RESEARCH ARTICLE

Whole-liver Radiotherapy Concurrent with Chemotherapy as a Palliative Treatment for Colorectal Patients with Massive and Multiple Liver Metastases: a Retrospective Study

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Abstract

The purpose of this study was to investigate whether whole-liver radiotherapy plus a tumor-boost dose with concurrent chemotherapy is beneficial for colorectal cancer patients with massive and multiple liver metastases. From January 2007 to December 2012, 19 patients who exhibited massive (with a longest diameter > 5 cm) and invasive liver metastases and multiple metastases were treated with radiotherapy and concurrent chemotherapy. The total radiation dose was 53.4 Gy (range 38.8 Gy-66.3 Gy). All of the patients received a continuous intravenous dose of 5 fluorouracil (5-FU) 225 mg/m2 concurrently with radiation. The median survival time was 19 months. The 1- and 2- year overall survival rates were 78.3% and 14.3%, respectively. Of all of the patients who presented with abdominal pain, 100% experienced a decrease in pain. Decreases in the rates of ascites and jaundice were confirmed by ultrasound and bilirubin levels. No cases of Grade 4 or 5 acute or late toxicity were recorded. There were only two cases of Grade 3 toxicity (elevated bilirubin). These data provide evidence that whole-liver radiotherapy plus a tumor-boost dose with concurrent chemotherapy is beneficial for colorectal cancer patients with massive and multiple liver metastases.

Keywords: Liver metastases - whole-liver irradiation - colorectal cancer - palliative therapy

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Introduction

Liver metastases are one of the most common metastatic tumors, especially in colorectal cancer cases (Chong et al., 2013). The increased use of imaging has improved the detection of liver metastases. Twenty percent of colorectal cancer patients have liver metastases at diagnosis, and most colorectal cancer deaths are attributed to metastases (Chung et al., 2005 et al; Cunningham et al., 2007; Lee et al., 2008) . Metastasectomy can achieve a promising survival rate. However, fewer than 25% of patients can tolerate the surgery because of poor performance status, and these patients often have extra-liver metastases or simply refuse surgery for other reasons (Nordlinger et al., 2002; Lochan et al., 2007), and two-thirds of patients who undergo surgery relapse within 2 years (Malik et al., 2007). Systemic chemotherapy is the standard treatment for these patients. However, most of these are at in the final stage, and there are multiple metastatic tumors in their liver (Timmerman et al., 2009). Thus most of them have severe hepatic dysfunction or metastatic hepatic lesions that they have become refractory to chemotherapy (Krishnan et al., 2006).

Radiation therapy has been increasingly used to treat liver metastases. Many studies have demonstrated that high-dose external beam radiotherapy can be delivered safely and can control focal hepatic tumors (Symon et al., 2001; Ben-Josef et al., 2005). Currently, there are two main radiotherapy approaches: focal liver metastasis irradiation and whole-liver irradiation (Topkan et al., 2008). Most often, the aim of focal liver metastasis irradiation at ablative doses is local control and ultimately improving survival (Ben-Josef et al., 2005). Unfortunately, many patients with liver cancer present with diffuse liver tumors. For these patients, therapeutic radiation is limited by a whole-liver tolerance of only about 30 Gy (Mornex et al., 2006). In contrast, low-dose whole-liver RT may be used for the palliation of symptomatic diffuse metastases (Hoyer et al., 2012).

In this study, we reported the results of 19 colorectal patients with massive liver metastases that were treated using a tumor-boost dose to partial liver volumes beyond the typical 20 to 30 Gy that is delivered to the whole-liver with concurrent chemotherapy. This treatment offered promising results without severe side-effects (Ben-Josef et al., 2005; Eccles et al., 2008). The first endpoint of this study was an evaluation of the treatment's efficacy. The second endpoint was an observation of its toxicity.

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Materials and Methods

Patients

We performed a retrospective analysis of 19 patients with liver metastases who received RT between January 2007 and December 2012 at the Cancer Hospital of Harbin Medical University in Harbin, China. This review was approved by our institutional review board. All of the patients were end-stage colorectal cancer patients who have had biopsies of their primary cancer. Liver metastases were clinically diagnosed by histology or imaging. Eligibility criteria included medically inoperable adult patients. The inclusion criteria were massive and invasive liver metastases, defined as those whose longest diameter was more than 5 cm, and multiple metastases. Child-Pugh Score C and primary liver cancers were excluded. Eight patients had mild ascites, and 6 patients were jaundiced. The main symptom before RT was abnormal pain and distension. The patients had received a median of 4 (range, 2–6) previous chemotherapy regimens. The details are summarized in Table 1.

Radiation therapy

The patients were immobilized in the supine position with their arms above their heads. A MED-TEC body frame and thermoplastic body mask were utilized. Enhanced CT images were obtained during free breathing using a large-aperture Philips CT simulator. All of the patients were asked to respire shallowly to minimize target movement. Transverse images were collected at 5-mm-thick intervals. The doctors then supervised the delineation of the gross tumor volume, the clinical tumor volume, the planed tumor volume and other sensitive organs on an ACQ-Sim workstation and sent the CT imagines to ELEKTA Precise Plan via DICOM RT Ethernet. After that, the physicists took responsibility for all directions of beam projection based on normal organ and PTV shapes and completed the IMRT plan by manually correcting and optimizing the fields or segments using a forward 3D planning system. All of the treatment plans were 8MV or 15 MV X ray-delivered using the Electa Synergy S. The isocenter projection was marked on the abdominal skin of each patient to verify that the patient set-up was accurately maintained during treatment at the first fraction and to ensure that the patient set-up remained unmovable throughout the treatment. Kilovoltage on-board cone beam CT was used to match the planning CT prior to each treatment. The patient's position was adjusted with an initial automatic bone alignment followed by a soft tissue alignment. The patient's position was corrected if the discrepancy was 2 mm or more in any direction.

Whole-liver radiation

The patients all underwent computed tomography simulation and intense modulated three-dimensional conformal radiation treatment planning to minimize the dose to the stomach, heart, kidneys, intestines and lungs. Whole-liver radiation (WLRT) was delivered at 1.7 Gy per fraction, 5 days per week. The radiation dose was 30.6 Gy (range, 25.5 Gy to 34 Gy).

Gross tumor- boost radiation

After the WLRT, enhanced CT images were obtained again to observe the changes in tumor volume. Boost radiation was used to treat the largest of multiple liver metastases. The clinical target volume (CTV) was defined as 1 cm beyond the gross target volume (GTV). The planning target volume (PTV) was defined as 1 cm beyond the CTV for setup uncertainty, plus an additional 0.3- to 3-cm margin in the craniocaudal direction of the liver's movement during breathing cycle treatment.

The treatment dose was prescribed to the isodose line covering 90% PTV. The boost dose was 22.8 Gy (range, 13.3 Gy to 38 Gy; 190 cGy/F). The total radiation dose was 53.4 Gy (range, 38.8 Gy to 66.3 Gy). DVH was used to evaluate the treatment plan. The maximum cumulative total doses to the spinal cord, stomach and duodenum were limited to 40, 50 and 50 Gy, respectively. The relative constraints included the left kidney, which was constrained to a D100 of <20 Gy and a D66 <18 Gy; the right kidney was specified to achieve a D100 <30 Gy and a D66 <20 Gy.

An example of RT is shown in Figure 1. First, the patient received whole-liver radiation at 1.7 Gy per fraction, as the first picture shows. Then the patient received the CT-Sim again. The largest tumor received the boost radiation of 1.9 Gy per fraction. The cord is outlined in blue; the heart is outlined in green. Three months after treatment, the patient underwent CT, as the second picture shows. The tumor (outlined in red) is smaller than it was in the first picture.

Chemotherapy

All of the patients received intravenous 5 fluorouracil (5-FU) 225 mg/m^2 continuously concurrently with radiation on each radiotherapy day.

Follow-up

All of the patients underwent computed tomography or PET-CT 3 months, 6 months and 12 months after treatment and computed tomography every 6 months after 1 year. Acute and late toxicities were defined as toxicities that occurred within or after 3 months of treatment completion, respectively. Toxicity was scored using the National Cancer Institute Common Toxicity Criteria. RILD was defined as the development of elevated liver function tests and nonmalignant ascites. Tumor response was assessed using the Response Evaluation and Criteria for Solid Tumors (RECIST) at approximately 3 months after the treatment. The responses were categorized as complete response, partial response, stable disease, or progressive disease. Because few patients had a complete response or progressive disease, these categories were merged for analysis into partial response or stable disease, respectively.

Statistical method

Statistical analyses used SPSS 19.0. Local control (LC) and overall survival (OS) were calculated using the Kaplan-Meier method. All of the results were compared using the log-rank test. A P value < 0.05 was considered statistically significant.

Table 1. ?????

Parameter	Value	*P*
Age (years)		
Median	56	
Range	47-68	
Sex		
Male	10	
Female	9	
KPS		
<80	8 (36.8%)	
≥80	11(63.2%)	0.02
Number of liver lesions (per patient)		
>1 and ≤3	9 (47.4%)	
>3	10 (52.6%)	0.49
The presence of extra-liver disease		
Yes	5 (26.3%)	
No	14 (73.7%)	0.01
Radiation dose		
Whole liver	3060 cGy (range, 2550 cGy-3400 cGy)	
Boost	2280 cGy (range, 1330 cGy-3800 cGy)	
Total	5340 cGy (range, 3880 cGy-6630 cGy)	
Total dose (per patient)		
≤4960 cGy	6 (31.5%)	
<4960 cGy	13 (68.5%)	0.84
Median longest lesion diameter(cm) (range)	7 (range, 6-12 cm)	
No. of previous chemotherapy regimens	4 (range, 2-6)	
The basic CEA level		
>50	5 (26.3%)	
≤50	14 (73.7%)	0.49

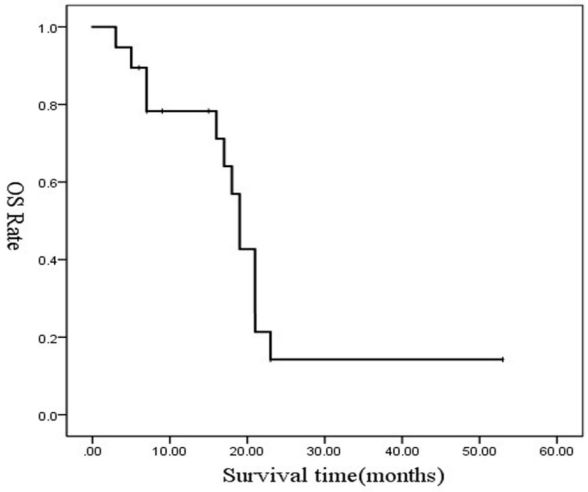

Figure 2. Overall Survival Time

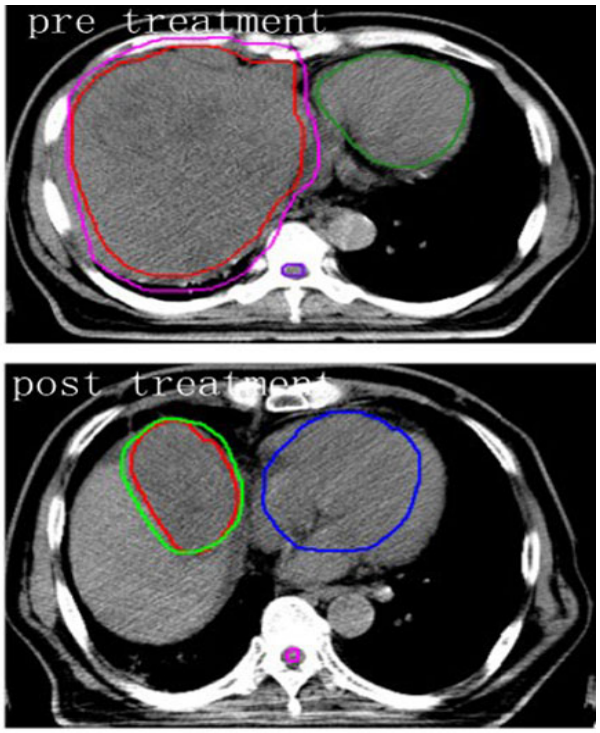

Figure 1. Assessment of a Colorectal Carcinoma Liver Metastasis Treated with Whole-liver Radiotherapy Concurrent with Chemotherapy

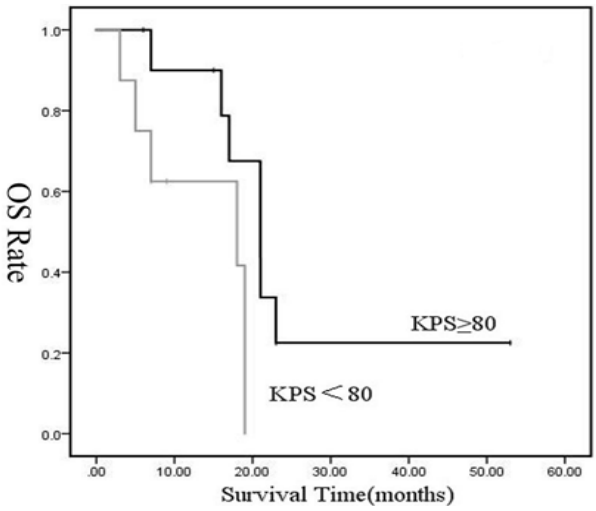

Figure 3. Overall Survival Rate by KPS

Results

Nineteen patients (70 lesions) were included in this study. The total radiation dose was 53.4 Gy (range, 38.8 Gy to 66.3 Gy). The mean number of liver lesions treated per patient was 3 (range, 2 to 6). The maximal diameter of all the lesions was 7 cm (range, 6 to 12 cm).

Palliation

Symptom improvement was assessed by both the patients and their physicians. Of the patients who presented with abdominal pain, 100% reported decreased pain, as measured by a reduced need for analgesics. The patients with ascites and jaundice all reported decreases in their symptoms that were confirmed by ultrasound and bilirubin levels.

Response and overall survival

The median survival time was 19 months. The 1- and 2- year overall survival rates were 78.3% and 14.3% (Figure 2). The therapy overall response rate was 52.6%. Ten of the 19 patients demonstrated an objective response, and the others showed stable disease. No patients showed progression.

The four effort of variables on survival were assessed using a log-rank analysis: 1.KPS, 2. the total radiation dose, 3.the presence of extra-liver disease, 4.the base line CEA. Univariate analysis showed that KPS and the presence of extra-liver disease were significant factors for overall survival (*P*=0.02 and 0.01; Table 1). Patients with KPS ≥80 and an absence of extra-liver disease had more favorable survival rates (Figures 3, 4). We did not perform a multivariate analysis because of a low number

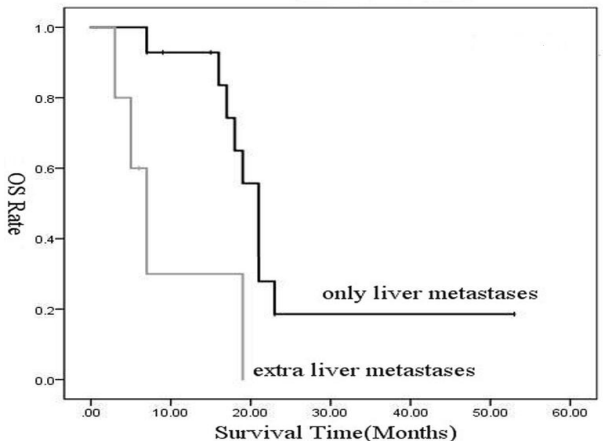

Figure 4. Overall Survival Rate by Extra-liver Disease

of cases; therefore, the calculated results are not reliable.

Toxicity

No cases of Grade 4 or 5 acute or late toxicity were recorded. The mosst common acute toxicities included nausea (seven) and alterations in liver function tests (seven). There was only two cases with Grade 3 toxicity (elevated bilirubin), and no Grade 4 or 5 toxicities were observed.

Discussion

Radiation therapy (RT) for liver metastases is viewed as a palliative intervention because of the initially low whole-liver tolerance to RT. Several previous studies have analyzed the outcomes of whole-liver RT for treating patients with liver metastases (Borgelt et al., 1981; Leibel et al., 1987; et al., Russell et al., 1993; Ajlouni et al., 1990). WLRT seems to be well tolerated when given at doses below 30 Gy in 2-Gy fractions or 21 Gy in 3-Gy fractions. Most of the colorectal cancer patients with liver metastases included in these studies had had previous chemotherapy and were treated with the region of 20 to 30 Gy at 1.5 to 3.0 Gy per fraction (Schefter et al., 2011). 50-90% of patients have their pain relieved, and up to 50% have their lesions size reduced (Mendez et al., 2012). Bydder et al. (Bydder et al., 2003) treated patients with a limited life expectancy using RT with 10 Gy in 2 fractions to the whole liver. Symptoms improved in 53% to 66% of the patients at 2 weeks. Recently, Yeo et al. (Yeo et al., 2010) treated 10 end-stage colorectal cancer patients using conformal RT at 21 Gy (range, 21-30 Gy) in seven fractions to the whole liver. Liver function improved in most of the patients, and 75% patients have their serum CEA level decreased. Pain level decreased was observed in all of the patients and no more than Grade 3 acute toxicity consisted of nausea/vomiting was observed. Previous studies have demonstrated a possible role of whole-liver RT in palliative care for colorectal cancer patients with massive liver metastases. Thus, whole-liver RT remains an option for patients experiencing pain from extensive liver metastases that stretch the liver capsule; however, safe doses are not associated with durable local control.

Precise radiation therapy techniques, such as intense modulated conformal radiation treatment (IMRT) and stereotactic body radiotherapy (SBRT), allow for partial liver irradiation. It has been recognized that higher tumor doses could be delivered safely as long as the mean dose to the liver was kept below safely tolerated doses. Recently, SBRT was widely used to treat oligo-metastases and achieved an excellent outcome (Tree et al., 2013). In recent SBRT studies, the 2-year local control and survival rates were 55 to 100% and 30 to 83% (van der Pool et al., 2010). However, a maximum liver lesion size of 5 to 6 cm and one to four metastases are considered ideal circumstances for SBRT.

It is widely believed that systemic chemotherapy is the mainstay of treatment for massive metastatic colorectal cancer (Chiu et al., 2013). Currently, regimens incorporating irinotecan, oxaliplatin, cetuximab, bevacizumab and fluoropyrimidine are used for colorectal cancer liver metastasis. With the introduction of these new agents, the median survival time has increased to 15-21 months with first-line therapy and 7-12 months with second-line therapy. Treatment with intravenous 5-fluorouracil (5-FU) achieved a median survival time of approximately 12 months, making this agent the drug of choice for many decades (Krishnan et al., 2006). In a subset of patients with metastases confined to the liver, a meta-analysis of fluoropyrimidine trials demonstrated a median survival time of 12 months (Thirion et al., 1999). However, irinotecan and oxaliplatin have both been associated with a significant incidence of liver damage (Yeo et al., 2010). In our study, all of the patients had colorectal cancer with liver multiple metastases and massive lesions. There were 5 patients with extra liver metastases (2 bone metastases, 2 lung metastases and 1 brain metastases). The bone and lung metastases had undergone palliative radiotherapy. The brain metastases underwent SBRT before treatment. The patients underwent an average of 4 (range, 2-6) chemotherapy cycles before treatment and were refractory to systemic treatment. We used WLRT to improve symptoms such as vomiting, pain and jaundice, and then delivered a boost to the largest gross tumor to improve the local control rate. Ten out of 19 patients demonstrated an objective response; the others showed stable disease. No patients showed progression.

Robenson et al. (Robenson et al., 1995) treated 20 colorectal liver metastases patients using conformal radiotherapy and regional chemotherapy. Eleven out of 20 showed an objective response. The overall survival time was 20 months. Recently, Yeo et al. (Yeo et al., 2010) reported a median survival time of 80 ± 80 days. Mohiuddin et al. (Mohiuddin et al., 1996) observed that addition boost dose to the dominant disease in colorectal cancer with multiple liver metastases can have their symptom improvement and median survival time (4 months vs. 14 months, P=0.01). A recent study (Krishnan et al., 2006) reported a favorable result in colorectal cancer patients with multiple liver metastases. The RT dose was increased only to the dominant tumor combined with chemotherapy that included celecoxib and capecitabine. The median size of the dominant liver metastasis and the median number of hepatic lesions was 10 cm (range, 3 to 19 cm) and four. The median survival time was 12.6

months. In comparison, the median survival time in our study was 19 months, and no cases of Grade 4 or 5 acute or late toxicity were recorded. The most common acute toxicities included nausea (seven) and alterations in liver function tests (seven). There were only two Grade 3 toxicity cases (elevated bilirubin) and no Grade 4 or 5 toxicities.

Although the prognostic factors associated with survival in colorectal patients with liver metastasis remain unclear, many studies have reported that the presence of extrahepatic disease (EHD) is a significant prognostic factor. The 5-year survival rates of patients with EHD after resection are worse (26 vs. 58%, $P < 0.01$) and recurrence rates are significantly higher when compared with patients without EHD disease (Pulitano et al., 2011). Wang et al. (Wang et al., 2007) reported that survival time was increased with fewer comorbidities, fewer positive lymph nodes, and lower grade. In this study, univariate analysis showed that patients with EHD had a lower one year survival rate compared with patients without EHD (30% vs. 92.9%, P=0.01). Patients with KPS ≥80 had a more favorable one year survival rate (62.5% vs. 90%, P=0.03) than patients with KPS < 80 did.

One-third to one-half of the liver can receive 40 Gy safely and without severe complications. Areas less than one-third to one-half of the liver volume can tolerate more than 55 Gy. A study reported that liver lesions could be boosted to a total of 83 Gy (Lausch et al., 2013). We found that conventional fraction intense-modulated radiotherapy reduced liver damage and encouraged more normal cell regeneration than hyperfractioned radiotherapy, according to radiation biology (Dimri et al., 2013). The use of IMRT may improve the ability to deliver high doses to the planned target volume while preserving the integrity of the surrounding normal tissues (Xiang et al., 2013). 5-Fu drugs can enhance radiosensitivity without increasing liver damage, according to many studies (Zeng et al., 2004).

There are limitations to our study that need to be addressed. For example, respiratory gating or tumor tracking systems are not currently compatible with IMRT systems. Therefore, accurate immobilization and four-dimensional CT simulation, which can better account for internal tumor motion throughout all phases of the respiratory cycle, are essential for minimizing tumor motion.

In conclusions, although our study was a single-institution one with a small sample size, our data suggest that whole-liver radiotherapy plus a tumor-boost dose with concurrent chemotherapy is beneficial for end-stage colorectal cancer patients with massive and multiple liver metastases. This treatment may relieve the patients' symptoms and improve survival time, and it has an acceptable toxicity profile. This approach merits further exploration.

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