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Contrast-enhanced ultrasound and color doppler ultrasound as guidance for transhepatic artery chemoembolization following three-dimensional conformal radiotherapy

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ABSTRACT

Background: To explore the application of contrast-enhanced ultrasound and color Doppler ultrasonography in the treatment of primary hepatocellular carcinoma (PHC) after Transhepatic Artery Chemoembolization (TACE). ***Materials and Methods***: 49 patients with primary hepatocellular carcinoma were treated with TACE for 3-5 times. Before and after treatment, digital subtraction angiography, contrast-enhanced ultrasound and color Doppler ultrasound were performed. The lesions before and after contrast-enhanced ultrasonography and color Doppler ultrasonography were compared. The residual or recurrence and swelling of lesions before and after contrast -enhanced ultrasonography and color Doppler ultrasonography were analyzed. Detection of the capsule of the lesion. ***Results***: The detection accuracy of contrast-enhanced ultrasound (95.77%) was significantly higher than that of color Doppler ultrasound (84.51%) ($P<0.05$). The detection rate of tumor envelope by contrast-enhanced ultrasound (22.54%) was significantly higher than that by color Doppler ultrasound (9.86%) ($P < 0.05$). The accuracy of detecting residual or recurrent lesions by contrast-enhanced ultrasound (91.67%) was significantly higher than that by color Doppler ultrasound (58.33%) ($P<0.05$). ***Conclusion***: The rate of bone metabolism of perimenopausal women in Xuzhou is not optimistic. We need to pay close attention to the risk of bone metabolism disorder of perimenopausal women with older age, diabetes mellitus and osteoporosis, so as to provide useful help for improving the quality of life of perimenopausal women in Xuzhou.

INTRODUCTION

As reported, primary liver cancer ranks third in prevalence only after gastric cancer and esophageal cancer in the world, with an increase of 600, 000 new cases per year, and in China, it has been severely threatening the health of Chinese people, with the confirmed cases taking up more than 50% of those all over the world [1]. The emergence of evident clinical symptoms in patients with primary liver cancer suggests the mid-term or advanced stage, where 80% of patients are not eligible for surgical resection or chemotherapy, so transhepatic artery chemoembolization (TACE) has become an available choice for these patients [2, 3]. TACE is featured by the minor trauma, safety and few complications, and has, thus, been frequently applied in the treatment of mid -term or advanced primary liver cancer, but there remains no efficient method in evaluating the efficacy of TACE [4]. Currently, the post-TACE efficacy is mostly assessed by the digital subtraction angiography (DSA), ultrasound contrast and color ultrasonography, in which DSA is currently applied in the clinical practice, while the other two methods requires more supporting data to be applied in guiding the TACE for primary liver cancer and assessing the post-TACE efficacy [5, 6].

Complications of TACE include infection, pain, bleeding, and extrahepatic artery thrombosis. Also, due to the possibility of liver and kidney damage, it is recommended to evaluate the function of the liver and kidneys seven days after it. Cirrhosis of the liver, vascular damage and severe liver failure are some of its contraindications. The most common side effect of this method is post-embolization syndrome with symptoms of pain, nausea, vomiting, ileal paralysis, and fever with increased liver enzymes [7]. Radioembolization is a safe procedure for patients whose experiencing side effects of nausea, fatigue, abdominal pain and vomiting (with less intensity and frequency than TACE) have been reported and the rate of tumor necrosis in patients with masses smaller than 3 cm was 90%. But the survival rate by this method is yet not known [8].

Efficiency of three-dimensional conformal radiotherapy (3D-CRT) combination with TACE is unknown in clinical practice [9]. Based on a Cochrane Systematic Review, there is an increased toxicity rate (rise in total bilirubin) in TACE followed by 3-DCRT; while it may be linked to lower all-cause mortality and improved tumor resolution [10].

As the efficiency of these medical procedures are unknown due to the difference performatic variables as well as the guidance in the procedure, there is a need for determining the best method of guiding TACE followed by 3-DCRT using imaging tools as well as Ultrasound to achieve the highest tumor resolution rate.

In this study, with 49 primary liver cancer patients who received the TACE followed by 3-DCRT as subjects, we explored the value of ultrasound contrast and color ultrasonography in guiding the TACE followed by 3-DCRT for primary liver cancer and assessing the post-TACE efficacy.

MATERIAL AND METHODS

Subjects

Upon the approval of the Ethical Board of Pu Ren Hospital Hospital and signature of the written informed consents, we recruited 49 primary liver cancer patients On march 06, 2020（Registration number:2020 NO.32）who underwent the TACE in this hospital as the subjects according to the following inclusion criteria: 1) Patients with the diagnosis of primary liver cancer made by clinicians, and confirmed by DSA; 2) Patients with no more than 5 intrahepatic tumor lesions; 3) Patients with non-diffuse lesions; 4) Patients with no contraindications for computed tomography (CT) or DSA; 5) Patients with no history of severe diseases in heart, brain, kidney or vessels.

Treatment methods

Primary liver cancer patients received TACE for 3 to 5 times. In brief, prior to the surgery, patients were required to take supine position, and following the regular sterilization and draping, they underwent the local anesthesia by injection of 5 mL 2% lidocaine. Then, puncture was performed through the regular site in the right femoral artery to place the arterial sheath. Arteriography was conducted by inserting the hepatic catheter into the celiac trunk, common hepatic artery, and left and right hepatic arteries, and once the tumor was found, hepatic catheter was guided to the tumor-nourishing arteries by superselection to perform the infusion chemotherapy via hepatic artery and thrombosis for tumor vessels, with no ectopic embolism, by Lipiodol. Following the surgery, hepatic catheter and arterial sheath were taken out, followed by the wound compressing and bandaging. Diameter of the microspheres for embolization was chosen upon the lesion size and blood supply, generally ranging from 100 to 700 μm.

3-DCRT

3-DCRT radiotherapy was planned with CMS- Xi0 framework (CMS- Xio TPS, USA). For 6 MV high-energy X-ray radiotherapy, the Varian23EX linear accelerator (California, USA) was used. The number of each individual's radiation doses in 5 days a week was set at 2 Gy / day.

Research methods

Before TACE, and within 2 to 6 months after the last time of TACE (hereinafter named as post-surgery), DSA, ultrasound contrast and color ultrasonography were adopted to perform the examination. In this study, the results of DSA, including the residual lesions, recurrence of lesions and detection of the capsule on the tumor lesions, were taken as the standard to analyze the detection efficiency of ultrasound contrast and color ultrasonography by using the Aloka 10 Color Doppler Ultrasonic Diagnostic Apparatus, with the frequency of probe being set between 3. 5 and 5 MHz. Prior to the ultrasound contrast, liver was scanned by using the regular ultrasound examination to observe the background echo, lesions and their sites, size, number, morphology, boundary and internal echo, and the blood supply to lesion was observed by using the color Doppler ultrasound examination to clarify the feature of lesions. The suspicious lesions or lesions detected by the regular ultrasound detection were taken as targets to identify the optical section plane for scanning, and patients were required to take the training for breath to cooperate with the arteriography. Then, apparatus was tuned into the arteriography mode in real-time double imaging mode, under the optimized condition. Visipaque, as the contrast reagent, was injected through the elbow vein at dose of 1. 5 mL/kg (body weight) and rate of 2. 5 to 3.0 mL/s, and simultaneously, images were dynamically recorded for 6 min to observe the changes in 3 different time phases, *i. e.* the arterial phase from emergence of contrast to 30 s, portal vein phase from 31 s to 120 s and delayed phase from 121 s to 360 s. With the characteristics of the surrounding liver parenchyma, changes in the pattern and scale of enhancement of lesions in different time phases were observed: In arterial phase and portal vein phase, target lesions were observed dynamically, while in the delayed phase, in addition to the observation of the enhancement pattern for target lesions, scanning

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procedures were carried out for the whole liver to search for the low enhancement region besides the target lesions. Tumor residual was evaluated according to the following criteria [7]: With the dynamic enhancement as criteria, significant enhancement of lesion in the arterial phase, or the low density of lesion in the portal vein phase should be considered as tumor residual. If no significant enhancement of lesion was not noted in the arterial phase, the lesion would be considered either as non-tumor residual or tumor residual, regardless of the uneven deposit of contrast. Evaluation of results should be charged by one senior radiologist and one senior interventional radiologist.

Statistical methods

Research data were subjected to the statistical analysis on SPSS version 19.0 software. Enumeration data, such as accuracy, were recorded as percentage, wherein the difference was testified by using the chi-square test. P<0.05 suggested the statistical significance of difference.

RESULTS

In this study, there were 34 men and 15 women, aged between 33 and 54 years old, with an average of 48. 8±6. 7 years old, and a total of 71 tumor lesions were detected, as shown in the table 1. Based on the LCSGJ grading there where 25 patients with type A, 15 with B, and 9 with C LCSGJ grade. Based on the Child–Pugh grading there where 24 patients with type A, 17 with B, and 8 with C LCSGJ grade.

Table 1. Statistics on the pre-TACE evaluation results using the ultrasound contrast and color ultrasonography for the lesions of primary liver cancer.

		Subject characteristics
Sex, male, n (%)		34 (69.38)
Age, year, Mean ± SD		48.8±6.7
LCSGJ grade, n (%)	A	25(51.02)
	B	15(30.61)
	C	9(18.37)
Child–Pugh, n (%)	A	24(48.98)
	B	17(34.69)
	C	8(16.33)

Analysis of the pre-TACE evaluation for the lesions of primary liver cancer

In this study, 49 primary liver cancer patients presented a total of 71 lesions according to the DSA, in which 50 lesions presented the significant tumor staining. For color ultrasonography, 60 lesions were detected, but 11 were not, with an accuracy of 76.92%, sensitivity of 68.09% and specificity of 100%. For ultrasound contrast, 68 lesions were detected, and only 3 lesions were not. Comparison showed no significant difference in the accuracy between the DSA and ultrasound contrast (P>0.05), whereas the ultrasound contrast excels in the accuracy when comparing to the color ultrasonography (P<0.05; table 2).

Table 2. Statistics on the pre-TACE evaluation results using the ultrasound contrast and color ultrasonography for the lesions of primary liver cancer.

Items	Detected	Non-detected	Accuracy
DSA	71	0	/
Ultrasound contrast	67	4	95. 77%
Color ultrasonography	60	11	84. 51%
X^2			5. 071
P			0. 024

Analysis of the post-TACE detection for the tumor capsule of primary liver cancer

In 71 lesions of 49 primary liver cancer patients, 7 post-TACE tumor capsules were detected by using color ultrasonography, with a detection rate of 6. 15% (7/71), while 16 by using ultrasound contrast, with a detection rate of 35. 38% (16/65). Thus, ultrasound contrast also excels the color ultrasonography in detecting the tumor capsule (P<0.05; table 3).

Table 3. Analysis of the post-TACE detection for the tumor capsule of primary liver cancer by using the ultrasound contrast and color ultrasonography.

Items	With tumor capsule	Without tumor capsule	Detection rate
Color ultrasonography	7	64	9. 86%
Ultrasound contrast	16	55	22. 54%
X^2			4. 202
P			0. 041

Detection of the different kinds of lesions or recurrent lesions after TACE

In 71 lesions of 49 primary liver cancer, iodized oil was deposited evenly in 26 lesions, while the remaining 46 lesions had unevenly deposited iodized oil according to the examination by pre-TACE DSA. However, post-TACE DSA manifested 24 recurrent lesions or lesion residual, consisting of 4 lesions with evenly deposited iodized oil and 20 with unevenly deposited iodized oil. Post-TACE ultrasound contrast results demonstrated 22 recurrent lesions or lesion residual, consisting of 3 lesions with evenly deposited iodized oil and 19 with unevenly deposited iodized oil, with an accuracy of 91.67%. Post-TACE color ultrasonography results indicated 14 recurrent lesions or lesion residual, consisting of 0 lesions with evenly deposited iodized oil and 14 with unevenly deposited iodized oil, with an accuracy of 58.33%. Thus, we found that ultrasound contrast excels the color ultrasonography in the accuracy in detecting the lesion residual or recurrent lesions (P < 0.05; table 4).

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Table 4. Detection of the different kinds of iodized oil-deposited residual lesions or recurrent lesions by using the ultrasound contrast and color ultrasonography after TACE for primary liver cancer.

Items	Lesions with evenly deposited iodized oil (n=26)		Lesions with unevenly deposited iodized oil (n=45)		Accuracy in detection
	Number of detected lesion residual or recurrent lesions	Number of non-detected lesion residual or recurrent lesions	Number of detected lesion residual or recurrent lesions	Number of non-detected lesion residual or recurrent lesions	
DSA	4	22	20	25	/
Ultrasound contrast	3	23	19	26	91. 67%
Color ultrasonography	0	26	14	31	58. 33%
X^2					12. 731
P					0. 000

DISCUSSION

Primary liver cancer, as one of the most common malignant tumors in the world, has brought about severe threatens to the life of patients (11-14). As the research regarding the primary liver cancer deepens, the value of surgical, partial resection of liver has been widely accepted (15). However, due to the unapparent clinical symptoms and signs of primary liver cancer in the early stage, many patients have progressed into the mid-term or advanced stage of liver cancer. However, these patients, having suffered long from the liver cirrhosis and the poor liver functional reserve, are no longer suitable for the partial resection of liver. Besides, as reported, the resection rate for Stage I is only 20% or so. Thus, non-surgical procedure is critical to the treatment for patients with mid-term or advanced liver cancer (16-17). Arterial embolization using chemicals is one of the primary treatments for localized and small liver masses that can be used as an adjunct therapy to reduce tumor volume or small metastases before surgery. With the use of gelatin, the blood supply to the tumor is reduced, leading to anoxia and necrosis of the tumor tissue. Intra-arterial radiotherapy is like arterial chemoembolization in which radioactive material Yttrium 90 or iodine 131 enters the tumor directly through an intra-arterial catheter. Each treatment method has its own consequences that appear immediately or shortly after treatment. It should also be noted that cancer can cause a wide range of physical and mental problems for patients (7,8).

TACE, as a method that can eliminate the local lesions, can deliver the high-concentration chemotherapeutics to the tumors, thereby altering the tumor environment, promoting the coagulation and necrosis of tumor, inhibiting the growth of tumor cells, thus becoming the popular choice for the primary liver cancer patients who are no long suitable for the surgical treatment (15-18). In spite of the efficacy of TACE in primary liver cancer, people have not yet developed the efficient method to perform the pre- or post-TACE examination to detect the lesions.

So far, spiral CT, DSA, ultrasound contrast and color ultrasonography have become the major methods for detecting the lesions before TACE and evaluating the TACE efficacy for primary liver cancer (19). CT scanning is mainly applied in detecting the vessels nourishing the tumors and hepatic arterioportal fistulas, where the efficiency in detecting the active tumor tissue is usually reduced by the interference of contrast deposit, whereas DSA, exceling in the high contrast and multi-plane stereoimaging ability, can better display the tumor lesions and their correlation with the surrounding anatomic structure. Besides, DSA has become the most extensive method in clinical practice, with the highest accuracy (17-20). In this study, with the results of DSA as standard, we detected the pre-TACE lesions, and post-TACE recurrent lesions or lesion residual, and the tumor capsule by using the ultrasound contrast and color ultrasonography. As indicated by the pre-TACE examination, comparison showed no significant difference in the accuracy between the DSA and ultrasound contrast ($P>0.05$), whereas the ultrasound contrast excels in the accuracy when comparing to the color ultrasonography ($P<0.05$), suggesting that the accuracy of ultrasound contrast is equivalent to that of DSA, but significantly higher than that of color ultrasonography, in detecting the pre-TACE lesions, which is consistent with the previous findings (21). Following the TACE for primary liver cancer, tumor capsule caused by the thrombosis surrounding the lesions are defensive to the tumors by dampening the growth, infiltration and metastasis of tumor cells (22-23). Therefore, to detect the integrity of tumor capsule is of great clinical significance in evaluating the post-TACE efficacy. Results of this study demonstrated that ultrasound contrast excels the color ultrasonography in the accuracy in detecting the lesion residual or recurrent lesions (P/0.05), indicating that ultrasound contrast can display the condition of tumor capsule after TACE, and, thus, is effective in evaluating the growth, infiltration and metastasis of tumor after TACE. As for the detection of different iodized oil-deposited lesion residual or recurrence after TACE, we found that ultrasound contrast excels color ultrasonography in accuracy ($P<0.05$) since the color ultrasonography can hardly transmit the iodized oil-deposited region, while ultrasound contrast, with the stereoimaging ability, can form the high-contrast image in scanning the lesions inside the liver tumors (24). Hence, ultrasound contrast is superior in assessing the different iodized

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oil-deposited lesion residual or recurrence (25,26).

Other studies have focused on various other modalities in TAEC as well as the study of Kubota *et al.* showed that after TACE in 98 individuals with 28 HCC tumors by injecting an Lipiodol, Lipiodol-CT, power Doppler (PD) sonography, and dynamic MRI were conducted five to 7 days later to assess association of the results with relapse rate in 1 year after TACE. Results showed that all patients undergoing sonography or intratumoral enhancement blood flow lesions on dynamic MRI experienced relapse, expect of Lipiodol-CT findings (27).

CONCLUSION

In conclusion, as compared to the color ultrasonography, ultrasound contrast excels in the accuracy in detecting the lesion that can display the tumor capsules effectively and reflect the different kinds of iodized oil-deposited lesion residual or recurrence. Thus, ultrasound contrast is superior in pre-TACE detection of lesions and assessment of TACE efficacy.

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Author contribution: (G.Zh), (Y.J) and (S.Zh) designed experiments; (L.H) and (M.C) carried out experiments; (G.Zh) and (Z.L) analyzed experimental results; (M.Ch) and (H.X) analyzed sequencing data and developed analysis tool; (Y.J) assisted with Illumina sequencing; (G.Zh), (Y.J) and (H.X) wrote the manuscript.

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