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Prognostic and predictive value of liver volume in colorectal cancer patients with unresectable liver metastases

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Purpose: To determine the prognostic and predictive value of liver volume in colorectal cancer patients with unresectable liver metastases.

Materials and Methods: Sixteen patients received whole liver radiotherapy (WLRT) between January 1997 and June 2013. A total dose of 21 Gy was delivered in 7 fractions.

Results: The median survival time after WLRT was 9 weeks. In univariate analysis, performance status, serum albumin and total bilirubin level, liver volume and extrahepatic metastases were associated with survival. The mean liver volume was significantly different between subgroups with and without pain relief (3,097 and 4,739 mL, respectively; p = 0.002).

Conclusion: A larger liver volume is a poor prognostic factor for survival and also a negative predictive factor for response to WLRT. If patients who are referred for WLRT have large liver volume, they should be informed of the poor prognosis and should be closely observed during and after WLRT.

Keywords: Colorectal cancer, Metastasis, Liver, Tumor burden, Radiotherapy

Introduction

Colorectal cancer is the third most common cancer in Korea [1]. The liver is the most common site for metastases from colorectal cancer and approximately 50% of patients develop liver metastases during the course of disease [2]. Among patients with liver metastasis of colorectal cancer, only 25% to 30% of patients are eligible for liver resection and the 5-year survival rate is approximately 25% to 58% [3]. Patients with unresectable liver metastases are usually treated with multi-agent chemotherapy including various combinations of 5-fluorouracil, irinotecan, oxaliplatin, bevacizumab, cetuximab or panitumumab [4-7].

Whole liver radiotherapy (WLRT) is useful for palliation of symptomatic liver metastases, which are refractory to systemic treatment. In a retrospective study conducted in the late 1970s, WLRT of 24 Gy in 8 fractions was administered for symptomatic liver metastases and 90% of patients had significant symptom palliation [8]. The Radiation Therapy Oncology Group (RTOG) conducted a prospective study comparing several dose schemes for WLRT including 30 Gy in 15 fractions, 25.6 Gy in 16 fractions, 20 Gy in 10 fractions, and 21 Gy in 7 fractions. The overall median survival was 11 weeks. Symptomatic palliation was achieved in 19% to 55%

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of cases, and liver function and performance also improved in 40% and 25% of cases, respectively. There were no reports of radiation-induced liver injury [9]. In another study by RTOG comparing 27, 30, and 33 Gy with 1.5 Gy per fraction delivered twice daily, radiation-induced liver injury occurred in 10% of patients who received 33 Gy and 0% who received 27 and 30 Gy [10]. Similar results were obtained in a recent study using computed tomography (CT)-based three-dimensional planning. The median dose was 21 Gy in 7 fractions. Four of 10 patients who had improvement in liver function after WLRT received further chemotherapy and showed better survival, with a mean survival time of 143 days [11].

However, medical oncologists are concerned about radiation-induced liver injury and tend to defer WLRT. As a result, some patients are referred for WLRT with deteriorated liver function and poor performance status. These patients tend to have poor prognosis. Therefore, we retrospectively investigated our results of WLRT in colorectal cancer patients with unresectable liver metastases, and analyzed the prognostic and predictive factors.

Materials and Methods

1. Patients

Between January 1997 and June 2013, a total of 16 colorectal patients with unresectable liver metastases received WLRT. The liver metastases were present with multiple tumor foci (Fig. 1). We retrospectively reviewed the medical records and radiographic examinations. Patients were referred for WLRT when they were refractory to multi-agent chemotherapy and had intractable abdominal pain or hepatic dysfunction that precludes further chemotherapy.

2. Treatment

All patients underwent CT simulation and received three-dimensional conformal radiotherapy. The clinical target volume included the entire liver. Radiotherapy was performed with 10 to 15 MV X-ray. The field was matched to the tangential fields or two opposite anterioposterior fields. A total dose of 21 Gy was delivered in 7 fractions. Considering the liver movement during respiration, nine patients received radiotherapy under respiratory control using the Real-time Position Management system (Varian Medical Systems, Palo Alto, CA, USA) and the others received radiotherapy with a generous margin in the craniocaudal direction.

3. Evaluation of liver function

Liver function was closely monitored during and after WBLT. A follow-up liver function test was performed 1 month after WLRT. If the patient expired or was lost to follow-up within 1 month after WLRT, we used their last liver function test.

4. Statistical analysis

Overall survival time was calculated from the initiation of radiotherapy until death. Overall survival rate was estimated using the Kaplan-Meier method. The log-rank test and Cox proportional hazard model were used to determine whether any characteristics were related to survival. Fisher exact test and independent samples t-test were used to determine differences in the characteristic profiles between the groups with and without pain relief. Statistical analysis was performed using SPSS ver. 18.0 (SPSS Inc., Chicago, IL, USA).

Results

1. Patient characteristics

The median age was 59 years (range, 41 to 75 years). Except in one case, all patients had liver metastasis at the time of initial diagnosis of colorectal cancer. Extrahepatic metastases were present in 12 patients (75.0%). Primary tumor resection was performed in 10 patients (62.5%) (Table 1). The time interval from diagnosis of colorectal cancer to initiation of WLRT ranged from 1 to 43 months (median, 20.5 months). Before WLRT, a median of 25 cycles (range, 1 to 41 cycles)

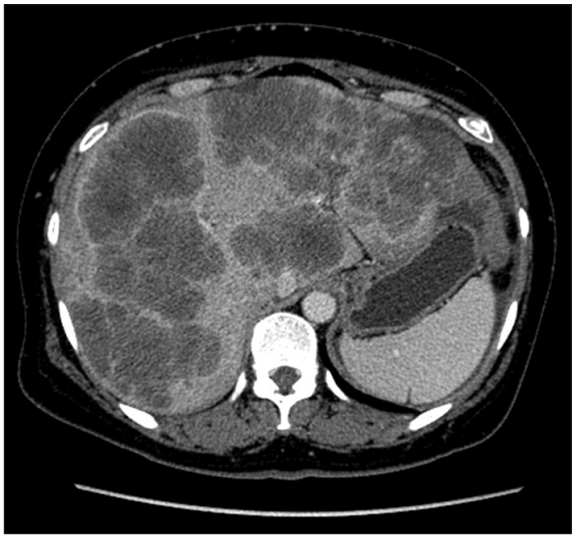

Fig. 1. Contrast-enhanced computed tomography scan of multiple liver metastases.

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Table 1. Patients' characteristics

Characteristic	Value
Age (yr)	59 (41–75)
Sex	
Male	12 (75.0)
Female	4 (25.0)
ECOG performance status	
0–1	7 (43.8)
2–4	9 (56.2)
Primary tumor location	
Colon	2 (12.5)
Rectosigmoid	14 (87.5)
Primary tumor resection	
Yes	10 (62.5)
No	6 (37.5)
Extrahepatic metastases	
Yes	12 (75.0)
No	4 (25.0)
CEA (ng/mL)	774.36 (23.61–1,000.00)

Values are presented as median (range) or number (%).
ECOG, Eastern Cooperative Oncology Group; CEA, carcinoembryonic antigen.

of chemotherapy were given, using various combinations of 5-fluorouracil, leucovorin, capecitabine, irinotecan, oxaliplatin, thymidylate synthase 1 (TS-1), simvastatin, bevacizumab, and cetuximab.

Mean liver volume and gross tumor volume, which was contoured and measured by two radiation oncologists using Pinnacle ver. 9.2 (Philips Medical Systems, Eindhoven, the Netherlands), were 3,855 mL (range, 1,797 to 5,448 mL) and 2,343 mL (range, 667 to 4,221 mL), respectively.

2. Treatment results

Treatment results are summarized in Table 2. Twelve patients (75.0%) completed radiotherapy. The status of the other four patients (25.0%) worsened after initiation of WLRT, and these patients refused to continue treatment and were referred to supportive care.

Before WLRT, the total number of patients who had an elevated serum aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), and total bilirubin (TB) was 15, 6, 16, and 11, respectively. The total number of patients who had improvements in serum AST, ALT, ALP, and TB by more than 10% was 11, 4, 10, and 3, respectively. Only one patient received further chemotherapy after completion of WLRT and lived 42 weeks.

3. Survival and prognostic factors

Median survival was 9 weeks. In univariate analysis, performance status, serum albumin and TB level, liver volume and extrahepatic metastases were associated with survival. Other factors including sex, age, location of primary tumor, and primary tumor resection were not associated with survival (Table 3).

4. Predictive factors for pain relief

Among 14 patients presenting with abdominal pain before WLRT, 10 patients completed radiotherapy and seven patients reported pain relief. Thirteen patients who were available for assessment of pain before and after WLRT were divided into two subgroups according to the pain response. The characteristics of the two groups were compared in Table 4. There were significant differences in performance status ($p = 0.021$), mean liver volume ($p = 0.002$), and mean gross tumor volume ($p = 0.008$). The other characteristics were not associated with pain response.

Discussion and Conclusion

We compared our study with a recent study conducted by Yeo et al. [11]. The previous study included 10 patients with replacement of over three-quarters of normal liver by metastatic tumors and Child-Pugh classification B or C. The serum levels of AST, ALP, and TB were higher in the previous study (median of 118 IU/L, 583 IU/L, and 6.5 mg/dL, respectively) than in our study (median of 94 IU/L, 364 IU/L, and 2.6 mg/dL, respectively). Liver volume was not reported in the previous study. A total dose of 21–30 Gy in 7–10 fractions was delivered. In spite of better liver function, our treatment results were not sufficiently good in comparison to those of the previous study. The median survival time was 88 days in the previous study and 9 weeks (63 days) in our study. Relief from abdominal pain occurred in all patients in the previous study and in 70% of patients in our study. In the previous study four patients who had received further chemotherapy after WLRT showed better survival, while only one patient (no. 16) with 1,797 mL liver volume in our study received further chemotherapy and showed better survival. Because there were few differences in radiation technique, we deduced that the differences in treatment results were associated with variation in patient characteristics.

Numerous studies have confirmed various prognostic

Table 2. Treatment results

Patient no.	Complete RT	Abdominal pain	AST (0–40 IU/L)	ALT (0–40 IU/L)	ALP (53–128 IU/L)	TB (0.2–1.5 mg/dL)	Albumin (3.5–5.2 g/dL)	Liver volume (mL)	Post-RT chemotherapy	No. of previous chemotherapy	Survival time (wk)
1	No	No change	92→115[b]	19→16	225→149[a]	2.7→9.3[b]	3.4→3.3	4,303	No	1	1[c]
2	Yes	No change	57→33[a]	28→20	317→213[a]	20.4→20.9	2.9→2.7	4,525	No	36	1
3	Yes	No change	131→102[a]	70→48[a]	751→763	10.8→22.1[b]	3.1→2.3[b]	5,026	No	8	2
4	Yes	No change	75→77	34→19	482→347[a]	1.8→13.5[b]	3.4→2.7[b]	4,045	No	41	2
5	No	No change	868→489[a]	91→85	169→158	12.8→21.5[b]	2.6→2.8	5,189	No	28	3
6	Yes	Decreased	144→76[a]	68→26[a]	227→248	2.3→1.8[a]	3.5→3.0[b]	2,899	No	31	3[c]
7	Yes	Decreased	148→130[a]	32→21	492→373[a]	6.9→4.1[a]	3.1→3.0	4,111	No	25	4[c]
8	No	Not assessed	54→125[b]	18→25	250→263	0.7→2.7[b]	2.7→2.4[b]	5,448	No	24	4
9	No	No change	95→67[a]	31→15	737→622[a]	10.6→28.5[b]	2.5→2.8	5,259	No	26	4
10	Yes	No pain before RT	71→80[b]	68→34[a]	692→683	2.7→5.0[b]	3.9→3.5[b]	3,883	No	25	6[c]
11	Yes	Decreased	184→164[a]	45→41	624→722[b]	2.4→4.8[b]	3.0→3.2	3,038	No	19	9
12	Yes	Decreased	239→74[a]	22→11	600→484[a]	4.9→3.3[a]	3.1→3.3	4,428	No	17	12
13	Yes	Decreased	79→64[a]	27→27	263→225[a]	0.8→1.0	4.4→4.1	2,680	No	8	20
14	Yes	Decreased	73→45[a]	38→28	411→214[a]	1.0→0.7	3.9→3.3[b]	2,728	No	1	26[c]
15	Yes	No pain before RT	147→112[a]	152→62[a]	292→245[a]	0.8→1.0	4.0→3.5[b]	2,226	No	37	27
16	Yes	Decreased	39→42	23→18	303→225[a]	0.5→0.4	4.1→4.3	1,797	Yes	12	42

RT, radiotherapy; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; TB, total bilirubin.
[a]Improvement more than 10% in liver function test. [b]Deterioration more than 10% in liver function test. [c]Patient who lost to follow-up.

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Table 3. Univariate analysis of prognostic factors

Factor	No. of patients	Median survival (wk)	p-value
Age (yr)			0.671
≤60	10	9	
>60	6	3	
Performance status			0.001
0–1	7	27	
2–4	9	4	
Primary tumor location			0.125
Colon	2	3	
Rectosigmoid	14	12	
Serum albumin (g/dL)			0.003
≤3.5	11	4	
>3.5	5	27	
Serum total bilirubin (mg/dL)			0.036
≤3	10	20	
>3	6	3	
Liver volume (continuous)[a]	-	-	0.008
Primary tumor resection			0.511
Yes	10	9	
No	6	4	
Extrahepatic metastases			0.052
Yes	12	4	
No	4	42	

[a]Cox proportional hazard model was used.

factors in colorectal cancer patients with unresectable liver metastases. According to a systematic review of 14 retrospective studies involving 3,209 patients, performance status, volume of liver metastases, nodal stage, bowel resection margins, and chemotherapy are consistently related to overall survival [12]. The Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 was significantly associated with better survival compared to a status of 2 or more [13,14]. Patients with metastatic mass replacing more than 50% of the entire liver had poor survival [13,15]. A negative bowel resection margin and chemotherapy were related to better survival [16,17]. Results regarding age, American Society of Anesthesiologists score, carcinoembryonic antigen, primary tumor location, tumor size and differentiation, peritoneal dissemination, and extrahepatic metastases were inconsistent. In our study, ECOG performance status, serum albumin and TB level, extrahepatic metastases and liver volume had significant associations with survival in univariate analysis. Although the number of patients was too small to perform multivariate analysis, our results are similar to those of previous studies. We analyzed liver volume as a continuous value and identified a negative correlation between survival time and liver volume (Fig. 2). To explain this negative correlation, two radiation oncologists contoured the gross tumor volume of multiple

Table 4. Differences in characteristics between subgroups according to pain response

Characteristic	Relief of abdominal pain		p-value
	Yes	No	
Age (yr)			0.592
≤60	5	3	
>60	2	3	
Performance status			0.021
0–1	5	0	
2–3	2	6	
Primary tumor location			0.192
Colon	0	2	
Rectosigmoid	7	4	
Serum albumin (g/dL)			0.192
≤3.5	4	6	
>3.5	3	0	
Serum total bilirubin (mg/dL)			0.286
≤3	5	2	
>3	2	4	
Extrahepatic metastases			0.070
No	4	0	
Yes	3	6	
Mean gross tumor volume (continuous) (mL)	1,724	3,150	0.008
Mean liver volume (continuous) (mL)	3,097	4,739	0.002

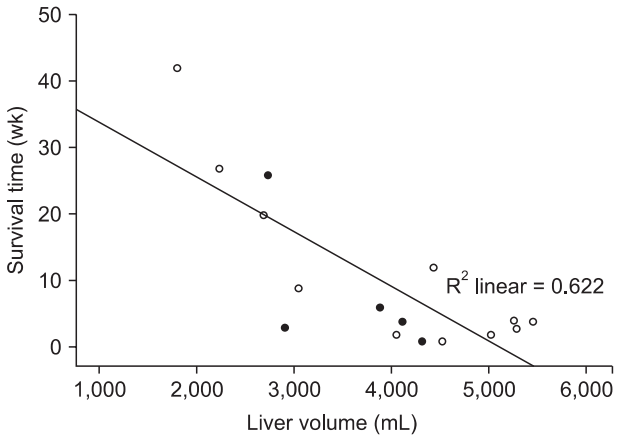

Fig. 2. Correlation between liver volume and survival: five patients were lost to follow-up (black dot).

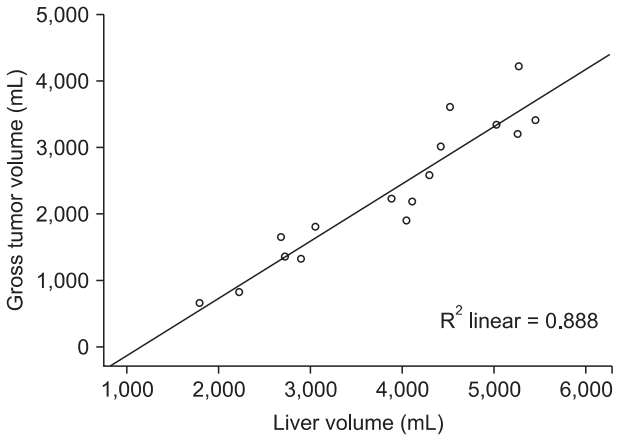

Fig. 3. Correlation between liver volume and gross tumor volume.

liver metastases on contrast-enhanced CT images. There was a strong positive correlation between gross tumor volume and liver volume (R^2 = 0.888; $p < 0.005$) (Fig. 3). These results suggest that a larger liver volume is indicative of higher tumor burden, and is directly related to survival.

Interestingly, liver volume was correlated not only with survival, but also pain response. Mean liver volume was significantly different between the two subgroups (3,097 and 4,739 mL, respectively; p = 0.002). We presume that the more the liver capsule distends, the less pain is relieved, because visceral pain arises from stretching or irritation of the liver capsule, not from liver parenchyma.

There was a discrepancy in liver toxicity between our study and previous studies. In the literature, a total dose of less than 30 Gy can be delivered safely [10]. However, in our study, eight patients had a more than 10% increase in serum bilirubin after WLRT. This is not consistent with classic radiation-induced liver disease (RILD), a clinical syndrome that manifests with fatigue, anicteric ascites and elevation in ALP out of proportion to other liver enzymes 2 to 4 months after radiation therapy of liver [18]. This acute liver toxicity can be explained by the fact that our patients received a median of 25 cycles (range, 1 to 41 cycles) of chemotherapy before WLRT. There have been reports on combined-modality induced liver disease (CMILD) after allogenic bone marrow transplantation including aggressive conditioning chemotherapy and total body irradiation [19]. In contrast to classic RILD, the onset of CMILD occurs early within 1 to 2 weeks after radiotherapy, with a significant elevation of bilirubin. This correlates well with acute deterioration of liver function observed in our study.

Our study sheds light on the negative correlation of liver volume with survival and pain relief. However, we could not suggest a cutoff value to predict who can be safely and effectively treated because of the small number of patients. Further studies are needed to validate our results and define an optimal liver volume for WLRT.

In conclusion, patients with poor performance status, abnormal serum albumin and TB level, larger liver volume and extrahepatic metastases have a poor prognosis. Also patients with larger liver volume had a poor response to WLRT and were at risk of CMILD. Clinicians who treat colorectal cancer patients with unresectable liver metastases should be concerned with WLRT as an effective palliative treatment and should be cautious if patients have a large liver volume.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

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