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Short-term effect of metronomic chemotherapy of low-dose Tegafur on patients with primary hepatic carcinoma after radiofrequency ablation

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Abstract. – OBJECTIVE: To investigate the therapeutic effect of metronomic chemotherapy with low-dose Tegafur on patients with primary hepatic carcinoma (PHC) after radiofrequency ablation (RFA).

PATIENTS AND METHODS: PHC patients who underwent RFA were assigned to RFA + Tegafur group and RFA group, respectively. Patients in RFA + Tegafur group received metronomic chemotherapy with low-dose Tegafur after RFA. PHC patients in RFA group only received radiofrequency ablation. Therapeutic efficacy of the two groups was prospectively analyzed within 18 months after RFA. Disease control rate (DCR) and progression-free survival (PFS) in both groups were evaluated.

RESULTS: Follow-up data showed that DCR in RFA + Tegafur group and RFA group at 9 months after RFA was 93.3% and 73.4%, respectively (p=0.038). Within the 18-month follow-up, median PFS in RFA + Tegafur group and RFA group was 16.25 months and 12.25 months, respectively (p<0.001). One-year PFS in RFA group was 53.3%, which was remarkably lower than that of RFA + Tegafur group (83.3%, p=0.012). Moreover, the prevalence of major complications in the present study was 13.3%. No treatment-related death occurred in both groups.

CONCLUSIONS: Metronomic chemotherapy with low-dose Tegafur after RFA can slow down tumor progression and prolong the progression-free survival of PHC patients.

Key Words
Hepatic carcinoma, Radiofrequency ablation, Tegafur, Metronomic chemotherapy, Therapeutic evaluation.

Introduction

Primary hepatic carcinoma (PHC) is a common malignant tumor of the digestive system. The high malignancy, rapid progression, and high mortality of PHC pose great harm to the affected population. Globally, there are 626,000 newly diagnosed PHC cases every year[1,2]. The etiology and pathogenesis of PHC have not been completely elucidated. PHC is currently believed to be related to some certain factors, such as cirrhosis, viral hepatitis, and aflatoxins[3]. For the insidious onset and lack of symptoms, PHC patients often have been in the middle or late stage when first diagnosed. So far, surgical resection and liver transplantation are the main treatments of PHC. However, only 9% to 29% of PHC patients conform to the conditions of surgical resection[4].

Most of PHC patients can only accept non-surgical treatments. In recent years, the minimally invasive treatment of tumors has made great progress, including radiofrequency ablation (RFA), ethanol injection, transarterial chemoembolization (TACE), etc. Among them, RFA is widely applied because of its small trauma, fast recovery, high damage rate of the lesion, easy procedure, and low cost[5,6]. However, incomplete tumor ablation, metastasis in needle track, and increased level of vascular endothelial growth factor (VEGF) are the main shortcomings of RFA. Studies have shown that serum levels of VEGF in PHC patients were increased one month after RFA[7,8]. It is suggested that VEGF can promote the growth of tumor blood vessels, which is closely related to the growth and metastasis of residual cancer cells[9,10].

Metronomic chemotherapy is a continuous low-dose chemotherapy that has a strong anti-angiogenic effect at very low doses[11]. Tegafur (Gimeracil and Oteracil Potassium Capsules) is an oral chemotherapeutic agent derived from fluorouracil. Tegafur presents lower toxicity and longer effect than that of 5-fluorouracil (5-FU). Functionally, Tegafur is applied in the metronomic chemotherapy be-

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cause of its strong anti-angiogenic effect[12]. EACH clinical trials in Asia-Pacific centers have shown that 5-FU has a great therapeutic effect on liver cancer[13], indicating that Tegafur may even perform better in treating PHC. In this study, PHC patients who underwent RFA under the guidance of spiral computed tomography (CT) were assigned to RFA + Tegafur group and RFA group, respectively. Patients in RFA + Tegafur group received metronomic chemotherapy with low-dose Tegafur after RFA. PHC patients only received RFA were regarded as control. Therapeutic efficacy of the two groups was prospectively analyzed.

Patients and Methods

Patients

A total of 114 PHC patients who received the first RFA in our hospital from January 2015 to December 2015 were enrolled. The first surgery and oral chemotherapy treatment of all enrolled patients were completed in our department. Meanwhile, complete clinical and imaging data were obtained before RFA and oral chemotherapy treatment. This study was approved by the Ethics Committee of Qianfoshan Hospital Affiliated to Shandong University. The signed written informed consents were obtained from all participants before the study. Among all the subjects, there were 93 male patients (81.7%) and 21 female patients (18.3%). A total of 80 cases (70%) were younger than 60 years and 34 were (60%) older than 60. According to the Child-Pugh score of liver function, 59 (51.7%) cases were diagnosed as Grade A and 55 (48.3%) were Grade B. Besides, there were 99 (86.7%) cases whose AFP were over 20 and 15 (13.3%) were under 20. For the etiology of PHC, 108 (95%) cases were infected with hepatitis B virus and 6 (5%) were infected with hepatitis C virus. Additionally, there were 65 (56.7%) cases suffered from individual tumor and 49 (43%) suffered from multiple tumors.

Treatment Procedures

RFA group: Briefly, the needle angle and depth were adjusted to detect the tumor location and size. Different RFA needles were selected according to the lesion sizes. Single needle was used in tumor with smaller than 2 cm in diameter and multipolar needle was used in tumor with larger than 2 cm in diameter. When RFA was performed, the target temperature reached 80-100°C with 10-35 min for each tumor lesion. The ablation range should exceed 1-2 cm away from the tumor edge in order to inactivate the infiltration part as much as possible. After the tumor was ablated, the needle track was electrocoaguled to prevent bleeding and tumor metastasis in the track. Postoperative liver protection, hemostasis, and anti-infection treatments were conventionally performed.

RFA + Tegafur group: Based on the procedure performed in RFA group, 25 mg of Tegafur was orally taken every morning and evening. One complete course of disease consisted of 14-d oral medication and 7-d withdrawal. Patients in RFA + Tegafur group persisted in taking Tegafur for at least 2 complete courses. Routine blood test, liver and kidney function were examined during the whole treatment period. Side effects were observed and recorded.

Follow-Up and Therapeutic Evaluation

Enhanced computed tomography (CT) examination of the liver was performed 1 month after RFA. Tumor necrosis evaluation criteria were applied as follows: (1) Complete ablation was manifested as 100% non-enhancement of tumor in enhanced CT or MRI examination; (2) Partial ablation was manifested as over 50% non-enhancement of tumor in enhanced CT or MRI examination; (3) No ablation was manifested as less than 50% non-enhancement of tumor in enhanced CT or MRI examination. All patients were followed up every 3 months for a total of 18 months.

Survival Indicators

Follow-up data were collected to evaluate PFS in both groups. Based on the Response Evaluation Criteria in Solid Tumors (RECIST)[14], complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and disease control rate (DCR) of each patient were evaluated (Table I). Safety evaluation was carried out based on anti-cancer drug toxicity rating criteria of WHO, including the incidence of bone marrow suppression and gastrointestinal toxicity.

Statistical Analysis

Statistical product and service solutions (SPSS19.0, Armonk, NY, USA) statistical software was used for data analysis. Measurement data were expressed as mean ± standard deviation (x±s). Comparison of measurement data was conducted using *t*-test. Categorical data were analyzed by Chi-square or Fisher test. Survival analysis was performed using Kaplan-Meier curve. $p<0.05$ was considered statistically significant.

Table I. Response evaluation criteria in solid tumors (RECIST).

Therapeutic response	Specific standard
CR	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
PR	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
PD	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
DCR=CR+PR+SD/CR+PR+SD+PDx100%	

Note: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), disease control rate (DCR).

Results

Basic Characteristics of Enrolled Patients

A total of 114 PHC patients were enrolled in this study. There were 57 patients in RFA + Tegafur group, including 47 males (83.3%) and 10 females (16.7%). Among them, 42 cases (73.3%) were younger than 60 years and 15 (26.7%) were older than 60. In RFA group, there were 11 (19%) female patients and 46 (81%) male patients. Among them, 38 cases (66.7%) were younger than 60 years and 19 (33.3%) were older than 60. There were no significant differences in gender, age, Child-Pugh grading, AFP level, medical history of viral hepatitis, tumor size, and number of tumors between the two groups (p>0.05, Table II).

Table II. Basic characteristics of enrolled patients.

Content	RFA (n=57)	RFA+S-1 (n=57)	p
Gender			0.5
Male	46	47	
Female	11	10	
Age			0.27
>60	19	15	
≤60	38	42	
Child-Pugh			0.5
A	33	32	
B	24	25	
AFP (μg/L)			0.21
>20	51	47	
≤20	6	10	
Etiology			0.339
HBV	55	53	
HCV	2	4	
Tumor diameter (±s, cm)	2.69±0.77	2.97±0.76	0.169
Number of tumor			0.286
Single	30	34	
Multiple	27	23	

Comparison of Tumor Ablation Rate

One month after RFA, all patients underwent enhanced CT examination of the liver to evaluate the size and enhancement condition of the lesion. Among the 86 PHC nodules in RFA + Tegafur group, 71 nodules were completely ablated, with the tumor ablation rate of 82.9%. However, among the 91 PHC nodules in RFA group, 70 nodules (77.1%) were completely ablated. No significant difference in the tumor ablation rate was found between the two groups (p>0.05, Table III).

Comparison of Disease Control Rate

Disease control rate (DCR) between the two groups after treatment for 9 months was calculated according to RECIST. The proportions of CR, PR, SD and PD in RFA + Tegafur group were 16.7%, 20.0%, 56.6% and 6.7%, respectively, while those in RFA group were 10%, 16.7%, 46.7% and 26.6%, respectively. DCR in RFA + Tegafur group and RFA group was 93.3% and 73.4%, respectively (p=0.038, Table IV).

Table III. Comparison of 1-year PFS.

Group	Number of tumor	Completed ablation	Rate (%)
RFA+S-1	86	71	82.9
RFA	91	70	77.1
p			0.229

Table IV. Comparison of volume change of solid tumor.

Group	CR (%)	PR (%)	SD (%)	PD (%)	DCR (%)
RFA+S-1 (n=57)	16.7	20	56.6	6.7	93.9
RFA (n=57)	10	16.7	46.7	26.6	73.4
p					0.038

Note: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), disease control rate (DCR).

Comparison of Progression-Free Survival Between the Two Groups

There were 41 cases in RFA + Tegafur group whose disease condition did not progress, with the 1-year PFS of 71.9% (41/57). However, the 1-year PFS in RFA group was 45.6% (26/57). A significant difference in 1-year PFS was observed between the two groups (p=0.004, Table V).

Moreover, median PFS in RFA + Tegafur group was 16.25 months after follow-up for 18 months (95% CI: 15.581-16.919), which was 12.25 months in the control RFA group (95% CI: 9.566-14.934). There was a significant difference in the median PFS between the two groups (p=0.008, Table VI, Figure 1).

Comparison of PFS in PHC Patients of RFA + Tegafur Group With Different Liver Function Grades and Tumor Lesions

We compared the effects of liver function grades and the number of tumor lesion on PFS in RFA + Tegafur group. The data showed that the median of PFS was 16.50 months in PHC patients with Child-Pugh A (95% CI: 15.761-17.187). PFS in those with Child-Pugh B was 16.00 months (95% CI: 15.542-16.475). No significant difference was found in PFS between patients with Child-Pugh A and B (p=0.938, Figure 2). Furthermore, the median of PFS in PHC patients with individual tumor was 16.80 months (95% CI: 15.988-17.834). PFS in those with multiple tumors was 16.34 months (95% CI: 15.549-17.152). No significant difference was found in PFS between PHC patients with individual and multiple tumors (p=0.643, Figure 3).

Table V. Comparison of 1-year PFS.

Group	Progression-free	Rate (%)
RFA+S-1 (n=57)	41	71.9
RFA (n=57)	26	45.6
p		0.004

Table IV. Comparison of median PFS after follow-up for 18 months.

Group	n	PFS (month)	*p*=0.008
RFA+S-1	57	16.25	
RFA	57	12.25	

Comparison of Safety Evaluation

Most PHC patients experienced different degrees of fever and transient increased levels of serum transaminases after RFA. In RFA + Tegafur group, 5 (8.8%) cases had endurable pain in ablation area, 2 (3.5%) had diarrhea, and 2 had nausea along with vomiting (3.5%). The above side effects were not severe, which usually were alleviated or disappeared within 1- 2 weeks. We didn't observe significant changes in routine blood test, liver and kidney function during the treatment.

Discussion

PHC is the sixth most frequent cancer (6%) in the world and the third leading cause of death from cancer (9%)[15]. Males are more often affected by PHC than females. More seriously, there are

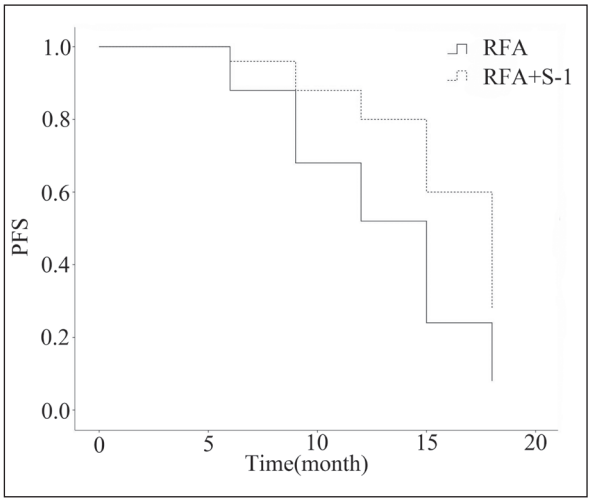

Figure 1. Comparison of PFS between the two groups.

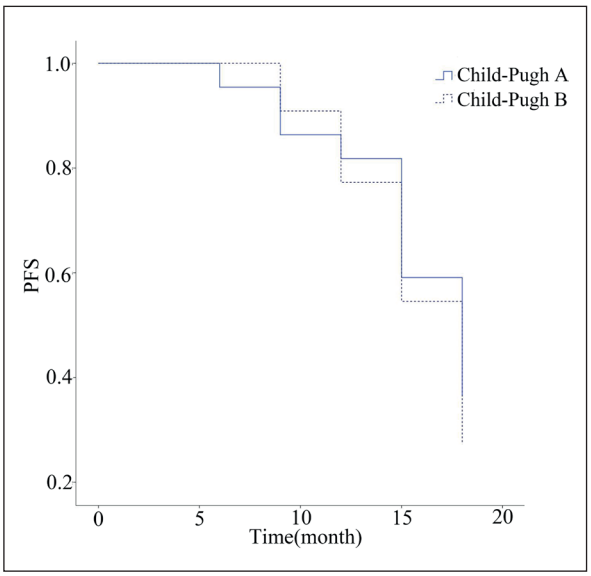

Figure 2. Comparison of PFS in patients of RFA + Tegafur group with different liver function grades.

over 85% of PHC cases in developing countries[16]. So far, viral infection with either hepatitis C virus (HCV) or Hepatitis B virus (HBV) is the chief cause of PHC[17].

Rossi et al[18] performed the RFA of intrahepatic tumors in 39 patients with liver cancer in the 1990s. The results showed that the 1-year, 2-year, 3-year, and 5-year survival rate was 94%, 86%, 68%, and 40%, respectively. No significant difference in the therapeutic efficacy of early-stage liver cancer between RFA and traditional surgical resection has been found[19]. Because of the advantages of small trauma, rapid recovery, high damage rate of the lesion, easy procedure and low cost, RFA is widely performed to treat tumors[20,21]. In addition, serum levels of vascular endothelial growth factor (VEGF) in most PHC patients were remarkably increased[22]. VEGF is capable of regulating angiogenesis, which exerts a crucial role in PHC development[23,24]. It was reported that serum level of VEGF was significantly decreased 1 week after RFA compared with the preoperative level. However, VEGF level was gradually increased at 1 and 3 months after RFA[25].

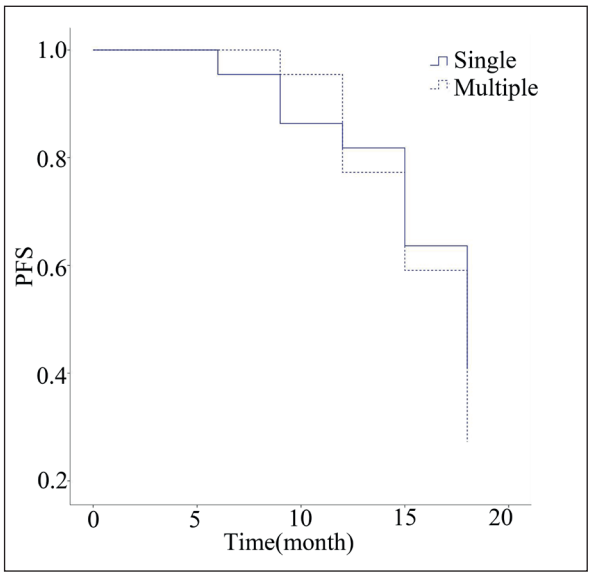

Figure 3. Comparison of PFS in patients of RFA + Tegafur group with different tumor lesions.

Tegafur is an oral chemotherapeutic agent derived from fluorouracil. Studies have shown that oral administration of Tegafur achieved higher blood concentration than 5-FU injection at the same dose[26]. More importantly, gastrointestinal toxicity was obvious after injecting 5-FU[27]. Since the small dose and high compliance of Tegafur, it has been widely applied in treating gastric cancer, colorectal cancer and esophageal cancer[28-31]. Terazawa et al[32] demonstrated that Tegafur achieved good results in treating advanced PHC patients combined with cisplatin arterial infusion chemotherapy.

In the present study, we explored the efficacy and safety of oral administration of Tegafur after RFA for the first time. The results showed that the combined use of RFA and Tegafur metronomic chemotherapy could effectively improve the local tumor ablation and expand the application of RFA. It provides a better control of the local tumor. A meta-analysis conducted by Yi et al[33] suggested that the median of 1-year PFS rate after RFA was 74.1% (42% -90.9%). Our data showed that median of PFS was 16.25 months in RFA + Tegafur group and 12.25 months in RFA group after follow-up for 18 months (p <0.05). Besides, 1-year PFS rate in RFA group was 45.6%, which was 71.9% in RFA + Tegafur group (p=0.004). Additionally, the 1-year PFS rate in RFA + Tegafur group was higher than that reported in other studies.

VEGF is capable of promoting the growth of tumor blood vessels. It is closely related to the growth and metastasis of residual cancer cells. Some studies indicated that serum levels of VEGF in PHC patients were increased after RFA. In our work, metronomic chemotherapy with Tegafur achieved better therapeutic efficacy, which may be explained by the inactivation of tumor cells via inhibiting VEGF expression[34]. Metronomic chemotherapy

can also inhibit tumor-induced autoimmune tolerance and enhance NK cell proliferation, so as to improve the immune function[35]. We demonstrated that PHC patients tolerated well the RFA and Tegafur. No death case occurred during the whole procedure. The prevalence of major complications was as low as 13.3%, which were alleviated within 1-2 weeks. Taken together, metronomic chemotherapy with low-dose Tegafur after RFA can reduce tumor progression and prolong PFS of PHC patients. We provide a new option in treating PHC.

Conclusions

We demonstrated that metronomic chemotherapy with low-dose Tegafur after RFA can slow down tumor progression and prolong the progression-free survival of PHC patients.

Conflict of interest

The authors declared no conflict of interest.

References

1) Parkash O, Hamid S. Are we ready for a new epidemic of under recognized liver disease in South Asia especially in Pakistan? Non alcoholic fatty liver disease. J Pak Med Assoc 2013; 63: 95-99.
2) Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87-108.
3) Yoshimoto S, Loo TM, Atarashi K, Kanda H, Sato S, Oyadomari S, Iwakura Y, Oshima K, Morita H, Hattori M, Honda K, Ishikawa Y, Hara E, Ohtani N. Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome. Nature 2013; 499: 97-101.
4) Marin-Hargreaves G, Azoulay D, Bismuth H. Hepatocellular carcinoma: surgical indications and results. Crit Rev Oncol Hematol 2003; 47: 13-27.
5) Zhu ZX, Huang JW, Liao MH, Zeng Y. Treatment strategy for hepatocellular carcinoma in China: radiofrequency ablation versus liver resection. Jpn J Clin Oncol 2016; 46: 1075-1080.
6) Oh IS, Sinn DH, Kang TW, Lee MW, Kang W, Gwak GY, Paik YH, Choi MS, Lee JH, Koh KC, Paik SW. Liver function assessment using albumin-bilirubin grade for patients with very early-stage hepatocellular carcinoma treated with radiofrequency ablation. Dig Dis Sci 2017; 62: 3235-3242.
7) Wang-Yuan Z, Jiang-Zheng Z, Lu YD, Hao XB, Hong T, Huang F, Lei JH, He ZH, Huang MZ. Clinical efficacy of metronomic chemotherapy after cool-tip radiofrequency ablation in the treatment of hepatocellular carcinoma. Int J Hyperthermia 2016; 32: 193-198.
8) Yuan G, Zeng CL, Zhu DD, Shi XJ. Influences of RFA combined with TACE on the HIF-1alpha and EGR level of patients with primary hepatic carcinoma. Eur Rev Med Pharmacol Sci 2017; 21: 1738-1745.
9) Zhang LQ, Xu XS, Wan Y, Song SD, Wang RT, Chen W, Wang ZX, Chang HL, Wei JC, Dong YF, Liu C. Prognostic implications of estrogen receptor 1 and vascular endothelial growth factor a expression in primary gallbladder carcinoma. World J Gastroenterol 2015; 21: 1243-1250.
10) Yang S, Gao Q, Jiang W. Relationship between tumour angiogenesis and expression of cyclo-oxygenase-2 and vascular endothelial growth factor-A in human renal cell carcinoma. J Int Med Res 2015; 43: 110-117.
11) Miller KD, Sweeney CJ, Sledge GJ. Redefining the target: chemotherapeutics as antiangiogenics. J Clin Oncol 2001; 19: 1195-1206.
12) Kurimoto M, Kimura M, Usami E, Iwai M, Hirose T, Kawachi S, Yoshimura T. Comparing the cost-effectiveness of FOLFIRINOX, nab-paclitaxel plus gemcitabine, gemcitabine and S-1 for the treatment of metastatic pancreatic cancer. Mol Clin Oncol 2017; 7: 125-130.
13) Qin S, Bai Y, Lim HY, Thongprasert S, Chao Y, Fan J, Yang TS, Bhudhisawasdi V, Kang WK, Zhou Y, Lee JH, Sun Y. Randomized, multicenter, open-label study of oxaliplatin plus fluorouracil/leucovorin versus doxorubicin as palliative chemotherapy in patients with advanced hepatocellular carcinoma from Asia. J Clin Oncol 2013; 31: 3501-3508.
14) Krajewski KM, Nishino M, Ramaiya NH, Choueiri TK. RECIST 1.1 compared with RECIST 1.0 in patients with advanced renal cell carcinoma receiving vascular endothelial growth factor-targeted therapy. AJR Am J Roentgenol 2015; 204: W282-W288.
15) Ozer ED, Suna N, Boyacioglu AS. Management of hepatocellular carcinoma: Prevention, surveillance, diagnosis, and staging. Exp Clin Transplant 2017; 15: 31-35.
16) Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90.
17) Miyazaki M. [Liver, pancreas, biliary tract cancer]. Gan To Kagaku Ryoho 2014; 41: 1207.
18) Rossi S, Di Stasi M, Buscarini E, Quaretti P, Garbagnati F, Squassante L, Paties CT, Silverman DE, Buscarini L. Percutaneous RF interstitial thermal ablation in the treatment of hepatic cancer. AJR Am J Roentgenol 1996; 167: 759-768.
19) Feng K, Yan J, Li X, Xia F, Ma K, Wang S, Bie P, Dong J. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. J Hepatol 2012; 57: 794-802.
20) Qi X, Tang Y, An D, Bai M, Shi X, Wang J, Han G, Fan D. Radiofrequency ablation versus hepatic resection for small hepatocellular carcinoma: a meta-analysis of randomized controlled trials. J Clin Gastroenterol 2014; 48: 450-457.
21) Ghanaati H, Alavian SM, Jafarian A, Ebrahimi DN, Nassiri-Toosi M, Jalali AH, Shakiba M. Imaging and imaging-guided interventions in the diagnosis and management of hepatocellular carcinoma (HCC)-Review of evidence. Iran J Radiol 2012; 9: 167-177.

22) Poon RT, Lau C, Pang R, Ng KK, Yuen J, Fan ST. High serum vascular endothelial growth factor levels predict poor prognosis after radiofrequency ablation of hepatocellular carcinoma: importance of tumor biomarker in ablative therapies. Ann Surg Oncol 2007; 14: 1835-1845.
23) Finn RS, Zhu AX. Targeting angiogenesis in hepatocellular carcinoma: focus on VEGF and bevacizumab. Expert Rev Anticancer Ther 2009; 9: 503-509.
24) Chao Y, Li CP, Chau GY, Chen CP, King KL, Lui WY, Yen SH, Chang FY, Chan WK, Lee SD. Prognostic significance of vascular endothelial growth factor, basic fibroblast growth factor, and angiogenin in patients with resectable hepatocellular carcinoma after surgery. Ann Surg Oncol 2003; 10: 355-362.
25) Guan Q, Gu J, Zhang H, Ren W, Ji W, Fan Y. Correlation between vascular endothelial growth factor levels and prognosis of hepatocellular carcinoma patients receiving radiofrequency ablation. Biotechnol Biotechnol Equip 2015; 29: 119-123.
26) Ho DH, Pazdur R, Covington W, Brown N, Huo YY, Lassere Y, Kuritani J. Comparison of 5-fluorouracil pharmacokinetics in patients receiving continuous 5-fluorouracil infusion and oral uracil plus N1-(2'-tetrahydrofuryl)-5-fluorouracil. Clin Cancer Res 1998; 4: 2085-2088.
27) Kodera Y, Ushijima M, Amano H, Suzuki JI, Matsutomo T. Chemical and biological properties of S-1-Propenyl-l-cysteine in aged garlic extract. Molecules 2017; 22. pii: E570. doi: 10.3390/molecules22040570.
28) Mahlberg R, Lorenzen S, Thuss-Patience P, Heinemann V, Pfeiffer P, Mohler M. New perspectives in the treatment of advanced gastric cancer: S-1 as a novel oral 5-FU therapy in combination with cisplatin. Chemotherapy 2017; 62: 62-70.
29) Wu FL, Lu DC, Ying YP, Huang JJ, Zhou AM, Jiang DK, Chen MW, Yang X, Zhou J, Huang HQ, Zeng HY. A meta-analysis reveals s-1-based chemotherapy improves the survival of patients with advanced gastric cancer. Medicine (Baltimore) 2015; 94: e652.
30) Matsuda C, Uemura M, Nakata K, Shingai T, Nishimura J, Hata T, Ikenaga M, Takemasa I, Mizushima T, Kato T, Ikeda M, Ohue M, Murata K, Hasegawa J, Satoh T, Yamamoto H, Sekimoto M, Nezu R, Doki Y, Mori M. Randomized phase II study of S-1 dosing schedule for resected colorectal cancer. BMC Cancer 2015; 15: 452.
31) Chang H, Shin SK, Cho BC, Lee CG, Kim CB, Kim DJ, Lee JG, Hur J, Lee CY, Bae MK, Kim HR, Lee SK, Park JC, Lee H, Kim HI, Chung H, Cha J, Lee YC, Kim JH. A prospective phase II trial of S-1 and cisplatin-based chemoradiotherapy for locoregionally advanced esophageal cancer. Cancer Chemother Pharmacol 2014; 73: 665-671.
32) Terazawa T, Kondo S, Hosoi H, Morizane C, Shimizu S, Mitsunaga S, Ikeda M, Ueno H, Okusaka T. Transarterial infusion chemotherapy with cisplatin plus S-1 for hepatocellular carcinoma treatment: a phase I trial. BMC Cancer 2014; 14: 301.
33) Yi HM, Zhang W, Ai X, Li KY, Deng YB. Radiofrequency ablation versus surgical resection for the treatment of hepatocellular carcinoma conforming to the Milan criteria: systemic review and meta-analysis. Int J Clin Exp Med 2014; 7: 3150-3163.
34) Iwamoto H, Torimura T, Nakamura T, Hashimoto O, Inoue K, Kurogi J, Niizeki T, Kuwahara R, Abe M, Koga H, Yano H, Kerbel RS, Ueno T, Sata M. Metronomic S-1 chemotherapy and vandetanib: an efficacious and nontoxic treatment for hepatocellular carcinoma. Neoplasia 2011; 13: 187-197.
35) Ghiringhelli F, Menard C, Puig PE, Ladoire S, Roux S, Martin F, Solary E, Le Cesne A, Zitvogel L, Chauffert B. Metronomic cyclophosphamide regimen selectively depletes CD4+CD25+ regulatory T cells and restores T and NK effector functions in end stage cancer patients. Cancer Immunol Immunother 2007; 56: 641-648.