Int J Clin Exp Med 2016;9(2):5206-5212
www.ijcem.com /ISSN:1940-5901/IJCEM0017709

Original Article

Clinical efficacy of accurate radiotherapy associated slow releasing cisplatin to the primary liver cancer

Zhiqiao Xu, Peijie Liu, Yan Zhang, Xin Gao

Central Hospital Cancer Center, No. 85 Hedao Street, Kaifeng 475001, Henan Province, China

Received October 12, 2015; Accepted January 27, 2016; Epub February 15, 2016; Published February 29, 2016

Abstract: The primary liver cancer (PHC) shares a substantial morbidity and mortality throughout the world, whose survival rate for 5 years only retains 3% to 5%. This study was to discuss the clinical efficacy of accurate radiotherapy associated slow releasing cisplatin to the primary Liver Cancer. 80 patients with primary Liver Cancer before treatment were randomly divided into the treatment group (n=40, medicine imbeding+radiotherapy) and the control group (n=40, merely radiotherapy). The medicine dose of imbeding was decided by the size of tumor, the patient's and the general condition of the patient, All patients accepted the three dimensional conformal Accurate radiation therapy. To evaluate the curative effect after four months' follow-up. The effective rate (RR) and the untoward effects between the two groups were observed and compared, the overall survival (OS) was analyzed. The RR of the treatment group was higher than the control group (77.5% vs 55.7%, x^2=4.528, P=0.03). The OS of the treatment group was longer than the control group (13.95±0.618 months vs 10.775±0.631 months x^2=10.535, P=0.001). The untoward effects were not significantly different between the two groups. The therapy of three dimensional conformal Accurate radiotherapy associated slow releasing cisplatin to the primary Liver Cancer can improve the curative effect and the overall survival of primary hepatic carcinomahe patients, And the patients can tolerant the untoward effects.

Keywords: Accurate radiotherapy, slow releasing cisplatin, tumor embedding, primary liver cancer, effective rate, overall survival

Introduction

The Primary Liver Cancer (PHC) shares a substantial morbidity and mortality throughout the world, whose survival rate for 5 years only retains 3% to 5% [1]. The current survival rate is even below 10% [2]. China is a high incidence area vulnerable to the PHC. One of every two new cases regarding PHC occurs in China, with the high mortality rate seconded to liver cancer [3]. Most of PHC sufferers in China simultaneously suffer from the chronic hepatitis B [4], liver cirrhosis and other liver diseases. The early stage of the PHC is not easy to discover. When being confirmed, 80% of the sufferers have already missed the appropriate time for surgeries. In a few cases where surgery possibility is still retained, there are approximately 50% of the sufferers had got the postoperative recurrence or suffered distant metastasis [5]. Thus, it remains essential to research the non-surgery therapies towards PHC. The current therapies contain the Transhepatic Arterial Embolization treatment, radiofrequency ablation, cryotherapy, chemotherapy, radiotherapy, biotherapy and targeted drugs, whose curative effects, however, are not so satisfactory [6]. Recent years witnessed the increasing clinical research about the slow releasing drugs in treatment of PHC and their certain achievements. This research undertakes the comparison between the curative effect of slow releasing cisplatin associated with 3DCRT and that of the 3DCRT. Through comparing the clinical curative effects, survival times and untoward reactions, this research aims at exploring the effective clinical treatment to PHC.

Materials and methods

Selective cases

This research selects 80 cases of the PHC sufferers from March of 2007 to July of 2011 in

Table 1. Comparison between the treatment group and the control group in terms of clinical data

	The Control Group (n=40)	The Treatment Group (n=40)	X^2	*P*
Gender			1.257	0.262
Male	24	19		
Female	16	21		
Age			3.232	0.072
<60 Younger than 60	14	22		
≥60 older than 60 (includes 60)	26	18		
Pathological patterns			1.25	0.264
PHC	34	30		
Cholangio carcer	6	10		
Diameter of tumor			2.813	0.094
>10 cm	11	5		
<10 cm	29	35		
Levels of Liver Functions			2.581	0.108
Level A	28	34		
Level B	12	6		
Viral hepatitis			1.726	0.189
Positive	33	28		
Negative	7	12		
Liver cirrhosis			0.392	0.531
Positive	7	5		
Negative	33	35		
KPS			1.805	0.179
≥80 Larger than 80 (includes 80)	18	24		
>80≥60 Between 60 to 80 (includes 60)	22	16		

the Kaifeng Central Hospital. The selection standards are as followed: All the sufferers had gone through the CT examination, AFP chemotherapy or aspiration biopsy. They should have been scanned by CT to verify that they had the measurable complete cytoreductions. Their liver functions were in level A or level B (child levels) while blood routines, renal functions all fell into the normal range. Their electrocardiogram also demonstrates a normal tendency. They should be free of any chemoradiotherapies and other antineoplastic treatments. They survival times were predicted to be longer than 3 months. Their KPS was lager or equal to 60 points. Exclusion Criteria: Not suitable to radiotherapy, liver function was in C level (child level), renal function abnormal, Blood Coagulation Index abnormal and suffering from diffuse liver cancer.

Allocate 40 cases into the treatment group and another 40 cases into the control group. The treatment group was given the slow releasing cisplatin together with the 3DCRT treatment while the control group was given the 3DCRT treatment. The treatment group contains 19 male sufferers and 21 female ones. 5 of the sufferers had diameters longer than or equal to 10 cm while 35 sufferers shorter than 10 cm. 22 of the sufferers were older than 60 years old while the remaining ones were younger than 60. 30 of the sufferers had the PHC while 10 suffered from the cholangio carcer. 34 of them were in level A of the liver function while 6 of them in level B. 28 cases suffered from the viral hepatitis while the remaining 12 cases were non-viral hepatitis sufferers. 5 cases demonstrated the liver cirrhosis while 35 cases did not suffer from this disease. 24 cases shared the above-80 KPS while the KPS for 16 cases was between 60 to 80 points. Regarding the control group, there were 24 males versus 16 females. 11 sufferers had an above-11-cm diameter while 29 cases below 10 cm. 14 cases were older than 60 years old. The remaining ones were younger conversely. 34 cases

Table 2. Comparison between the treatment group and the control group in terms of curative effect

	Case	CR	PR	SD	PD	RR	x^2	P
Treatment Group	40	2	29	6	3	77.50%	4.528	0.003
Control group	40	1	21	10	8	55.00%		

Table 3. Comparison between the control group and the treatment group in terms of total survival time

	Case	Total Survival Time (Month)	x^2	P
Treatment Group	40	13.95±0.618	10.535	0.001
Control Group	40	10.775±0.631		

suffered from the PHC while 6 cases referred to the cholangio carcer. 28 sufferers were in the Level A of liver function while 12 in the Level B. 33 cases were with the viral hepatitis while 7 sufferers had the non-viral hepatitis. 7 sufferers in the group had the liver cirrhosis while 33 did not. 18 sufferers had the KPS above 80 points while 22 between 60 and 80 points. Two groups of cases demonstrated no statistical difference in terms of clinical features (**Table 1**).

Observation items and criteria

Researchers would visit all the sufferers in both of the groups one time monthly. They would be required to have the CT reexamination four months after the treatment. The results of the reexamination would be taken into the comparison with the measurements of the targeted lesion demonstrated by the CT films four months before the treatment. This research concluded the survival times and the untoward reactions of the sufferers into a list and applied the statistical approach to this list.

Evaluation on curative effects: four months right after the treatment, researchers would adopt the Response Evaluation Criteria in Solid Tumors by WHO for assessing the curative effects (CT would be conducted in the same position before and after the treatment to measure the maximum diameter and vertical diameter of the lesion in the same-layer image). The purpose was to observe the response rates, survival times and untoward reactions for two groups.

Response rate (RR): (CR+RR)/n. Complete Remission (CR): All the measureable lesions completely disappeared for 4 weeks. Partial Remission (PR): The sum of products of the maximum diameters and the maximum vertical diameters of each lesion reduced by over 50%, which lasted for at least 4 weeks. Stable Disease: the sum of products of two vertical diameters for each lesion reduced by more than 50% or increased by more than 25%, which should last for at least 4 weeks without new lesions. Progress Development: the sum of the product of two diameters for the lesions was over 25%, or the new lesions appeared.

Overall survival: this term defines the time between the patient's first visit and the death date (or the last follow-up visit).

Evaluation on the untoward reaction: Evaluation will be conducted based on the classificatory criteria for the accurate and sub-accurate untoward reactions of the anti-cancer drugs by WHO.

Follow-up clinic approach: undertake telephone follow-up or follow-up visit periodically. After all courses of the treatment, undertake the visit one time per month. Evaluate the curative effect through CT reexamination after four months. The last follow-up visit was conducted in September of 2013.

Research methodologies

Drugs: Slow releasing cisplatin for implant provided by the Anhui Zhongren Technological Limited Company, Anhui, China., Ltd with a diameter at 0.8 mm × 2.0 mm. Each pill contains cisplatin 20 mg. (Batch Number: 20071215, 20091324). The effective radius is about 1 cm. The time of effective local concentration lasts for 240 hours. The guiding device is color Doppler ultrasound or CT.

Devices: Puncture needles for implant; 23EX linear accelerator provided by USA Varian Inc.; PQ6000 Spatial CT produced by Picker USA; ACUSON X300 color Doppler ultrasound produced by Siemens.

Operational approaches: Accurate radiation therapy: patients in two groups would be given

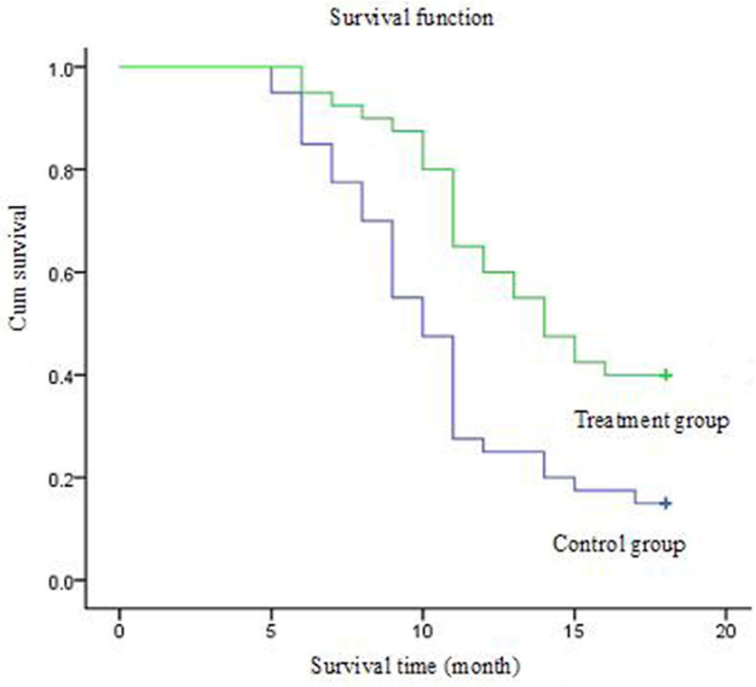

Figure 1. Comparison between the control group and the treatment group in terms of total survival time.

the 3DCRT with dose at 50 Gy (Due to the fact that most of the sufferers had the medical history of viral hepatitis and some of the sufferers had the liver functional abnormality or liver cirrhosis, the moderate radiological doses were adopted in an attempt to reduce the possibility of radiation induced liver injury). Slow Release Cisplatin Implant: The doses and needle insertion methods to be adopted were dependent on the tumor size, age, general situation of patients in the treatment group and the treatment plans. Under the guidance of CT or color Doppler ultrasound, this research undertook the multipoint punctures to implant the Cisplatin. Implant one particular every 1 to 1.5 cm^3. The 3DCRT would start within 48 hours after the implant (observation revealed no hemorrhage, infection or other complications).

Statistics

SPSS 13.0 would be applied as the statistical tool for analysis on the clinical features of two groups. The chi-square test (or Fisher Precise Inspection Analysis) was used to analyze the response rate. The survivorship curve was produced by the logistic regression analysis and Kaplan-Meier method. All statistical analysis process would define the significance testing as α=0.05.

Outcome

Response rate

The Response Rate for the treatment group and the control group were respectively 77.5% and 55.0%. Comparing these two groups, the result turned out to be x^2=4.528, *P=0.003,* which demonstrated the statistical difference. See **Table 2** for more details.

Survival time

The total survival time for the treatment group was 13.95±0.618 months. 95% CI was (12.738-15.162). The one for the control group was 10.775±0.631 months. The 95% CI was (9.538-12.012). They demonstrated the statistically significant difference. See **Table 3** and **Figure 1** for details.

Untoward reactions

The untoward reactions for both groups were reflected to: radiation induced liver disease, liver functional abnormality and I-II degree of myelosuppression. The main features were demonstrated by the reduction of leukocytes, I-II degree of nausea, emesis and other gastrointestinal reactions. These reactions were released after being correctly treated. Both groups showed no obvious difference in terms of untoward reactions. See **Table 4**.

Complications

2 cases of the treatment group suffered from the circumscribed peritonitis, 1 case had the pneumothorax. After being treated with the anti-infectious therapy and taking enough rest, they got released. No complications were found in the control group.

Discussion

PHC is one of the common clinical cancers. It is characterized by its concealed nature, high

Table 4. Comparison between the treatment group and the control group in terms of the major untoward reactions

Group	Case	Radiation induced liver disease	*P* value	Liver functional abnormality	*P* value	Myelosuppression	*P* Value	Nausea, emesis	*P* Value
The control group	40	7	0.189	14	0.072	16	0.262	28	0.108
The Treatment group	40	12		22		21		34	

severity, poor curative effect, easy relapse and metastasis and difficult treatment. The morbidity and mortality both go up gradually. Current treatments offered to this disease contain surgeries, radiotherapy, chemotherapy, biotherapy, radiofrequency ablation, freeze, intervention and others, despite of the poor curative effects. The external beam radiotherapy technology can be applied via certain processes, including radiotherapy for the entire liver, local radiotherapy, the entire liver moving strip radiotherapy, local superfractioned radiotherapy, 3DCRT and accurate intensity modulated radiotherapy, among which the accurate radiotherapy remains the mainstream technology for the external beam radiotherapy. The hepatic tissues are subjected to the late-response tissue category [7]. The hepatocellular carcinoma will not vary in the earlier stage of the treatment, which will subsequently shrink or disappear from 2 to 3 months after the treatment [8]. Cisplatin is the poisonous substance with broad spectrum, aperiodicity and specificity, which has been widely applied to the gastrointestinal tumors [9]. The conventional pharmacy intravenous only retains the limited drug concentration when it reaches the local lesions of the tumors, leading to its difficulty of effectively killing the tumor cell [10]. Increase of the doses and enhancement of the plasma concentration, however, will inevitably strengthen the severe untoward reactions in stomach and intestine, renal and the nervous system, resulting in the limited clinical application [11]. The sustained-release and controlled-release preparations belong to the third generation dosage forms, which bury the traditional medication packages into some certain matrixes or carriers. They utilize the matrixes' functions of absorption, increasing viscosity, connecting scaffolds or membrane barrier to stabilize the drugs and to extend the releasing speed. The reaction time will also be prolonged while the toxicity will be reduced [12]. The slow-release dose for implant has the following advantages: (1) Clear Target: Directly implant the drugs into the tumor body via percutaneous injections. The drug concentration in the focal area is obviously higher than the one of intravenous injection. The local drug concentration in the tumor body is enhanced as well. (2) Control- and Sustained-Release Effect: Stabilize the drug concentration while avoid the "Valley Phenomenon". (3) Safety: Effectively decrease the cisplatin content in blood so that the poisonous effect will be mitigated. (4) Effectiveness: High local drug concentration with positive curative effect. Some researchers like Liu Huading contended [13]. The drug concentration in the implant area of the tumor body was conspicuously higher than the one of the intravenous injection which leaded to the extension of the reaction time of the drugs in the local area, the increase of intensity, the lower cisplatin content in blood, and the decrease of poisonous effects [14]. (5) Long residual action: The drugs belong to the slow-release doses. Cisplatin will be released smoothly and evenly with the effective local concentration time at as long as 240 hours. Thus, the slow-release doses for tumor body implant contributed to solving the problem of drug targetability, which helps to overcome the difficulty to retain the effective concentration for long time because of the short half-life period, and to settle down the problems of strong untoward reactions.

3DCRT is the mainstream technology for the liver cancer external radiation. According to reports from corporations like Park, the effective curative rate for 3D-CRT on PHC is ranging from 50% to 70% [15]. In this experiment, the response rate for the radiotherapy group is about 55%, which is consistent with the literatures. The curative effect of the radiotherapy is strongly associated with the radiotherapy dose [16]. Takayama offered the conformal radiotherapy to 13 sufferers of PHC. When the average dose was smaller than 60 Gy, RR was about

45.5%. When the average dose was larger than 60 Gy (included 60 Gy), the RR was 71.4% [17]. In this research, the radiotherapy dose was 50 Gy, with the response rate at 55%. The result is consistent with the one of literatures. The major complications for liver radiotherapy are the radiation-induced hepatic injuries despite of the distinguishing incidence rates [18]. According to Balter, when the radiotherapy dose was larger than 60 Gy (included 60 Gy), the incidence rate was obviously enhanced [19]. In an attempt to prevent the radiation-induced hepatic injuries with II degree or above, the radiotherapy condition should be set as V30≤60% [20]. Major reason leading to the failure of liver treatment was the failed effort for local control of the tumors [21]. If the local and regional control over the liver cancer can be more effective, the survival rate for patients will obviously be improved. Therefore, how to improve the curative effect while reduce the incidence rate of radiation-induced liver disease (RILD) remains a puzzle for the oncologists.

In this experiment, the treatment group was given the treatment of 3DCRT and of the slow-release cisplatin for tumor body implant. The control group was given the treatment of 3DCRT. The result revealed that the response rate for the treatment group was 77.5% while the one for the control group was 55.0%. Comparing two groups, x^2=4.528, P=0.003. Two groups demonstrated the statistically significant difference. If these two treatments were combined, the response rate would be severely improved. Radiation-induced hepatic injury: The treatment group 12/40, the control group 7/40, P=0.189. Bone marrow suppression: The treatment group 21/40, the control group 16/40, P=0.262. Digestive Symptoms: The treatment group 34/40, the control group 28/40, P=0.108. Liver dysfunction: The treatment group 22/40, the control group 14/40, P=0.072, no statistically significant differences, no differences between two groups in terms of untoward reactions. According to Takayama, when applying the conformal radiotherapy to curing the PHC, if the average dose was higher than 60 Gy (included 60 Gy), the response rate was about 71.4%. If the radiotherapy dose was higher than 60 Gy (included 60 Gy), the incidence rate of the radiation-induced hepatic injury obviously went up. The result of this research demonstrated that if the radiotherapy dose was 50 Gy and the response rate was 77.5% when jointly applying two treatments, the incidence rates of the radiation-induced hepatic injury for two groups showed no clear differences, which proved that the combination of two treatments could effectively enhance the curative effect without untoward reactions increased. Most of the PHC sufferers also had the chronic hepatitis B, cirrhosis of liver, portal vein tumor thrombus and others. Their liver reserve capacity was quite poor. It is possible to properly reduce the local radiotherapy dose while retain the curative effect at the same level. The reduction of the incidence of radiation-induced hepatic injury is expected, which prolongs the sufferers' progression-free survival and improves their life qualities. Certain social benefits are generated thereby.

The results of this research demonstrated that the combination of both 3DCRT and slow-release cisplatin for tumor body implant as treatment of PHC was able to improve the curative effect, if compared to the adoption of 3DCRT. The sufferers' total survival time can be therefore prolonged. (1) The slow-release formation for tumor body implant enables the local drug concentration in lesion to retain at a comparatively high effective concentration. The curative effect is expected to improve. (2) Cisplatin has the function of sensitivity enhancement for radiotherapy. The slow-release cisplatin for tumor body implant can slow down and even the release of cisplatin, so that the repair of DNA of liver cancer cell can be suppressed and the sensitivity for radiotherapy gets continuously improved. (3) The combination of two treatments can effectively improve the curative effect. Benefiting from this, the local radiotherapy dose is properly reduced and the incidence of radiation-induced hepatic injury collapse. This research believes that the 3DCRT combined with the slow-release cisplatin for tumor body implant can be more effective in improving the curative effect, prolonging the total survival time and suppressing the untoward reactions, if compared to the 3DCRT only. The combination of 3DCRT and slow-release cisplatin for tumor body implant is the effective methods to cope with the PHC. Yet, this research is a small sample research, whose conclusion still needs to be verified clinically.

Acknowledgements

Kaifeng Science Development Project (Project Num. 070315).

Disclosure of conflict of interest

None.

Address correspondence to: Yan Zhang, Central Hospital Cancer Center, No. 85 Hedao Street, Kaifeng 475001, Henan Province, China. Tel: 0371-25672672; E-mail: docyanzhang@163.com

References

[1] Parkin DM, Bray F, Ferlay J, Pisani P. Global CanCer statistics, 2002, CA Cancer J Clin 2005; 55: 74-108.

[2] Jemal A, Brqay F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA cancer J Clin 2011; 61: 69-90.

[3] Snariff MI, Cox IJ, Goman AL, Khan SA, Gedroyc W, Taylor-Robinson SD. Hepatocevllular carcinoma: curruent trendes in Wordwide epidemiology, risk factors, diagnosis ande therapeutics. Expert Rev Gastroenterol Hepatol 2009; 3: 353-367.

[4] Zhao Y, Sun L, Li G. Noveknow for Radiotherapy function of liver Cancer. Cancer Prev Treat Res 2013; 40: 395-399.

[5] Wu MC, Wu D. Current situation and Distance for Synthetic Treatment of Recent advance liver Cancer. Cancer March Journal 2012; 3: 410-412.

[6] Rahbari NN, Mehrabi A, Mollberg NM, Müller SA, Koch M, Büchler MW, Weitz J. Hepatocevllular carcinoma: curruent management and perspectives for the future. Ann Surg 2011; 253: 453-469.

[7] Zeng ZC. Radiotherapy Teatment for liver Hepatocyte Cancer. Practical Tumour Journal 2011; 22: 380-384.

[8] Zhang SM, Zeng ZC, Tang ZZ, et al. Experiment Study for liver Hepatocyte Cancer Cell MHCCP7H Die of Coffee impel Irradiate. Practical Tumour Journal 2007; 22: 23-27.

[9] Xu ZQ, Pang GM. Practical Tumour Clinical Drug Manual. Beijing: China Medicine Science and Technology Publishing house; 2013. pp. 6-54.

[10] Yapp DT, Lloyd DK, Zhu J. Cisplatin delivery by biodcgradable polymer inplant is superior to eyetem ic delivery by osmotic pump or ip in Jection in tumor-bearing mice. Anticancer Drugs 1998; 9: 791-796.

[11] Gryparis Ec, Hatziapostplou M, Papad Mitriou E. Anticancer activity of cisplatin-loaded PLGA-mPEG nanoparticles on LNC approstate cancer cells. Eur J Phaum Biophaum 2007; 67: 1-8.

[12] Zhou JY, Yie SF. Niu Make Progress for slow releasing Teatment to liver Cancer. Foreign Medicine Tumourology 2005; 32: 933-935.

[13] Liu HX, Wang SL, Yie HY. Pharm acokinetics of cisplatin Implants with Percutaneous Liver Insertion in the Liver Cancer Therapy. China Pharmacology Journal 2010; 45: 1753-1757.

[14] Km Jh, Km Ys, Park K. Antitum or efficacy of cisplatinlosd glycol chitosan nanoparticles intumor-bearing mice. J Controlled Release 2008; 127: 41-49.

[15] Park W, Lindo H, Paik SV, Koh KC, Choi MS, Park CK, Yoo BC, Lee JE, Kang MK, Park YJ, Nam HR, Ahn YC, Huh SJ. Local radiotherapy for patients with unresectable hepatocellular carcinoma. Int JR adiat Oncol Biol Phys 2005; 61: 1143-1147.

[16] Wang LH, Yin WB. The Liver Cancer radiotherapy Therapy. Practical Surgery Journal 1991; 11: 276-278.

[17] Yin WB, Yu ZH, Xu GZ, et al. Tumour radiotherapy Teatmentology. Beijing Xiehe Medical University Publice 2008; 12: 832-833.

[18] Seoug J, Park HC, Han KH, Chon CY, Chu SS, Kim GE, Suh CO. Clinical results of 3-Dinensional contoimal rnditnerapy canbined with transarterial chenonaboliaztiox ternepatoce ua lar Carcincmu in the cirrhotic patieats. Hepato Res 2003; 27: 30-35.

[19] Balter JM, Brock KK, Litzenbery DW, McShan DL, Lawrence TS, Ten Haken R, McGinn CJ, Lam KL, Dawson LA. Daily taryeting of intrahepatic tumors for radiotherapy. Int J Radiat Oncol Biol Phys 2002; 52: 266-271.

[20] Ben-Josef E, Normolle D, Ensminger WD, Walker S, Tatro D, Ten Haken RK, Knol J, Dawson LA, Pan C, Lawrence TS. Phase Iltrial of high-dose conformal radiation therapy with concurrent hepatic artery floxuridine for unresectable intrahepatic malignancies. J Clin Oncol 2005; 23: 8739-8747.

[21] Kim TH, KimDy, Park JW, Kim SH, Choi JI, Kim HB, Lee WJ, Park SJ, Hong EK, Kim CM. Dose Volumetric parameters predicting radiation. Induced hepatic toxicity in unresectable hepatocellular caricinoma patients treated with three dimensional conformal radiotherapy. Int J Radiat Oncol Biol Phys 2007; 67: 225-231.