (Omnipaque; Nycomed Imaging, Oslo, Norway) was injected under fluoroscopic guidance (Figure 1B). A 0.035-inch guide wire (Cook, Bloomington, MA) was inserted and the needle was advanced into the cecum (Figure 1C). A T-fastener (Meditech/Boston Scientific, Watertown, MA) was then deployed to fix the anterior wall of the cecum to the anterior abdominal wall (Figure 1D). The retention suture threads were clamped with mosquito forceps. The tract was dilated by the use of an 8-F Coons dilator (Cook, Bloomington, MA; Figure 1E). After dilatation, a 8.5-F, 15-cm latex-free Dawson Mueller Mac-Loc locking pigtail catheter (Cook, Bloomington, MA) was inserted (Figure 1F). The catheter was connected to a drainage bag into which liquid drained to empty the colon and decrease the risk of leakage around the cecostomy tube site.

Post procedure care

The antibiotic regimen was continued for 48 h and followed by orally administered metronidazole (10 mg/kg every 8 h) for 5 d. Analgesia after the procedure comprised intravenously administered morphine (0.05 mg/kg) every 4 h, as needed, for 12 h, followed by orally administered acetaminophen (15 mg/kg) every 4 h as needed. The patients could eat after 12 h, if there was no paralitic ileus and early ambulation was advised as tolerated. Patients who were free of complications were discharged within 2 d or 3 d. Patients that suffered from postprocedure paralytic ileus were usually discharged on the 5th or 6th day after the procedure. When patients were discharged from the hospital, the drainage bags were removed at the time of discharge, and the patients were asked to flush the catheter by 5 mL of saline twice daily. A week after the insertion of the cecostomy tube, antegrade enema irrigations began according to individual needs. Patients and their relatives were trained on how to use the two irrigation bags for routine antegrade colonic evacuation and cleansing. The first bag was a sodium phosphate enema (Merck-Frost, Mississauga, Ontario, Canada), which was intro-

duced at a dose of 2 mL/kg up to a total dose of 130 mL. After 15 min, the second bag (200-400 mL saline solution) was introduced, which could be easily prepared (10 mL salt for one liter of water). The retention sutures were cut 10 d after the procedure.

Long-term care

After 6 wk, the Dawson Mueller Mac-Loc catheter was exchanged by the permanent Chait Trapdoor cecostomy catheter (Cook, Bloomington, MA). The exchange was performed over a guidewire under fluoroscopic guidance. No sedation or antibiotic coverage was necessary, and the procedure was performed on an outpatient basis (Figure 1G). The Chait Trapdoor catheter is to be replaced every year or when a problem arises. Catheter replacement was performed by cutting the old one below the "trapdoor" and advancing the new catheter over a guidewire. This displaced the distal part of the old catheter into the ascending colon, and then it passed easily through the rectum. Long-term care of the cecostomy patients was performed by a team comprising an interventional radiologist, a general surgeon and a pediatrician. Data regarding effectiveness, complications and satisfaction of treatment were obtained by interviewing the children and their parents during follow-up consultation.

RESULTS

Twenty three cecostomy tube placements were performed on 21 children with organic fecal incontinence. In all cases, an 8.5-F Dawson-Mueller catheter were placed in the cecum and exchanged after 6 wk with a cecostomy button (Trapdoor catheter). Tube placement was successful in 20 patients (primary success rate is 95%). Cecostomy tube insertion failed in one patient due to tube breakage during its insertion and replacement by another tube was successfully done in the same setting. Another patient required repeated tube placement after accidental dislodgement of the previously inserted tube after 5 d (secondary success rate is 100%). Functional results (effectiveness, complications and satisfaction) were obtained at a follow-up period of at least 1 year after the procedure. The cecostomy catheters were *in situ* for an average of 18 mo (range 12-23 mo). Eighteen of the 21 patients (87%) expressed satisfaction in the effectiveness of the procedure. Resolution of continuous soiling was achieved in all patients with neurogenic fecal incontinence (100%) and in 5 out of 8 patients with anorectal anomalies (62.5%). Antegrade enemas were administered according to the needs of the patient (range, every 12-48 h; mean, every 18 h).

Eleven patients (52%) experienced minor cecostomy tube related problems at some point during the follow-up period; a cecostomy tube infection occurred in 2 patients, which required oral antibiotic treatment, clogging of the cecostomy tube in 2 patients, partial dislodgment of the tube in 2 patients, the development of granulation tissue accompanied with redness at the cecostomy site appeared in 4 patients and vomiting related to the phosphate enema occurred in one patient. These problems were easily corrected at home and did not require surgical intervention. Among the patients that underwent cecostomies, no procedure related death or major complication requiring surgical intervention or hospital admission was noted.

DISCUSSION

Fecal incontinence is a major health problem in that it affects the quality of life and causes significant embarrassment. In childhood and adolescence, fecal soiling represents a psychologically devastating problem and there is both physical and emotional distress associated with daily rectal enemas. Pediatric fecal incontinence is classified into organic or true fecal incontinence, which is either neurogenic or secondary to anorectal anomalies, and functional fecal incontinence, which is either retention-type due to fecal withholding with overflow or nonretentive-type of fecal soiling with antidiarrheal agents[3]. The majority of cases of fecal incontinence in children are functional, which is fortunately a self-limiting problem and usually disappears at puberty. Organic fecal incontinence may be permanent, as with myelodysplasia; self-limiting, as after a pull-through operation for Hirschsprung's disease; or partial, as with an anorectal malformation[2]. Traditional treatment options for fecal incontinence include dietary modification, drugs, retrograde enemas, manual disimpaction, biofeedback, electrostimulation and cognitive and behavioral interventions that facilitate continence. These options work well in controlling functional fecal incontinence[3,15,16]. However, these options are ineffective in controlling organic fecal incontinence, which may benefit from techniques that completely cleanse the colon and decrease the chance of soiling such as with percutaneous cecostomy. Administration of antegrade enemas through a cecostomy is a therapeutic option for children with severe fecal incontinence. However, there is great variation in postsurgical functional outcomes of these procedures.

In this study, the primary and secondary technical success rates of insertion of cecostomy tubes were 95% and 100%, respectively, which are similar to other studies[8-11,14,15,17]. Long term follow up of patients showed resolution of continuous soiling in all patients with neurogenic fecal incontinence. These results confirm the effectiveness of cecostomy in the management of patients with neurogenic fecal incontinence secondary to spina bifida or traumatic spinal injury, which was reported in other studies[3,18,19]. On the other hand, resolution of continuous soiling was achieved in 5 of 8 patients with anorectal anomalies (62.5%). This result is lower than that of Sierre *et al*[20] in which 90% of their 20 patients (18 of them had anorectal anomalies) reported satisfaction with the procedure. However, our results are similar to other studies that noted there is great variation in postsurgical functional outcomes of cecostomy in the management of patients with anorectal malformations[3,21,22]. The reason for this relatively low success rate can be explained by the complexity of anorectal anomalies, such as the presence of

distal rectovesical or rectovaginal fistulae that may cause soiling.

Regarding post procedure complications in this study, there were no major complications and 11 patients (52%) experienced minor cecostomy tube related problems at some point during the follow-up period. These problems were easily corrected at home and did not require medical or surgical intervention. These complications are within the range of complications noticed in other studies[17,22].

In conclusion, imaging-guided percutaneous cecostomy and antegrade enemas improved symptoms and the quality of life in children with organic fecal incontinence with minor early and late complications. The success rate was more evident in patients with neurogenic fecal incontinence rather than those with anorectal anomalies. However, further evaluation by double-blinded, randomized controlled trials is recommended to define the role of cecostomy in the management of different kinds of organic fecal incontinence.

COMMENTS

Background

In childhood, fecal incontinence represents a psychologically devastating problem. Pediatric fecal incontinence is classified into organic or true fecal incontinence, which is either neurogenic or secondary to anorectal anomalies, and functional fecal incontinence, which is either retention-type due to fecal withholding with overflow or a nonretentive-type of fecal soiling with antidiarrheal agents. The majority cases of fecal incontinence in children are functional, which a self-limiting problem, while organic fecal incontinence is permanent and needs surgical intervention.

Research frontiers

Traditional treatment options of fecal incontinence work well in controlling functional fecal incontinence. These options are ineffective in controlling organic fecal incontinence, which may benefit from techniques that completely cleanse the colon, such as surgical or imaging-guided percutaneous cecostomy.

Innovations and breakthroughs

Imaging-guided percutaneous cecostomy and antegrade enemas improved symptoms and the quality of life in children with organic fecal incontinence with minor early and late complications.

Applications

Administration of antegrade enemas through a percutaneous cecostomy is a therapeutic option for children with organic fecal incontinence.

Terminology

Percutaneous cecostomy is imaging-guided construction of an opening into the cecum with a tube through the abdominal wall. It is an alternative to the traditional surgical technique for cecal decompression.

Peer review

The manuscript is accepted without modification.

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CASE REPORT

Transarterial chemoembolization with miriplatin-lipiodol emulsion for neuroendocrine metastases of the liver

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Abstract

Miriplatin, a cisplatin derivative with a high affinity for iodized oil, is a novel chemotherapeutic agent designed for use in the transarterial treatment of hepatocellular carcinoma. This case report describes our experience with transarterial chemoembolization (TACE) using miriplatin in 2 patients with neuroendocrine liver metastases. A 38-year-old man with multiple neuroendocrine liver metastases was treated by whole liver chemoembolization, and a 35-year-old woman with a single hepatic lesion was treated by superselective chemoembolization. No serious adverse events were noted during the interventional procedures, or during the observation period of 3 mo in either patient. Sufficient iodized oil uptake was observed in the hypervascular lesions on the unenhanced computed tomography (CT) at 7 d after the procedure. Contrast-enhanced CT obtained at 3 mo after chemoembolization revealed that all hepatic lesions were substantially reduced in size irrespective of tumor vascularity or degree of cystic degeneration, although iodized oil accumulation was only marginal for lesions with cystic degeneration. Thus, TACE with miriplatin can be a safe and effective therapeutic option for the treatment of neuroendocrine metastases of the liver.

Key words: Chemoembolization; Liver; Metastatic tumor; Miriplatin; Neuroendocrine tumor

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INTRODUCTION

Neuroendocrine tumors (NET) are a group of carcinomas that secrete various polypeptides with hormonal activity[1]. NETs are sometimes indolent but most cases eventually present with systemic metastases. A significant percentage of patients already have hepatic metastases at the time of initial diagnosis[2]. Hepatic metastases from NET are intrinsically hypervascular, thus necessitating transarterial chemoembolization (TACE) as an alternative option for managing these unresectable liver lesions.

Miriplatin, a novel lipophilic platinum complex with a high affinity for iodized oil, has been developed to treat hepatocellular carcinoma[3]. Miriplatin suspended in iodized oil has demonstrated antitumor effects in hepatic tumors after intrahepatic arterial administration in several animal models[4-6] as well as in humans[7]. However,

transarterial administration of miriplatin in patients with hepatic metastases from NET has not been previously documented. Here, we describe the treatment of two patients with hepatic metastases from NET using TACE with miriplatin suspended in iodized oil, along with the safety and efficacy of miriplatin during the course of this therapy.

CASE REPORT

Case 1

A 38-year-old man, who had undergone surgical resection of NET of the pancreas 15 mo before, was admitted to our hospital for the treatment of multiple liver metastases from NET. The liver lesions were first observed at 8 mo after surgery and gradually increased in size and number despite systemic chemotherapy with octreotide (Sandostatin LAR; Novartis Pharma) and tegafur, gimeracil, and oteracil (TS-1; Taiho Pharmaceutical, Tokyo, Japan). Contrast-enhanced computed tomography (CT) at the time of admission showed numerous early-enhanced tumors throughout the liver, accompanied by several hypovascular tumors with cystic degeneration (Figure 1A). Histopathological examination of needle biopsy specimens of one of the hypovascular tumors revealed a glucagon-producing islet cell carcinoma, a finding compatible with the histopathological results for the surgical specimens of the primary pancreatic tumor. Since systemic chemotherapy had been ineffective, TACE was scheduled 16 mo after the initial surgical resection of the pancreatic NET: the patient opted to receive whole liver treatment instead of lobar treatment in two sessions, despite the increased risk of adverse events. TACE was performed using a coaxially placed 2.4-F microcatheter (Sniper 2; Terumo Clinical Supply, Gifu, Japan) through a 4-F catheter *via* the femoral artery. Selective proper hepatic angiography revealed innumerable hypervascular tumors located throughout the liver (Figure 1B). In order to treat lesions in the whole liver, the right and left hepatic arteries were separately embolized with gelatin particles (Gelpart; Astellas Pharma, Tokyo, Japan) after infusion with 120 mg of miriplatin (Miripla; Dainippon Sumitomo Pharma, Osaka, Japan) suspended in 10 mL of iodized oil (Lipiodol Ultrafluid; Guerbet, Aulnay-sous-Bois, France) at a ratio of 5:2, respectively. The maximum permissible dose in a single session of 120 mg of miriplatin was used, as per the recommendation of the Ministry of Health, Labour and Welfare of Japan, for transarterial administration to the liver. During intra-arterial infusion of miriplatin, the patient complained of slight transient numbness of both limbs; however, no other adverse effects were observed during the course of the therapy. Serum creatinine levels (1.0 mg/dL) were unchanged after treatment. Serum aspartate transaminase, alanine transaminase, and bilirubin levels were transiently elevated from 31 to 214 IU/L, from 26 to 116 IU/L, and from 1.2 to 2.7 mg/dL, respectively, at one day after the treatment, but returned to normal within 6 d. Serum neuron-specific enolase, a tumor marker, remained unchanged

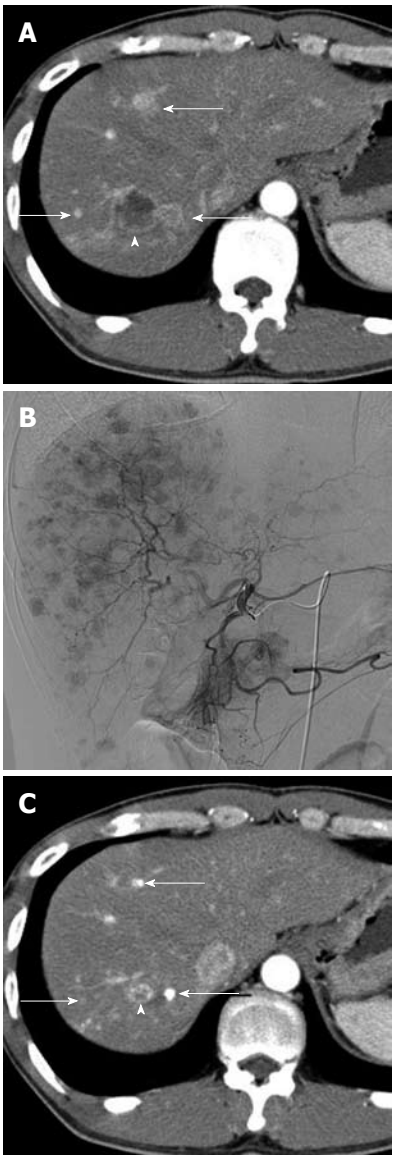

Figure 1 Images obtained in the case of a 38-year-old man with systemic chemotherapy-resistant multiple hepatic metastases from a pancreatic neuroendocrine tumor. A: Arterial phase image of contrast-enhanced computed tomography (CT) shows well-enhanced metastatic tumors (arrows) as well as a hypodense tumor due to cystic degeneration with marginal enhancement (arrowhead); B: A selective hepatic angiogram delineates innumerable hypervascular metastatic tumors throughout the liver; C: Arterial phase image of contrast-enhanced CT at 3 mo after chemoembolization with miriplatin-iodized oil suspension demonstrates a significant reduction in the size of all lesions, with compact accumulation of iodized oil in the hypervascular tumors (arrows). It should be noted that the tumor with cystic degeneration was also reduced in size (arrowhead).

(5.7 ng/mL) before and after treatment with miriplatin. Other tumor markers such as 5-hydroxyindole acetic acid were not investigated. Follow-up CT at 3 mo after TACE revealed a significant reduction in the size of all metastatic lesions, irrespective of tumor vascularity or the degree of cystic degeneration (Figure 1C): the diameter of the largest tumor decreased from 26 mm to 12 mm (size reduction rate, 54%). Prior to TACE, the patient complained of diarrhea, nausea, and epigastric pain. After chemoembolization, however, the patient was almost symptom-free.

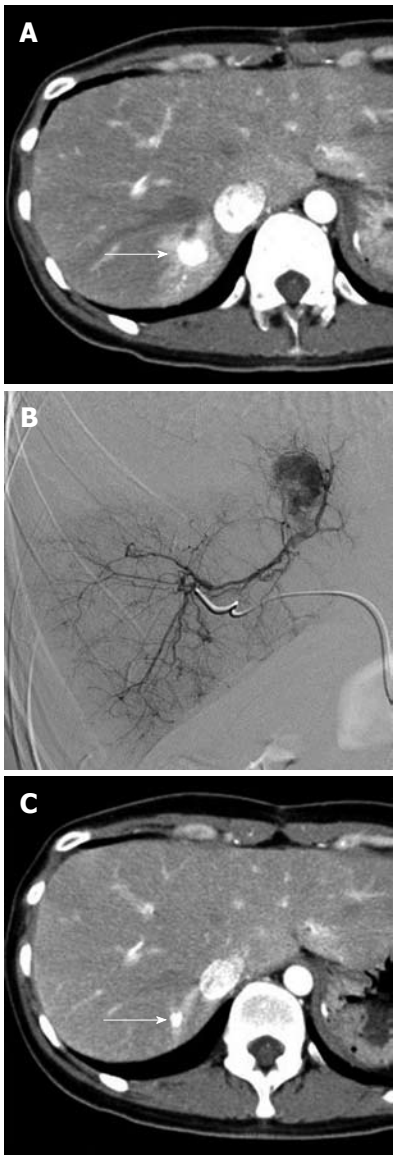

Figure 2 Images obtained in the case of a 35-year-old woman with a solitary neuroendocrine metastasis of the liver. A: Arterial phase image of contrast-enhanced computed tomography (CT) before intervention shows a hyperdense metastatic tumor in the right posterior segment surrounded by arterioportal shunting (arrow); B: Selective angiogram from the right posterior arterial segment delineates a single hypervascular metastatic tumor with arterioportal shunting; C: Arterial phase image of contrast-enhanced CT at 3 mo after chemoembolization with miriplatin-iodized oil suspension demonstrates a significant reduction in tumor size with compact accumulation of iodized oil accompanied by surrounding arterioportal shunting (arrow).

Case 2

A 35-year-old woman with no prior medical history presented at our hospital for the treatment of a pancreatic tumor detected by abdominal ultrasound in a general screening examination. Contrast-enhanced CT at admission showed a hypervascular tumor at the pancreatic tail and a single hypervascular tumor at hepatic segment Ⅶ accompanied by distal arterioportal shunting (Figure 2A). The pancreatic tumor was surgically removed 1 mo after initial diagnosis. Concurrent needle biopsy and histopathological examination of the liver tumor during surgery revealed the tumor to be a well-differentiated neuroendocrine carcinoma compatible with metastasis from the pancreatic NET. One month after surgery, we performed TACE for the hepatic metastasis, using a coaxially placed 2.4-F microcatheter (Sniper 2) through a 4-F catheter *via* the femoral artery. Selective angiography from the right posterior arterial branch revealed a single hypervascular tumor at hepatic segment Ⅶ accompanied by arterioportal shunting (Figure 2B). We embolized the right posterior arterial segment with gelatin particles (Gelpart) following infusion of 70 mg of miriplatin (Miripla) suspended in 3.5 mL of iodized oil. No adverse events were noted during the interventional therapy. Serum creatinine levels (0.5 mg/dL) remained unchanged after the treatment. Serum aspartate transaminase, alanine transaminase, and bilirubin levels were elevated from 15 to 295 IU/L at day 1, from 13 to 389 IU/L at day 4, and from 0.4 to 0.9 mg/dL at day 1 after the treatment, respectively, and returned to normal within 20 d. The eosinophil count gradually increased from 3.3% (before treatment) to 39.8% (at 20 d after treatment) and decreased to 7.8% at 61 d after treatment. Eosinophilia observed in this patient may be attributed to an allergic reaction to miriplatin; however, the precise reason remains unknown. Levels of serum neuron-specific enolase, a tumor marker, remained normal (4.8 ng/mL) after the treatment. Other tumor markers were not investigated. Follow-up CT at 3 mo after TACE confirmed dense iodized oil accumulation in the metastatic lesion with a significant reduction in tumor size (Figure 2C): the diameter of the tumor decreased from 14 mm to 6 mm (size reduction rate, 57%). No local recurrence was evident over a follow-up period of 3 mo.

DISCUSSION

Although several studies have established the beneficial therapeutic effects of TACE for hepatic metastases from NET, there is no consensus on the most effective chemotherapeutic agent for use in this procedure. Various chemotherapeutic agents including doxorubicin, streptozocin, 5-FU, mitomycin C, cisplatin, and a combination of these agents have been used to perform TACE for hepatic metastases of NETs[8]. However, there were no significant differences in the response rate to these agents[8].

Miriplatin is a lipophilic platinum complex designed for the transarterial treatment of hepatocellular carcinoma. This agent can be easily suspended in iodized oil and is gradually released after the oil accumulates in the target tumor[6]. This novel feature of miriplatin can be potentially beneficial for long-acting antitumor effects, thus making it a superior chemotherapeutic agent as compared to other hydrophilic agents. In addition, since the oil-suspended miriplatin remains in the tumor for a long period, its rapid release into the systemic circulation is inhibited, resulting in reduced systemic side effects such as nausea/vomiting, renal damage, and other acute toxic events[7].

In this report, we have described the treatment of hepatic metastases from NET using TACE with miriplatin in

2 patients, who achieved a significant reduction in the size of each lesion as well as sufficient uptake of the iodized oil in hypervascular lesions, without major complications. TACE with miriplatin was effective not only for treating hypervascular metastases but also for hypovascular lesions with cystic degeneration. This might be predominantly attributable to the ischemic effect of arterial embolization, but also to the long-acting antitumor effect of miriplatin accumulated in the wall of the cystic lesions. Furthermore, it is possible that miriplatin accumulated in the hypervascular tumors might be released gradually into the surrounding liver parenchyma or into the bloodstream, resulting in a persistent steady platinum concentration adequate for inhibiting tumor growth within the hypovascular lesions.

In contrast to hepatocellular carcinoma, TACE for NET poses a potential risk of crisis or other hormonal symptoms attributable to acute hormone release due to tumor necrosis. We treated a patient with progressive tumor burden throughout the liver in a single session. This treatment procedure carried the potential risk of hormonal crisis or tumor lysis syndrome. We suggest that NET patients with massive tumor involvement should be treated by selective TACE for separate lesions in multiple treatment sessions: selective TACE has the added benefit of increasing the total amount of chemotherapeutic agent delivered to each lesion as well as reducing the risk of post-embolization syndrome.

At present, there are no data on the effects of TACE on survival benefits in patients with hepatic metastases from NET. The reported median survival times in patients with metastatic NETs after TACE or bland embolization vary considerably, ranging from 13 to 80 mo in various studies[8]. Moreover, the prognostic factors for survival in patients with NET undergoing TACE have not been studied. Since we have treated only 2 cases with a follow-up of 3 mo, the long-term outcomes of TACE with miriplatin for liver metastases from NET, including chronic toxicities, local control, and survival benefits are not yet known. Long-term observations are necessary in order to assess whether miriplatin is superior to other chemotherapeutic agents in the intraarterial treatment of hepatic metastases from NET.

In conclusion, we performed TACE using miriplatin-iodized oil emulsion in 2 patients with neuroendocrine liver metastases and achieved an acceptable response in short-term observation periods, with no serious adverse events. TACE with miriplatin can be a safe and effective therapeutic option for the management of NET hepatic metastases. However, further investigations are required to assess the long-term outcomes of chemoembolization with miriplatin for liver metastases from NET.

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Missed incidental vertebral compression fractures on computed tomography imaging: More optimism justified

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Abstract

Missed incidental vertebral compression fractures on computed tomography (CT) imaging are a common problem. Although numerous publications are available on this topic, recent publications still show a high percentage of such missed fractures. The rate of such missed fractures in the authors department is much lower than that in the reported literature when routine multiplanar reconstructions are used for reporting CT scans. Therefore, a more optimistic view on this topic seems to be justified.

Key words: Vertebral compression fractures; Spine; Multidetector computed tomography

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TO THE EDITOR

I have read with great interest the article by Bartalena *et al*[1] about the dilemma of missed incidental vertebral compression fractures on computed tomography (CT) imaging. As this topic has already been discussed for a long time, the rate of such missed fractures, especially in recent publications, should be concerned. However, the chronological presentation of data suggests that the performance of radiologists is getting worse over time, and this view is in my opinion too pessimistic. Follow-up data of the institutions with poor results after recognition of the problem would be interesting but are lacking. Having the problem of poor visualization of the spine on the primary axial slices in mind, we started reading all scans on a work station (Vitrea 2®, Vital Images) with routine use of multiplanar reconstructions after the implementation of our new multislice CT scanner. A retrospective review of selected CT scans of the chest and abdomen from August this year for 50 patients (25 men and 25 women) at the mean age of 71.6 years (1 mm-thic slice, preliminary visual grading followed by semi-quantitative morphometry with a cut off of 25% height loss of abnormal vertebral bodies) showed that incidental vertebral compression fractures could be identified in 9 patients on CT imaging. In the original reports, such fractures were mentioned in 8 patients. The reporting rate therefore is about 89%. Only 11% of such fractures were not reported and eventually missed. This is better than the reported data, and I believe that other institutions perform CT scans as well. The rate of missed incidental vertebral compression fractures on CT imaging seems to depend highly on the local environment, especially the availability of high quality multiplanar reconstructions and an understanding of

the problem of missed incidental vertebral compression fractures.

In conclusion, a more optimistic view on this topic may be justified as some radiologists may have learned their lessons. However, until more data with improved detection rates are available, more education is thoroughly needed.

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Takao Hiraki's work on interventional radiology

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Figure 1 Takao Hiraki, MD, Assistant Professor, Department of Radiology, Okayama University Medical School, Shikatacho 2-5-1, Okayama 700-8558, Japan.

Abstract

Dr. Takao Hiraki is a scientist carrying out interventional radiology research in the Department of Radiology at Okayama University Medical School, Japan. He has conducted animal and human clinical studies on interventional radiology for various conditions. For example, he clarified the hepatic hemodynamic changes caused by hepatic venous occlusion. He also developed new devices, such as hydrogel coils for the occlusion of the aneurismal sac after an endovascular stent-graft of an aortic aneurysm to prevent endoleakage and small intestinal submucosa-covered stents for transjugular intrahepatic portosystemic shunts. Further, he performed a number of studies on the radiofrequency ablation of lung cancer, mediastinal lymph node metastasis, and computed tomography-fluoroscopy-guided lung biopsies. He intends to continue to dedicate his academic career to expand the role of interventional radiology in clinical medicine.

Key words: Radiology; Interventional radiofrequency ablation; Lung cancer; Computed tomography fluoroscopy; Lung biopsy; Hepatic hemodynamics; Pneumothorax; Mediastinal lymph node metastasis

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INTRODUCTION AND EDUCATIONAL EXPERIENCE

Dr. Takao Hiraki (Figure 1) was born in February 1971 and aspired to become a medical doctor at an early age. He received his medical degree from Okayama University Medical School in Japan in 1995. He embarked upon his scientific career in the Department of Radiology at Okayama University Medical School by clarifying the hepatic hemodynamic changes caused by hepatic venous occlusion with Doppler sonography in 2001[1]. In 2002, Dr. Hiraki worked as a research fellow in the Dotter Interventional Institute, Oregon, USA and carried out various animal studies on interventional radiology[2-5], developing new devices such as hydrogel coils for occlusion of the

aneurismal sac after the endovascular stent-graft of an aortic aneurysm to prevent endoleakage and small intestinal submucosa covered stents for transjugular intrahepatic portosystemic shunts. He returned to Japan in 2004 and was employed as a clinician in the Department of Radiology at Okayama University Medical School. Since then, he has performed a number of animal and human clinical studies, mainly focusing on nonvascular interventional radiology[6-31].

He has received various awards from the Japanese Society of Interventional Radiology, Japan Radiological Society, and Okayama Medical Association for his outstanding academic achievements. In addition, he has been an invited speaker at international meetings, and is a peer reviewer for a number of international scientific journals, such as Lancet Oncology, Cancer, Journal of Vascular and Interventional Radiology, and Cardiovascular and Interventional Radiology. He has been an editorial board member of the World Journal of Radiology since 2009.

ACADEMIC ACHIEVEMENTS

Hepatic hemodynamic change induced by hepatic venous occlusion

Although it has been well known that characteristic findings on hepatic arteriography are observed in patients with primary or secondary Budd-Chiari syndrome, the hepatic hemodynamic changes induced by hepatic venous occlusion were poorly understood. Dr. Hiraki and his coworkers clarified these altered hepatic hemodynamics by hepatic venous occlusion with the use of Doppler ultrasonography[1].

Extracorporeal ultrasonography and a transducer-tipped guide wire were used to evaluate the hemodynamics of the portal vein and hepatic artery, respectively. Such hemodynamics were evaluated before and after balloon occlusion of the right hepatic vein. The maximum peak velocity of the right portal vein was significantly decreased with occlusion. In the majority of cases, hepatic venous occlusion changed the Doppler signal in the portal venous branch of the occluded area from hepatopetal to no signal. The average peak velocity of the right hepatic artery showed a decrease or plateau for 15-30 s after the start of occlusion and then rapidly increased to reach a plateau at approximately 75-90 s with 1.5-2 times higher velocity than before the occlusion. Such altered hepatic hemodynamics are thought to enhance the effect of interventional therapies. Increased hepatic arterial flow may lead to higher concentrations of chemotherapeutic agents during transcatheter chemoembolization; furthermore, decreased portal flow may increase the coagulation volume during radiofrequency (RF) ablation.

Percutaneous RF ablation of mediastinal lymph node metastasis

Hiraki *et al*[6] were the first to perform RF ablation of mediastinal lymph node metastasis. It is quite challenging to perform RF ablation of the mediastinal lymph node because the mediastinum is relatively crowded with major vessels and the trachea. In all of the 7 cases examined, the electrode was successfully inserted into the target lymph node without damaging major vessels. As all of the treated lymph nodes were directly adjacent to the trachea, the trachea was protected from thermal damage by using a balloon filled with chilled saline that was introduced into the trachea at the level of the lymph node. RF ablation was carried out while monitoring the temperature of the tracheal mucosa by using a thermocouple attached to the balloon. Three of the 7 lymph node metastases were locally controlled with 1 or 2 ablation sessions, and thermal damage of the trachea was avoided in 5 of the 7 cases. This preliminary study was considered to have made a substantial impact on the use of RF ablation in the mediastinum.

Percutaneous RF ablation of lung cancer

Local tumor control: Hiraki *et al*[7] clarified local tumor control and the affecting factors. Their preliminary study showed that the local control rates of 342 tumors were 72% at 1 year, 60% at 2 years, and 58% at 3 years. Larger tumors and the use of an internally cooled electrode were revealed as independent risk factors for local failure[7]. When a 2-cm diameter array of multitined expandable electrodes was expanded at the center of tumors that were $\leqslant$ 1 cm and separate from the bronchus, local control was 96%[8].

Besides tumor size and electrode type, tumor type may also affect the local control outcomes because of varying tumor characteristics related to cytology, pathophysiology, and biology. Hiraki *et al*[9] evaluated the local control outcomes of 5 types of cancer: primary lung cancer and pulmonary metastases from colorectal cancer; lung cancer; renal cell carcinoma; and hepatocellular carcinoma. The overall local control rates were 86% and 76% at 1 and 2 years, respectively. According to univariate analysis, metastatic colorectal cancer showed significantly higher local control rates than the other 4 types of cancer. However, multivariate analysis, by which various factors significantly affecting local tumor control can be adjusted among the 5 tumor types, indicated that the relative risk of local progression for a given tumor type was comparable to the risks for the other 4 types. This result indicated that RF ablation may provide similar local efficacy, independent of tumor type.

The notable advantage of RF ablation may be the ability to repeat the procedure in case of local failure. Hiraki *et al*[10] were successful in clarifying that repetition of the procedure significantly improved local control outcomes. The aorta and the heart are substantial obstacles when performing RF ablation for tumors that are located near these structures. Dr. Hiraki and his coworkers showed that while the procedure may be safely performed for these tumors, local efficacy was quite limited with a local control rate of 9%[11].

Patient survival: Hiraki *et al*[12] clarified patient survival

after RF ablation in the lung. For 20 nonsurgical candidates (11 males and 9 females; mean age, 75.6 years) with clinical stage I (I A, n = 14; I B, n = 6) non-small cell lung cancer, the overall survival rates were 90% at 1 year, 84% at 2 years, and 74% at 3 years; the cancer-specific survival rates were 100% at 1 year, 93% at 2 years, and 83% at 3 years with a mean survival time of 42 mo. As for pulmonary metastases from colorectal cancer, the survival rates after RF ablation were 96% at 1 year, 54% at 2 years, and 48% at 3 years during a median follow-up period of 20.1 mo for 27 patients (19 males and 8 females; mean age, 61.6 years)[13]. A significant prognostic factor was the presence of extrapulmonary metastasis[13].

With regard to pulmonary metastases from hepatocellular carcinoma, Hiraki *et al*[14] reported two very promising cases of long-term survival after RF ablation for pulmonary metastasis. Further, they performed a multicenter study to investigate survival after pulmonary metastases from hepatocellular carcinoma[15]. For 32 patients (24 males and 8 females; mean age, 61.9 years), the overall survival rates were 87% at 1 year and 57% at 2 and 3 years during a median follow-up period of 20.5 mon[15]. Significantly better survival rates were obtained for patients with an absence of viable intrahepatic recurrence, Child-Pugh grade A, absence of liver cirrhosis, absence of hepatic C virus infection, and α-fetoprotein levels ≤ 10 ng/mL at the time of RF ablation[15].

Complications: Pneumothorax is the most common complication following RF ablation. Hiraki *et al*[16] evaluated pneumothorax after the RF ablation of lung cancer. The incidence of pneumothorax and chest tube placement for pneumothorax following RF ablation was 52% and 21%, respectively. Risk factors for pneumothorax included male gender, no history of pulmonary surgery, a greater number of tumors ablated, involvement of the middle or lower lobe, and increased length of the aerated lung traversed by the electrode[16].

Although the vast majority of pneumothorax can be treated conservatively or *via* the placement of a chest tube, air leakage rarely persisted despite chest tube placement. Dr. Hiraki and his coworkers reported 2 cases of such intractable pneumothorax caused by the development of a bronchopleural fistula[18]. Dr. Hiraki and coworkers also investigated the relationship between pleural temperature and pleural events (e.g. pneumothorax and pleural effusion) after the RF ablation of lung tumors. The occurrence of pleural effusion was shown to be associated with higher pleural temperatures during the procedure, whereas pneumothorax was not related to pleural temperature[18].

Dr. Hiraki and coworkers also reported rare but important complications following lung RF ablation: 2 cases of needle-tract seeding[19]; 4 cases of brachial nerve injury[20]; 1 case of pulmonary artery pseudoaneurysm[21]; and 1 case of *Aspergillus* infection[22].

Attempts to enhance the efficacy of RF ablation: In an attempt to enhance the local efficacy of RF ablation in the lungs, Dr. Hiraki and his coworkers conducted studies on animal models[23,24]. They noted a heat sink effect in the pulmonary artery and performed RF ablation after pulmonary artery embolization. Pulmonary artery embolization significantly increased coagulation size[23]. Dr. Hiraki and his coworkers also noted that alveolar air was an obstacle to ablation because air has limited electrical and thermal conductivity. They infused saline into the lung parenchyma, resulting in significantly enlarged coagulation[24].

In the clinical setting, Dr. Hiraki and his coworkers completely treated a 4.7 cm hypervascular metastasis from hepatocellular carcinoma that was in contact with the pulmonary hilum[25]. Transcatheter embolization, then RF ablation, and lastly external beam radiation were applied for the treatment of the tumor. Considering that it was a large hilar tumor, the successful result indicated the synergistic effect of embolization and radiation on the efficacy of RF ablation.

Percutaneous computed tomography fluoroscopy-guided lung biopsy: Although conventional computed tomography (CT)-guided needle biopsy is an established diagnostic tool for pulmonary lesions, few large studies have clarified the diagnostic outcomes of the procedure using CT fluoroscopy. Thus, Dr. Hiraki and his coworkers conducted a retrospective study on the diagnostic outcomes of 1,000 CT fluoroscopy-guided lung biopsies performed with 20-gauge coaxial cutting needles[26]. The biopsy results were nondiagnostic in 0.6% of the lesions. The sensitivity and specificity for the diagnosis of malignancy was 94% and 99%, respectively, while diagnostic accuracy was 95%. The significant independent risk factors for diagnostic failure were as follows: the acquisition of 2 or fewer specimens; lesions in the lower lobe; malignant lesions; and lesions < 1.0 cm and > 3.1 cm. It was notable that the diagnostic accuracy reached 93% even for lesions < 1.0 cm. This surprising result was suggested to depend on the use of CT fluoroscopy.

Dr. Hiraki and coworkers also clarified that CT fluoroscopy-guided lung biopsy was useful for the correct diagnosis of lesions for which bronchoscopy-guided biopsy gave false negative results[27]. Further, a high diagnostic yield by CT fluoroscopy-guided lung biopsy was observed for pure ground glass opacity lesions, with a sensitivity of 95%, specificity of 100%, and diagnostic accuracy of 95%[28].

Dr. Hiraki and his coworkers also evaluated the complications following CT fluoroscopy-guided lung biopsy. First, they clarified that the overall incidence of pneumothorax after 1098 CT fluoroscopy-guided lung biopsies was 42% and chest tube placement was required in 12% of pneumothoraces[29]. The significant independent risk factors for pneumothorax were no prior pulmonary surgery, lesions in the lower lobe, greater lesion depth, and a needle trajectory angle of < 45°; those for chest tube placement for pneumothorax were pulmonary emphysema and greater lesion depth[29]. Attention should be paid to patients with a congenital pericardial defect because pneumothorax may result in pneumopericardium[30].

Systemic air embolism is a rare but potential fatal complication following a percutaneous lung biopsy. Dr. Hiraki and his coworkers reported 4 cases of systemic air embolism following a CT fluoroscopy-guided lung biopsy[31]. They observed that the incidence of systemic air embolism was 0.4%. All patients experienced paroxysms of coughing during the procedure. In 3 patients without cardiac or cerebral symptoms, the presence of systemic air was confirmed on postprocedural CT scan images; it was resolved after immediate therapy without causing morbidity. The presence of systemic air was missed in 1 initially asymptomatic patient, resulting in a subsequent neurologic deficit. Considering that the number of reports on this complication is increasing in proportion to increased awareness, the true incidence is probably much higher than expected. Dr. Hiraki and his coworkers are currently conducting a multicenter study to analysis the risk factors for this complication. The results of this study will help to understand its etiology and to design prophylaxis against it.

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World J Radiol 2010 December 28; 2(12): I
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Meetings

Events Calendar 2010

January 4-8
Beaver Creek, Colorado, United States
18th Annual Winter Diagnostic Imaging Update

January 7-9
Leuven, Belgium
4th Leuven Course on Ear Imaging

January 16-17
Hollywood, Florida, United States
The Symposium on Clinical Interventional Oncology

January 17-21
Hollywood, Florida, United States
The International Symposium on Endovascular Therapy

January 21-22
Cairo, Egypt
BGICC Breast Gyne International Cancer Conference

January 21-24
Phoenix, AZ, United States
13th Society for Cardiovascular Magnetic Resonance (SCMR) Annual Scientific Sessions

January 23-23
Atlanta, GA, United States
Emory Winship Cancer Institute: Breast Cancer 2010: Advances in Science, Emerging Data, and Novel Therapeutics

January 25-29
Maui, HI, United States
Musculoskeletal & Neuroradiology MR Imaging Update in Maui

January 27-February 2
Albuquerque, NM, United States
2010 SNM Conjoint Mid-Winter Meetings

January 29-30
Barcelona, Spain
7th European Congress: Perspectives in Gynecologic Oncology

February 7-12
Vail, CO, United States
15th Annual Vail 2010: Multislice CT in Clinical Practice

February 11-13
Las Vegas, NV, United States
5th Annual Symposium on PET/CT and Molecular Imaging

February 16-19
Park City, UT, United States
6th Interventional/ Neurointerventional Conference

February 18-19
London, United Kingdom
Diagnostic and Interventional Radiology

February 18-21
Las Vegas, NV, United States
American Society of Spine Radiology Annual Symposium

February 20-20
Jacksonville, Florida, United States
Mayo Clinic Molecular Markers and Management of Breast Cancer

February 20-21
Bethesda, Maryland, United States
25th Anniversary Washington Neuroradiology Review

February 21-26
Orlando, FL, United States
The Abdominal Radiology Course

February 21-27
Snowmass, CO, United States
16th Annual Snowmass 2010: Clinical Ultrasound

February 22-26
Bethesda, MD, United States
48th Annual Dr. Kenneth M. Earle Memorial Neuropathology Review

February 24-27
Lake Buena Vista, FL, United States
ACRO 2010 American College of Radiation Oncology Symposium: Clinical Radiation Oncology Challenges

February 25-27
Chandler, AZ, United States
Multidisciplinary Head and Neck Cancer Symposium

February 26-27
Brussels, Belgium
10èmes Mises au Point en Imagerie Ostéo-Articulaire

February 27-March 1
Cairo, Egypt
7th Gastroenterology Hepatology & Endoscopy Symposium

February 28-March 4
Scottsdale, AZ, United States
International Congress XXIII on Endovascular Interventions

February 28-March 5
Breckenridge, CO, United States
5th Annual Breckenridge 2010: Musculoskeletal MRI

March 3-6
Las Vegas, Nevada, United States
11th Annual Advances in Breast Imaging and Interventions

March 4-8
Vienna, Austria
European Congress of Radiology (ECR 2010) Annual Meeting

March 5-7
Mt Tremblant, QC, Canada
Neuroimaging and Head & Neck Radiology Update in Mt Tremblant

March 7-11
San Diego, CA, United States
SCBT-MR Masters in Body Imaging: "What's New, What's Hot, What You May Not Have Known"

March 10-13
San Antonio, Texas, United States
Clinical Osteoporosis 2010: An ISCD-NOF Symposium

March 11-13
Barcelona, Spain
EORTC Group Meeting: EORTC Radiation Oncology Group

March 11-13
Hannover, Germany
40. Kongress der Deutschen Gesellschaft für Endoskopie und Bildgebende Verfahren e.V.

March 13-18
Tampa, FL, United states
Society of interventional radiology 35th Annual Scientific Meeting

March 14-17
Park City, UT, United States
14th Annual Park City 2010: MRI in Clinical Practice

March 22-26
Beaver Creek, CO, United States
NYU Radiology Spring Skiing Symposium in Beaver Creek

March 22-26
Maui, HI, United States
18th Annual Spring Diagnostic Imaging Update

March 24-27
San Diego, California, United States
2010 American institute of ultrasound in Medicine Annual Convention Preliminary Program

March 24-27
Barcelona, Spain
7th European Breast Cancer Conference

April 8-12
Shanghai, China
The 26th International Congress of Radiology

September 8-12
Guangzhou, China
Chinese Society of Interventional Radiology, 2010 CSIR

November 28-December 03
Chicago, United States
Radiological Society of North America: 2010 Annual Meeting

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Instructions to authors

GENERAL INFORMATION

World Journal of Radiology (*World J Radiol*, *WJR*, online ISSN 1949-8470, DOI: 10.4329), is a monthly, open-access (OA), peer-reviewed journal supported by an editorial board of 319 experts in Radiology from 40 countries.

The biggest advantage of the OA model is that it provides free, full-text articles in PDF and other formats for experts and the public without registration, which eliminates the obstacle that traditional journals possess and usually delays the speed of the propagation and communication of scientific research results. The open access model has been proven to be a true approach that may achieve the ultimate goal of the journals, i.e. the maximization of the value to the readers, authors and society.

Maximization of personal benefits

The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. So, to realize these desired attributes of *WJR* and create a well-recognized journal, the following four types of personal benefits should be maximized. The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others. (1) Maximization of the benefits of editorial board members: The primary task of editorial board members is to give a peer review of an unpublished scientific article via online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in that field at first hand. As leaders in their field, they have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution; (2) Maximization of the benefits of authors: Since *WJR* is an open-access journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJR* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public reading; (3) Maximization of the benefits of readers: Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion; and (4) Maximization of the benefits of employees: It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wisdom to edit and publish high-quality articles, thereby realizing the maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

Aims and scope

The major task of *WJR* is to rapidly report the most recent improvement in the research of medical imaging and radiation therapy by the radiologists. *WJR* accepts papers on the following aspects related to radiology: Abdominal radiology, women health radiology, cardiovascular radiology, chest radiology, genitourinary radiology, neuroradiology, head and neck radiology, interventional radiology, musculoskeletal radiology, molecular imaging, pediatric radiology, experimental radiology, radiological technology, nuclear medicine, PACS and radiology informatics, and ultrasound. We also encourage papers that cover all other areas of radiology as well as basic research.

Columns

The columns in the issues of *WJR* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Articles: To report innovative and original findings in radiology; (9) Brief Articles: To briefly report the novel and innovative findings in radiology; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJR*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of radiology; and (13) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on the research in radiology.

Name of journal

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CSSN

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SPECIAL STATEMENT

All articles published in this journal represent the viewpoints of the authors except where indicated otherwise.

Biostatistical editing

Statisital review is performed after peer review. We invite an expert in Biomedical Statistics from to evaluate the statistical method used in the paper, including *t*-test (group or paired comparisons), chi-

squared test, Ridit, probit, logit, regression (linear, curvilinear, or stepwise), correlation, analysis of variance, analysis of covariance, *etc*. The reviewing points include: (1) Statistical methods should be described when they are used to verify the results; (2) Whether the statistical techniques are suitable or correct; (3) Only homogeneous data can be averaged. Standard deviations are preferred to standard errors. Give the number of observations and subjects (*n*). Losses in observations, such as drop-outs from the study should be reported; (4) Values such as ED50, LD50, IC50 should have their 95% confidence limits calculated and compared by weighted probit analysis (Bliss and Finney); and (5) The word 'significantly' should be replaced by its synonyms (if it indicates extent) or the *P* value (if it indicates statistical significance).

Conflict-of-interest statement

In the interests of transparency and to help reviewers assess any potential bias, *WJR* requires authors of all papers to declare any competing commercial, personal, political, intellectual, or religious interests in relation to the submitted work. Referees are also asked to indicate any potential conflict they might have reviewing a particular paper. Before submitting, authors are suggested to read "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research: Conflicts of Interest" from International Committee of Medical Journal Editors (ICMJE), which is available at: http://www.icmje.org/ethical_4conflicts.html.

Sample wording: [Name of individual] has received fees for serving as a speaker, a consultant and an advisory board member for [names of organizations], and has received research funding from [names of organization]. [Name of individual] is an employee of [name of organization]. [Name of individual] owns stocks and shares in [name of organization]. [Name of individual] owns patent [patent identification and brief description].

Statement of informed consent

Manuscripts should contain a statement to the effect that all human studies have been reviewed by the appropriate ethics committee or it should be stated clearly in the text that all persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study should be omitted. Authors should also draw attention to the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964, as revised in 2004).

Statement of human and animal rights

When reporting the results from experiments, authors should follow the highest standards and the trial should conform to Good Clinical Practice (for example, US Food and Drug Administration Good Clinical Practice in FDA-Regulated Clinical Trials; UK Medicines Research Council Guidelines for Good Clinical Practice in Clinical Trials) and/or the World Medical Association Declaration of Helsinki. Generally, we suggest authors follow the lead investigator's national standard. If doubt exists whether the research was conducted in accordance with the above standards, the authors must explain the rationale for their approach and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study.

Before submitting, authors should make their study approved by the relevant research ethics committee or institutional review board. If human participants were involved, manuscripts must be accompanied by a statement that the experiments were undertaken with the understanding and appropriate informed consent of each. Any personal item or information will not be published without explicit consents from the involved patients. If experimental animals were used, the materials and methods (experimental procedures) section must clearly indicate that appropriate measures were taken to minimize pain or discomfort, and details of animal care should be provided.

SUBMISSION OF MANUSCRIPTS

Manuscripts should be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Number all pages consecutively, and start each of the following sections on a new page: Title Page, Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgements, References, Tables, Figures, and Figure Legends. Neither the editors nor the publisher are responsible for the opinions expressed by contributors. Manuscripts formally accepted for publication become the permanent property of Baishideng Publishing Group Co., Limited, and may not be reproduced by any means, in whole or in part, without the written permission of both the authors and the publisher. We reserve the right to copy-edit and put onto our website accepted manuscripts. Authors should follow the relevant guidelines for the care and use of laboratory animals of their institution or national animal welfare committee. For the sake of transparency in regard to the performance and reporting of clinical trials, we endorse the policy of the ICMJE to refuse to publish papers on clinical trial results if the trial was not recorded in a publicly-accessible registry at its outset. The only register now available, to our knowledge, is http://www.clinicaltrials.gov sponsored by the United States National Library of Medicine and we encourage all potential contributors to register with it. However, in the case that other registers become available you will be duly notified. A letter of recommendation from each author's organization should be provided with the contributed article to ensure the privacy and secrecy of research is protected.

Authors should retain one copy of the text, tables, photographs and illustrations because rejected manuscripts will not be returned to the author(s) and the editors will not be responsible for loss or damage to photographs and illustrations sustained during mailing.

Online submissions

Manuscripts should be submitted through the Online Submission System at: http://www.wjgnet.com/1949-8470office. Authors are highly recommended to consult the ONLINE INSTRUCTIONS TO AUTHORS (http://www.wjgnet.com/1949-8470/g_info_20100316162358.htm) before attempting to submit online. For assistance, authors encountering problems with the Online Submission System may send an email describing the problem to wjr@wjgnet.com, or by telephone: +86-10-85381892. If you submit your manuscript online, do not make a postal contribution. Repeated online submission for the same manuscript is strictly prohibited.

MANUSCRIPT PREPARATION

All contributions should be written in English. All articles must be submitted using word-processing software. All submissions must be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Style should conform to our house format. Required information for each of the manuscript sections is as follows:

Title page

Title: Title should be less than 12 words.

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Authorship: Authorship credit should be in accordance with the standard proposed by International Committee of Medical Journal Editors, based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

Institution: Author names should be given first, then the complete name of institution, city, province and postcode. For example, Xu-Chen Zhang, Li-Xin Mei, Department of Pathology, Chengde Medical College, Chengde 067000, Hebei Province, China. One author may be represented from two institutions, for example, George Sgourakis, Department of General, Visceral, and Transplantation Surgery, Essen 45122, Germany; George Sgourakis, 2nd Surgical

Department, Korgialenio-Benakio Red Cross Hospital, Athens 15451, Greece

Author contributions: The format of this section should be: Author contributions: Wang CL and Liang L contributed equally to this work; Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; and Wang CL, Liang L and Fu JF wrote the paper.

Supportive foundations: The complete name and number of supportive foundations should be provided, e.g., Supported by National Natural Science Foundation of China, No. 30224801

Correspondence to: Only one corresponding address should be provided. Author names should be given first, then author title, affiliation, the complete name of institution, city, postcode, province, country, and email. All the letters in the email should be in lower case. A space interval should be inserted between country name and email address. For example, Montgomery Bissell, MD, Professor of Medicine, Chief, Liver Center, Gastroenterology Division, University of California, Box 0538, San Francisco, CA 94143, United States. montgomery.bissell@ucsf.edu

Telephone and fax: Telephone and fax should consist of +, country number, district number and telephone or fax number, e.g., Telephone: +86-10-85381892 Fax: +86-10-85381893

Peer reviewers: All articles received are subject to peer review. Normally, three experts are invited for each article. Decision for acceptance is made only when at least two experts recommend an article for publication. Reviewers for accepted manuscripts are acknowledged in each manuscript, and reviewers of articles which were not accepted will be acknowledged at the end of each issue. To ensure the quality of the articles published in *WJR*, reviewers of accepted manuscripts will be announced by publishing the name, title/position and institution of the reviewer in the footnote accompanying the printed article. For example, reviewers: Professor Jing-Yuan Fang, Shanghai Institute of Digestive Disease, Shanghai, Affiliated Renji Hospital, Medical Faculty, Shanghai Jiaotong University, Shanghai, China; Professor Xin-Wei Han, Department of Radiology, The First Affiliated Hospital, Zhengzhou University, Zhengzhou, Henan Province, China; and Professor Anren Kuang, Department of Nuclear Medicine, Huaxi Hospital, Sichuan University, Chengdu, Sichuan Province, China.

Abstract

There are unstructured abstracts (no more than 256 words) and structured abstracts (no more than 480). The specific requirements for structured abstracts are as follows:

An informative, structured abstracts of no more than 480 words should accompany each manuscript. Abstracts for original contributions should be structured into the following sections. AIM (no more than 20 words): Only the purpose should be included. Please write the aim as the form of "To investigate/study/…; MATERIALS AND METHODS (no more than 140 words); RESULTS (no more than 294 words): You should present *P* values where appropriate and must provide relevant data to illustrate how they were obtained, e.g. 6.92 ± 3.86 *vs* 3.61 ± 1.67, $P < 0.001$; CONCLUSION (no more than 26 words).

Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

Text

For articles of these sections, original articles and brief articles, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both. The main text format of these sections, editorial, topic highlight, case report, letters to the editors, can be found at: http://www.wjgnet.com/1949-8470/g_info_20100313183720.htm.

Illustrations

Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Figures should be either Photoshop or Illustrator files (in tiff, eps, jpeg formats) at high-resolution. Examples can be found at: http://www.wjgnet.com/1007-9327/13/4520.pdf; http://www.wjgnet.com/1007-9327/13/4554.pdf; http://www.wjgnet.com/1007-9327/13/4891.pdf; http://www.wjgnet.com/1007-9327/13/4986.pdf; http://www.wjgnet.com/1007-9327/13/4498.pdf. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: …*etc.* It is our principle to publish high resolution-figures for the printed and E-versions.

Tables

Three-line tables should be numbered 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each table. Detailed legends should not be included under tables, but rather added into the text where applicable. The information should complement, but not duplicate the text. Use one horizontal line under the title, a second under column heads, and a third below the Table, above any footnotes. Vertical and italic lines should be omitted.

Notes in tables and illustrations

Data that are not statistically significant should not be noted. $^{a}P < 0.05$, $^{b}P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of *P* values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used. A third series of *P* values can be expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$. Other notes in tables or under illustrations should be expressed as ^{1}F, ^{2}F, ^{3}F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc.*, in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

REFERENCES

Coding system

The author should number the references in Arabic numerals according to the citation order in the text. Put reference numbers in square brackets in superscript at the end of citation content or after the cited author's name. For citation content which is part of the narration, the coding number and square brackets should be typeset normally. For example, "Crohn's disease (CD) is associated with increased intestinal permeability[1,2]". If references are cited directly in the text, they should be put together within the text, for example, "From references[19,22-24], we know that..."

When the authors write the references, please ensure that the order in text is the same as in the references section, and also ensure the spelling accuracy of the first author's name. Do not list the same citation twice.

PMID and DOI

Pleased provide PubMed citation numbers to the reference list, e.g. PMID and DOI, which can be found at http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed and http://www.crossref.org/SimpleTextQuery/, respectively. The numbers will be used in E-version of this journal.

Style for journal references

Authors: the name of the first author should be typed in bold-faced letters. The family name of all authors should be typed with the initial letter capitalized, followed by their abbreviated first and middle initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR). The title of the cited article and italicized journal title (journal title should be in its abbreviated form as shown in PubMed), publication date, volume number (in black), start page, and end page [PMID: 11819634 DOI: 10.3748/wjg.13.5396].

Style for book references

Authors: the name of the first author should be typed in bold-faced letters. The surname of all authors should be typed with the initial letter capitalized, followed by their abbreviated middle and first initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR) Book title. Publication number. Publication place: Publication press, Year: start page and end page.

Format

Journals

English journal article (list all authors and include the PMID where applicable)

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/1949-8470/g_info_20100313185816.htm.

Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics
Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
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