Clinical effects of high frequency hyperthermia-assisted irinotecan chemotherapy on patients with middle and advanced colorectal cancer and its safety assessment

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Abstract. Clinical effects of high frequency hyperthermia-assisted irinotecan chemotherapy on patients with middle and advanced colorectal cancer and its safety assessment were investigated. A retrospective analysis was performed on the medical records of 103 patients with middle and advanced colorectal cancer treated in Cancer Center of Guangzhou Medical University from May 2011 to June 2015, including 48 patients receiving irinotecan plus conventional treatment (irinotecan group) and 55 patients receiving high frequency hyperthermia-assisted irinotecan plus conventional treatment (combination group). The treatment effects, severity and incidence of adverse reactions, quality of life and 3-year survival rates of patients were analyzed and compared between the two groups. After 4 courses of treatment, there were statistically significant differences in the proportions of patients with partial remission and objective remission, with those in combination group higher than those in irinotecan group (both $P<0.05$). After 4 courses of treatment, no patient died. After 4 courses of treatment, those that increased in different degrees (all $P<0.05$), compared with those in combination group were significantly higher than those in irinotecan group (all $P<0.05$). The 1-, 2- and 3-year survival rates of patients in irinotecan group were 31.25% (15 cases), 22.92% (11 cases) and 12.50% (6 cases), respectively. Those in combination group were 58.18% (32 cases), 29.09% (16 cases) and 16.36% (9 cases), respectively. The results of K-M survival curve analysis showed that there was no statistically significant difference in survival rate between the two groups of patients ($P=0.050$). High frequency hyperthermia-assisted chemotherapy for patients with middle and advanced colorectal cancer can effectively improve its treatment effects and patients' quality of life, with better treatment safety, worthy of clinical promotion.

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Introduction

Colorectal cancer is the most common malignant tumor of the digestive tract, more common in people over 45 years old and more in male than female, as one of the main causes of human death (1,2). With changes in people's eating habits and lack of physical exercise, the incidence of colorectal cancer has been increasing year by year, with nearly 1,000,000 new patients each year worldwide (3,4). Approximately 81% of its sites are near the anal sphincter. Surgical resection is a very effective treatment method for malignant tumors. However, for most colorectal cancer patients, the preservation of anus and its function is a difficult problem to be treated by surgical treatment, and the most controversial disease in surgical treatment (5,6).

Chemotherapy has always been one of the basic treatment methods for colorectal cancer patients, but as it continues, it becomes unbearable for patients due to its toxic side effects, and decreased efficacy over time. For decades, there has been no new breakthrough in the treatment for colorectal cancer (7,8). FOLFIRI chemotherapy regimen is currently the main chemotherapy drug regimen in middle and advanced colon cancer (9), and some scholars have been trying to improve it. High frequency hyperthermia is a physical therapy, and the energy transmitted is absorbed by cells through the high frequency electromagnetic field. Due to its characteristics of rapid growth, the tumor tissue has disordered structure and abnormal blood vessel growth, which is often squeezed together, with slow heat dissipation. The sustained energy absorption of tumor cells causes a rapid rise in temperature, ultimately resulting in their irreversible damage and death, thereby treating tumors (10,11). However, worldwide there have been few studies related to high frequency hyperthermia combined with chemotherapy.

Therefore, in this study, the clinical effects of high frequency hyperthermia-assisted irinotecan chemotherapy on patients with middle and advanced colorectal cancer were investigated, to analyze the application of high frequency

hyperthermia in patients with middle and advanced colorectal cancer.

Materials and methods

Clinical information. A retrospective analysis was performed on the medical records of 103 patients with middle and advanced colorectal cancer treated in Cancer Center of Guangzhou Medical University (Guangzhou, China) from May 2011 to June 2015, including 48 patients receiving irinotecan plus conventional treatment (irinotecan group) and 55 patients receiving high frequency hyperthermia-assisted irinotecan plus conventional treatment (combination group). All patients were diagnosed with middle and advanced colorectal cancer by pathology combined with imaging in Cancer Center of Guangzhou Medical University. Patients without abnormal leucocyte and lymphocyte counts were eligible for chemotherapy; without drug allergy history and contraindications; without organ dysfunction such as the heart and kidney before operation; without abnormal bleeding or coagulation dysfunction before operation; without portal hypertension, gastrointestinal diseases and past history of tumors; receiving a series of examinations and treatments in the Cancer Center of Guangzhou Medical University after diagnosis; willing to cooperate with medical staff in the Cancer Center of Guangzhou Medical University; and with complete medical records. Patients with a preoperative simple intelligence scale MMSE score of <24 points were excluded; with incomplete medical records; with a history of hepatitis; with mental or learning dysfunction; with excessive diameter of the tumor; with other cardiovascular and cerebrovascular diseases; with other respiratory tract diseases; with other digestive tract diseases; transferred to other hospitals halfway; and taking antibiotics prescribed by other hospitals or with rehabilitation treatment arranged by other hospitals during treatment. The study was approved by the Ethics Committee of Cancer Center of Guangzhou Medical University, Guangzhou, China. Patients or their families signed an informed consent form.

Treatment methods. Irinotecan group was treated with irinotecan plus conventional treatment, and combination group with high frequency hyperthermia-assisted irinotecan plus conventional treatment. Both groups of patients were treated with FOLFIRI chemotherapy regimen, with irinotecan (guoyaozhunzi: H20020687, manufacturer: Jiangsu Hengrui Medicine Co., Ltd., Jiangsu, China) 180 mg/m^2 and calcium folinate (guoyaozhunzi: H33020913, Zhejiang Wansheng Pharmaceutical Co., Ltd., Zhejiang, China) 400 mg/m^2 intravenously infused for 2 h at the same time. 5-fluorouracil (guoyaozhunzi: 05501H201, Xi'an Haixin Pharmaceutical Co., Ltd., Xi'an, China) 400 mg/m^2 was intravenously injected, and then 5-fluorouracil 2,400-3,000 mg/m^2 was pumped within 46 h. Based on this, combination group was treated with high frequency hyperthermia (NRL-004 endogenous field tumor hyperthermia system, Jilin Maida Medical Equipment Co., Ltd., Jilin, China). The height of the electrode plate was adjusted, to lower the upper electrode plate to 5-7 cm on the skin surface corresponding to the lesion, with a working frequency of 13.56 MHz and a treatment power of 1,300-1,400 W. The computer fitting temperature was adjusted to 41-43˚C according to the patient's condition and tolerance, each treatment time for 40-60 min, 2-3 times a week. All treatment methods were every 2 weeks for one course, for a total of 4 courses.

Observation indicators. The Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (12) was used to evaluate treatment effects on the two groups of patients after 4 courses of treatment. Complete remission: The target lesion disappears, and the short diameter of the lymph node does not exceed 10 mm. Partial remission: The sum of the measurement results of the target lesion diameter is reduced by no less than 30% compared to baseline measurements. Stable disease: The measurement results of the target lesion after treatment are between those of partial remission and disease progression. Disease progression: The sum of the measurement results of target lesion diameter is increased by no less than 20% compared to baseline measurements, and the absolute increase is no less than 5 mm. The objective remission rate is the ratio of the sum of patients with complete remission and partial remission in the total number of patients. The CTCAE version 4.0 (13) was used to evaluate the severity of adverse reactions in the two groups of patients, divided into 1-5 grades. The higher the grade is, the more severe the adverse reactions are. The incidence of adverse reactions in the two groups of patients was recorded (neutrophil deficiency and leukopenia), and the treatment safety was evaluated. The QLQ-C30 scale was used to evaluate the quality of life (emotional, role, cognitive, physiological and social function) in the two groups of patients before and after treatment. The higher the score is, the higher the quality of life is.

Statistical analysis. SPSS 19.0 (IBM Corp., Armonk, NY, USA) was used. Count data were expressed as n (%). χ^2 test was used for the comparison of ratio. Measurement data were expressed as mean ± SD. A t-test was used for comparison between the two groups, paired t-test for comparison before and after treatment, K-M survival curve for analyzing the 3-year survival rate of the two groups of patients. $P<0.05$, indicates a statistically significant difference.

Results

General information. Altogether 48 patients were in irinotecan group, including 26 male and 22 female patients, aged 53.76±9.48 years, with a BMI of 23.42±3.47 kg/m^2. Fifty-five patients were in combination group, including 30 male and 25 female patients, aged 54.13±11.29 years, with a BMI of 24.25±3.14 kg/m^2. There was no statistically significant difference in sex, age and BMI between the two groups of patients (all $P>0.05$), and in tumor pathological type, metastasis, site, α-fetoprotein level, hemoglobin level, smoking history, drinking history, education status and place of residence (all $P>0.05$) (Table I).

Analysis of treatment effects on two groups of patients. After 4 courses of treatment, there was no statistically significant difference in the proportions of patients with complete remission, stable disease and disease progression between the two groups of patients (all $P>0.05$), but there were statistically significant

Table I. General information.

Variables	Irinotecan group (n=48)	Combination group (n=55)	χ^2/t value	P-value
Sex [n (%)]			0.001	0.969
Male	26 (54.17)	30 (54.55)		
Female	22 (45.83)	25 (45.45)		
Age (years)	53.76±9.48	54.13±11.29	0.179	0.859
BMI (kg/m^2)	23.42±3.47	24.25±3.14	1.274	0.206
Pathological type [n (%)]			0.406	0.939
Adenocarcinoma	32 (66.67)	34 (61.82)		
Squamous carcinoma	1 (2.08)	2 (3.64)		
Mucous carcinoma	6 (12.50)	8 (14.55)		
Undifferentiated carcinoma	9 (18.75)	11 (20.00)		
α-fetoprotein (ng/ml)	19.42±3.25	19.58±3.64	0.234	0.816
Hemoglobin (g/l)	12.33±3.86	13.49±3.73	1.549	0.125
Metastasis [n (%)]			1.334	0.248
Yes	40 (83.33)	50 (90.91)		
No	8 (16.67)	5 (9.09)		
Site [n (%)]			0.733	0.693
Colon	32 (66.67)	40 (72.73)		
Rectal	9 (18.75)	7 (12.73)		
Colon plus rectal	7 (14.58)	8 (14.55)		
Smoking history [n (%)]			0.149	0.699
Yes	28 (58.33)	30 (54.55)		
No	20 (41.67)	25 (45.45)		
Drinking history [n (%)]			1.258	0.262
Yes	19 (39.58)	16 (29.09)		
No	29 (60.42)	39 (70.91)		
Education status [n (%)]			1.324	0.250
High school and below	21 (43.75)	18 (32.73)		
High school above	27 (56.25)	37 (67.27)		
Place of residence [n (%)]			0.014	0.905
Rural	23 (47.92)	27 (49.09)		
Urban	25 (52.08)	28 (50.91)		

Table II. Analysis of treatment effects on two groups of patients.

Variables	Irinotecan group (n=48)	Combination group (n=55)	χ^2 value	P-value
Complete remission	2 (4.17)	5 (9.09)	0.981	0.322
Partial remission	15 (31.25)	29 (52.73)	4.832	0.028
Stable disease	23 (47.92)	17 (30.91)	3.121	0.077
Disease progression	8 (16.67)	4 (7.27)	2.197	0.138
Objective remission	17 (35.42)	34 (61.82)	7.147	0.008

differences in the proportions of patients with partial remission and objective remission, with those in combination group higher than those in irinotecan group (both P<0.05) (Table II).

Safety assessment of two treatment methods. After 4 courses of treatment, no patient died. There was no statistically significant difference in the severity of adverse reactions between the two groups of patients (P>0.05). The results of the statistical analysis of the incidence of complications in the two groups of patients showed that there was no statistically significant difference in the proportions of patients with neutrophil deficiency, leukopenia, nausea and vomiting,

Table III. Assessment of severity of adverse reactions after 4 courses of treatment in two groups of patients.

Items	Groups		χ^2 value	P-value
	Irinotecan (n=48)	Combination (n= 55)		
1	12 (25.00)	14 (25.45)	0.016	0.901
2	20 (41.67)	22 (40.00)	0.029	0.864
3	12 (25.00)	13 (23.64)	0.026	0.872
4	4 (8.33)	6 (10.91)	0.194	0.660
5	0 (0.00)	0 (0.00)		

diarrhea, scald, anemia and fatigue between the two groups of patients (all P>0.05) (Tables III and IV).

Analysis of quality of life in two groups of patients. There was no statistically significant difference in emotional, role, cognitive, physiological and social function scores between the two groups of patients before treatment (all P>0.05). After 4 courses of treatment, those that increased in different degrees (all P<0.05), compared to those in combination group were significantly higher than those in irinotecan group (all P<0.05) (Table V).

Analysis of 3-year survival rate in two groups of patients. The 1-, 2- and 3-year survival rates of patients in irinotecan group were 31.25% (15 cases), 22.92% (11 cases) and 12.50% (6 cases), respectively. Those in combination group were 58.18% (32 cases), 29.09% (16 cases) and 16.36% (9 cases), respectively. The results of K-M survival curve analysis showed that there was no statistically significant difference in survival rate between the two groups of patients (P=0.05). (Fig. 1).

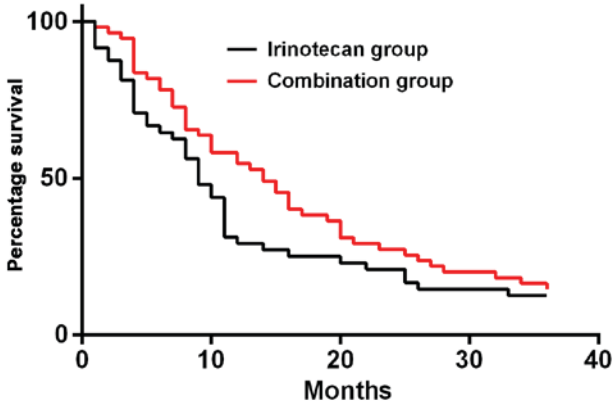

Figure 1. Analysis of 3-year survival rate in two groups of patients. The 1-, 2- and 3-year survival rates of patients in irinotecan group were 31.25% (15 cases), 22.92% (11 cases) and 12.50% (6 cases), respectively. Those in combination group were 58.18% (32 cases), 29.09% (16 cases) and 16.36% (9 cases), respectively. The results of K-M survival curve analysis showed that there was no statistically significant difference in survival rate between the two groups of patients (P=0.05).

Discussion

Colorectal cancer is a type of malignant tumor with high incidence. In some studies, the proportion of colorectal cancer patients that can be found in the early stage is only approximately 2% of all colorectal cancer patients (14). The current chemotherapy regimens for patients with middle and advanced colorectal cancer are mainly FOLFIRI regimen containing irinotecan and FOLFOX regimen containing oxaliplatin. They effectively improve the survival and prognosis of patients, but adverse reactions caused by them in nervous, blood and digestive systems also increase with the increase of chemotherapy course (15,16). In recent years, hyperthermia has been confirmed not to cause adverse reactions such as bone marrow suppression in patients, which has better killing effects on tumor cells (17). However, there are few studies on hyperthermia combined with chemotherapy for patients with middle and advanced colorectal cancer. In this study, the application effects of high frequency hyperthermia combined with FOLFIRI regimen containing irinotecan on patients with middle and advanced colorectal cancer were analyzed, to provide references for the clinical treatment of colorectal cancer.

In this study, the medical records of 103 patients with middle and advanced colorectal cancer were included in strict accordance with inclusion and exclusion criteria. There was no statistically significant difference in the basic data between the two groups of patients after grouping, suggesting that they are comparable in this study, and the results of the study are credible. The results of their efficacy analysis after 4 courses of treatment showed that the proportion of patients with partial remission was significantly higher in combination group than that in irinotecan group, and the objective remission rate was also higher in combination group than that in irinotecan group. It is indicated that high frequency hyperthermia can improve the treatment effects of irinotecan chemotherapy on patients with middle and advanced colorectal cancer.

In recent years, there have been some studies on hyperthermia combined with chemotherapy improving the treatment effects on tumors, which confirm the positive effects of hyperthermia as an adjunctive therapy for treating tumors (18,19). Hyperthermia is one of the oldest cancer treatment methods. The tumor tissue is similar to heat storage due to its structure. Hyperthermia regulates the temperature to 39-45˚C to selectively heat the tumor tissue, thereby killing tumor cells under high temperature. Recent advances based on its biological principles suggest that hyperthermia is an effective radiation sensitizer that is considered as a safe and effective supplementary method for treating tumors (20,21). Adverse reactions caused by chemotherapy have always been one of the most important problems that clinicians want to overcome, seriously influencing the treatment effects on tumors and the use of drugs, which is one of the important reasons that hinder the improvement of chemotherapy regimens in recent decades (22). The results of this study showed that there was no statistically significant difference in the severity and incidence of adverse reactions between the two groups of patients, suggesting that high frequency hyperthermia as an adjunctive therapy does not change the safety of current chemotherapy regimens. However, there was one scalded patient in combination group, which should also be taken seriously.

Table IV. Statistics on incidence of adverse reactions after 4 courses of treatment in two groups of patients.

Variables	Irinotecan group (n=48)	Combination group (n=55)	χ^2 value	P-value
Neutrophil deficiency	19 (39.58)	25 (45.45)	0.361	0.548
Leukopenia	9 (18.75)	10 (18.18)	0.006	0.941
Nausea and vomiting	9 (18.75)	8 (14.55)	0.329	0.566
Diarrhea	1 (2.08)	2 (3.64)	0.219	0.640
Scald	0 (0.00)	1 (1.82)		
Anemia	2 (4.17)	2 (3.64)	0.019	0.889
Fatigue	8 (16.67)	7 (12.73)	0.320	0.572

Table V. Analysis of quality of life in two groups of patients before and after treatment.

Variables	Irinotecan group (n=48)	Combination group (n=55)	t value	P-value
Emotional function				
Before treatment	50.69±11.47	51.33±11.24	0.286	0.776
After treatment	59.72±11.05[a]	64.38±11.67[a]	2.072	0.041
Role function				
Before treatment	46.54±11.25	48.31±11.87	0.774	0.441
After treatment	61.28±11.69[a]	69.84±11.72[a]	3.705	<0.001
Cognitive function				
Before treatment	50.42±12.03	51.75±11.54	0.572	0.569
After treatment	62.74±9.87[a]	74.59±10.66[a]	5.825	<0.001
Physiological function				
Before treatment	45.33±8.72	44.96±9.28	0.208	0.836
After treatment	59.86±9.35[a]	67.33±10.24[a]	3.845	<0.001
Social function				
Before treatment	49.64±10.65	48.27±10.43	0.659	0.512
After treatment	62.78±10.68[a]	72.24±11.45[a]	4.315	<0.001

[a]P<0.05, compared to before treatment in the same group.

It is necessary to pay close attention to changes in patients and make more detailed planning for temperature regulation in hyperthermia. Nevertheless, the effects of hyperthermia on the treatment safety have not been found in some hyperthermia-related reports (23,24). Patients' quality of life in the two groups was also analyzed. For patients with middle and advanced colorectal cancer, improving their quality of life is one of the most important goals of the treatment. The results of this study also showed that the quality of life scores of patients after treatment were higher in combination group than those in irinotecan group. This should be related to the treatment effects of the two methods. The better recovery of patients in combination group can effectively çimprove their quality of life. Some studies (25) have reported that promoting blood circulation and enhancing immune function, hyperthermia can reduce muscle tone, thereby alleviating cancer pain, which should also be an important reason for patients' higher quality of life in combination group. In this study, the results of the 3-year survival rate analysis showed that there was no statistically significant difference in it between the two groups of patients. In related reports, hyperthermia is also found to be able to reduce the risk of poor prognosis of patients, and no difference in the survival rate was found (26,27). This is similar to our findings.

In summary, high frequency hyperthermia-assisted chemotherapy for patients with middle and advanced colorectal cancer can effectively improve its treatment effects and patients' quality of life, with better treatment safety, worthy of clinical promotion.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

ZL conceived and designed the study, collected and interpreted the data, and treated patients. The author read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Cancer Center of Guangzhou Medical University (Guangzhou, China). Patients who participated in this research, signed the informed consent and had complete clinical data.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, Yamazaki K, Shimada Y, Tabernero J, Komatsu Y, *et al*; RECOURSE Study Group: Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med 372: 1909-1919, 2015.
2. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global patterns and trends in colorectal cancer incidence and mortality. Gut 66: 683-691, 2017.
3. Imperiale TF, Ransohoff DF, Itzkowitz SH, Levin TR, Lavin P, Lidgard GP, Ahlquist DA and Berger BM: Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med 370: 1287-1297, 2014.
4. Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW Jr, García FAR, Gillman MW, Harper DM, Kemper AR, Krist AH, *et al*; US Preventive Services Task Force: Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. JAMA 315: 2564-2575, 2016.
5. Koehler BC, Jassowicz A, Scherr AL, Lorenz S, Radhakrishnan P, Kautz N, Elssner C, Weiss J, Jaeger D, Schneider M, *et al*: Pan-Bcl-2 inhibitor Obatoclax is a potent late stage autophagy inhibitor in colorectal cancer cells independent of canonical autophagy signaling. BMC Cancer 15: 919, 2015.
6. Brown DG, Rao S, Weir TL, O'Malia J, Bazan M, Brown RJ and Ryan EP: Metabolomics and metabolic pathway networks from human colorectal cancers, adjacent mucosa, and stool. Cancer Metab 4: 11, 2016.
7. Matsuda C, Munemoto Y, Mishima H, Nagata N, Oshiro M, Kataoka M, Sakamoto J, Aoyama T, Morita S and Kono T: Double-blind, placebo-controlled, randomized phase II study of TJ-14 (Hangeshashinto) for infusional fluorinated-pyrimidine-based colorectal cancer chemotherapy-induced oral mucositis. Cancer Chemother Pharmacol 76: 97-103, 2015.
8. Gustavsson B, Carlsson G, Machover D, Petrelli N, Roth A, Schmoll HJ, Tveit KM and Gibson F: A review of the evolution of systemic chemotherapy in the management of colorectal cancer. Clin Colorectal Cancer 14: 1-10, 2015.
9. Loupakis F, Cremolini C, Masi G, Lonardi S, Zagonel V, Salvatore L, Cortesi E, Tomasello G, Ronzoni M, Spadi R, *et al*: Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. N Engl J Med 371: 1609-1618, 2014.
10. Ji J, Weng Q, Zhang F, Xiong F, Jin Y, Hui J, Song J, Gao J, Chen M, Li Q, *et al*: Non-small-cell lung cancer: Feasibility of intratumoral radiofrequency hyperthermia-enhanced herpes simplex virus thymidine kinase gene therapy. Radiology 288: 612-620, 2018.
11. Thomas RG, Moon MJ, Lee H, Sasikala AR, Kim CS, Park IK and Jeong YY: Hyaluronic acid conjugated superparamagnetic iron oxide nanoparticle for cancer diagnosis and hyperthermia therapy. Carbohydr Polym 131: 439-446, 2015.
12. Beriwal S, Shukla G, Shinde A, Heron DE, Kelley JL, Edwards RP, Sukumvanich P, Richards S, Olawaiye AB and Krivak TC: Preoperative intensity modulated radiation therapy and chemotherapy for locally advanced vulvar carcinoma: Analysis of pattern of relapse. Int J Radiat Oncol Biol Phys 85: 1269-1274, 2013.
13. Bui QC, Lieber M, Withers HR, Corson K, van Rijnsoever M and Elsaleh H: The efficacy of hyperbaric oxygen therapy in the treatment of radiation-induced late side effects. Int J Radiat Oncol Biol Phys 60: 871-878, 2004.
14. van de Wetering M, Francies HE, Francis JM, Bounova G, Iorio F, Pronk A, van Houdt W, van Gorp J, Taylor-Weiner A, Kester L, *et al*: Prospective derivation of a living organoid biobank of colorectal cancer patients. Cell 161: 933-945, 2015.
15. Heinemann V, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, Heintges T, Lerchenmüller C, Kahl C, Seipelt G, *et al*: FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): A randomised, open-label, phase 3 trial. Lancet Oncol 15: 1065-1075, 2014.
16. García-Carbonero R, van Cutsem E, Rivera F, Jassem J, Gore I Jr, Tebbutt N, Braiteh F, Argiles G, Wainberg ZA, Funke R, *et al*: Randomized phase II trial of parsatuzumab (anti-EGFL7) or placebo in combination with FOLFOX and bevacizumab for first-line metastatic colorectal cancer. Oncologist 22: 375-e30, 2017.
17. Rahman MA, Matsumura Y, Yano S and Ochiai B: pH-responsive charge-conversional and hemolytic activities of magnetic nanocomposite particles for cell-targeted hyperthermia. ACS Omega 3: 961-972, 2018.
18. Quinto CA, Mohindra P, Tong S and Bao G: Multifunctional superparamagnetic iron oxide nanoparticles for combined chemotherapy and hyperthermia cancer treatment. Nanoscale 7: 12728-12736, 2015.
19. Wan Y, Wang X, Zheng N and Shi J: Clinical research of selective bronchial artery infusion and chemotherapy of lung cancer. Zhongguo Fei Ai Za Zhi 6: 378-380, 2003 (In Chinese).
20. Yao X, Niu X, Ma K, Huang P, Grothe J, Kaskel S and Zhu Y: Graphene quantum dots-capped magnetic mesoporous silica nanoparticles as a multifunctional platform for controlled drug delivery, magnetic hyperthermia, and photothermal therapy. Small 13: 1602225, 2017.
21. Datta NR, Ordóñez SG, Gaipl US, Paulides MM, Crezee H, Gellermann J, Marder D, Puric E and Bodis S: Local hyperthermia combined with radiotherapy and-/or chemotherapy: Recent advances and promises for the future. Cancer Treat Rev 41: 742-753, 2015.
22. Ma L, Ruan L, Liu H, Yang H and Feng Y: ABCB1 C3435T polymorphism is associated with leukemia susceptibility: Evidence from a meta-analysis. Onco Targets Ther 8: 1009-1015, 2015.
23. Gao LZ, Gao EM, Bai YF, Su HL, Zhang F, Ge MQ, Liu DL and Huang YK: Hyperthermic intraperitoneal chemotherapy plus high-frequency diathermic therapy followed by intravenous chemotherapy versus intravenous chemotherapy alone for postoperative adjuvant treatment of gastrointestinal cancer: A comparative research study. J BUON 21: 1510-1517, 2016.
24. Narayan P, Crocker I, Elder E and Olson JJ: Safety and efficacy of concurrent interstitial radiation and hyperthermia in the treatment of progressive malignant brain tumors. Oncol Rep 11: 97-103, 2004.
25. Chi MS, Yang KL, Chang YC, Ko HL, Lin YH, Huang SC, Huang YY, Liao KW, Kondo M and Chi KH: Comparing the effectiveness of combined external beam radiation and hyperthermia versus external beam radiation alone in treating patients with painful bony metastases: A phase 3 prospective, randomized, controlled trial. Int J Radiat Oncol Biol Phys 100: 78-87, 2018.
26. Gani C, Schroeder C, Heinrich V, Spillner P, Lamprecht U, Berger B and Zips D: Long-term local control and survival after preoperative radiochemotherapy in combination with deep regional hyperthermia in locally advanced rectal cancer. Int J Hyperthermia 32: 187-192, 2016.
27. Chen K, Zhu S, Xiang G, Duan X, He J and Chen G: Ablation effects of noninvasive radiofrequency field-induced hyperthermia on liver cancer cells. Saudi Pharm J 24: 329-332, 2016.