Outcome of Colorectal Liver Metastases

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Objective : *To determine the median survival of colorectal liver metastatic (CRLM) patients treated at King Chulalongkorn Memorial Hospital over the past 10 years and to determine the outcome of the various treatment modalities (surgery , chemotherapy and supportive treatment)*

Material and Method : *Between January , 1992 and December, 2001, 86 consecutive patients were recorded. Of whom 26 (30.23%) received liver resection , 39 (45.34%) received chemotherapy and 21(24.41%) received supportive treatment. All the patients were followed up to December 31 , 2001 or death. Survival was calculated by Kaplan-Meier method and studied for statistical differences between various treatment groups with Cox regression model. The 95% confidence intervals for median assessment were determined.*

Results : *Overall survival of CRLM patients was 18 months. Significant differences in survival were seen among the three groups of patients. Median survival was 33 months in the liver resection group, 17 months in the chemotherapy group and 5 months in the supportive treatment group. Three-year survival in the liver resection group was 23% while it was 7.6% in the chemotherapy group. Type of treatment, primary tumor staging and extrahepatic metastasis were the three independent determinant factors of survival.*

Conclusion : *Survival of patients with colorectal liver metastases depends on the type of treatment. Liver resection is the best treatment which offers long term survival to the patients in selected cases.*

Keywords : *Colorectal cancer, Metastases, Liver cancer, Hepatectomy*

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Metastatic neoplasm is the most common tumor of the liver and the common primary origin is colorectal cancer. Nearly half of the colorectal cancer patients have liver metastasis at death [1,2]. The natural history of patients with colorectal liver metastasis is dismal. The median survival, if untreated, is 5-10 months and most of the patients survive less than 5 years [1-5].

In the past, these patients were categorized into end stage diseases and had not been treated aggressively. Most patients received systemic chemotherapy with median survival only 12 months [4]. However, because of improving knowledge in liver anatomy, better perioperative care and surgical techniques during the last 2 decades, liver resection has become safer and more effective. Recently, liver resection has been accepted as the treatment of choice with prospect of long term survival to these patients [6].

The aims of this study was to compare the survival after 3 different methods of treatment (liver resection, chemotherapy and supportive care) and to study factors influencing survival in patients with colorectal liver metastasis.

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Material and Method

All patients who had been treated for colorectal liver metastasis between 1992 and 2001 at King Chulalongkorn Memorial Hospital were enrolled into the present study. Colorectal liver metastasis was diagnosed by pathological reports of primary colorectal cancer and imaging or operative findings suggestive of liver metastasis in patients aged more than 15 years. Data were collected from OPD card, IPD chart, operative records, by telephone contact and written correspondence.

Data collection included age, gender, site of primary tumor, stage of primary tumor, preoperative CEA level of primary colorectal cancer, type of liver metastasis (simple or complex), extrahepatic metastasis, time interval to the diagnosis of colorectal liver metastasis after primary tumor treatment, type of treatment. Simple and complex colorectal liver metastasis were defined as 1-3 tumor nodules in the same lobe and at least 2 nodules in different lobes, respectively [7]. All patients were classified into 3 groups according to the method of treatment, i.e. liver resection in group

I, chemotherapy (5-FU and leucovorin based regimen) in group II and supportive care in group III.

Survival in each group was recorded and compared. The survival curve was determined by the Kaplan Meier method. The type of study to determine survival was cross section analysis study at December 1, 2002. Factors influencing patients' survival were tested by univariate and multivariate analysis using Cox regression model. A p value of < 0.05 was considered statistically significant.

Results

During the study period, the data was collected in 86 patients as shown in Table 1. There were 41 men (48%) and 45 women (52%). Mean age was 57.6 $\pm$ 12.9 years. There were 26 patients in group I (30%), 39 patients in group II (45%) and 21 patients in group III

Table 1. General characteristics of patients enrolled in the study

		Liver resection (n=26)	Chemo-therapy (n=39)	Supportive treatment (n=21)
Sex	Male	10	20	11
	Female	16	19	10
Age (year)		55.15	56.97	62.00
Site	Colon	15	25	14
	Rectum	11	14	7
Differen-tiation	Well differentiated	6	15	6
	Moderately differentiated	16	21	7
	Poorly differentiated	1	3	1
	Unknown	3	0	7
T staging	T2	5	5	0
	T3	15	25	10
	T4	1	7	7
	Unknown	4	2	4
N staging	N0	4	10	4
	N1	10	14	8
	N2	8	9	3
	N3	0	3	0
	Unknown	4	3	6
Preoperative CEA	<5 ng/ml	3	4	3
	5-100 ng/ml	10	17	5
	101-200 ng/ml	6	2	1
	>200 ng/ml	0	8	3
	Unknown	7	8	9
Liver metastasis	Simple	16	7	5
	Complex	10	32	16
Extrahepatic metastasis	Absent	22	19	11
	Present	4	20	10
Time to Diagnosis	Synchronous	17	22	15
	Metachronous	9	17	6

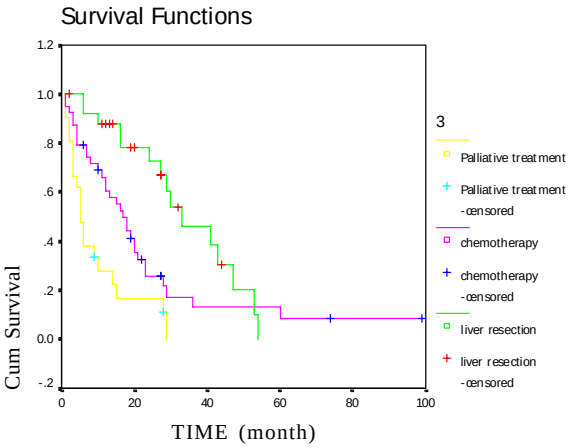

Fig 1. Kaplan Meier showed cumulative survival of patients

(25%). Fifty four patients (63%) had colonic cancer while 32 patients (37%) had rectal cancer. Fifty patients (58%) had primary tumor staging in T3, 10 patients (12%) in T2 and 15 patients (17%) in T4. Fifty five patients (64%) had lymph node metastases when primary tumors were found, 18 (33%)in group I, 26 (47%) in group II and 11 (20%) in group III. Fifty two patients (60%) had elevation of CEA at the time of diagnosis. Fifty seven percent of the patients who had simple liver metastases were in group I whereas 55% of the patients who had complex liver metastases were in group II. Most patients in group I had no extrahepatic metastasis (22 in 26 patients) while nearly half of the patients in group II and III had. Fifty four patients (62.7%) had synchronous liver metastases. Survival of all 86 patients was 18 $\pm$ 2.2 months and survival in group I, II and III were 33 $\pm$ 6.7 months,17 $\pm$ 2.2 months and 5 $\pm$ 0.9 months respectively. Survival in the liver resection group was the best among the 3 groups ($p = 0.0001$) as shown in Table 2. Cumulative survival determined by Kaplan Meier is demonstrated in Fig. 1.

The authors compared subgroup survival analysis between liver resection and the chemotherapy group in terms of type of liver metastasis, extrahepatic disease and time to diagnosis. It showed that liver resection in simple metastasis had survival statistically significant better than chemotherapy as shown in Table 3.

Three-year survival in group I was 23% while patients in group II had a 3-year survival of only 7.6%. There was no 3-year survival in group III. However , 2 patients in group II survived more than 5 years (77 and 89 months; 5-year survival 5.2%). The longest survival in group I was 54 months.

Type of treatment , primary tumor staging (T and N staging) and extrahepatic metastasis affected

Table 2. Median survival of the various treatment modalities and statistical significance of comparison between treatment methods

Treatment	Number of patients	Death	Alive	Median survival (mo)	Adjusted odd	95% CI	P value
Liver resection	26 (30.23%)	15	11	33 ± 6.7	0.2052	0.1007-0.4183	0.0001
Chemotherapy	39 (45.34%)	31	8	17 ± 2.2	0.407	0.2257-0.7472	0.0036
Supportive treatment	21 (24.41%)	19	2	5 ± 0.9			
Over all	86	65	21	18 ± 2.2			

Table 3. Subgroup survival analysis between the liver resection group and chemotherapy group

		N	Median survival (mo)	P value
1. Liver metastasis				
- Simple	Liver resection	16	33	0.0405
	Chemotherapy	7	16	
- Complex	Liver resection	10	29	0.2480
	Chemotherapy	32	17	
2. Extrahepatic metastasis				
- Absent	Liver resection	22	33	0.7913
	Chemotherapy	19	23	
- Present	Liver resection	4	12	0.0766
	Chemotherapy	20	8	
3. Time to diagnosis				
- Synchronous	Liver resection	17	43	0.0546
	Chemotherapy	22	17	
- Metachronous	Liver resection	9	27	0.4619
	Chemotherapy	17	16	
4. Overall				
	Liver resection	26	33	0.0230
	Chemotherapy	39	17	

the patient survival by univariate analysis (Table 4). However, only primary tumor staging - N staging and extrahepatic metastasis influenced the patient survival from Cox regression model (Table 5).

Discussion

In 1994, Stangl et al[4] reported factors influencing the natural history of colorectal liver metastasis. They showed that type of treatment affected the patient survival i.e. liver resection had median survival 30-41 months which was better than 12 months in the chemotherapy group and 7.5 months in the supportive group. The present results showed median survival of 33 ± 6.7 months in the liver resection group, 17 ± 2.2 months in chemotherapy and 5 ± 0.9 months in the supportive group which was similar to the previous reports[1-5]. Three-year survival in the presented liver resection and chemotherapy group was 23% and 7.6% respectively.

Table 4. Univariate analysis of prognostic determinants in patients with colorectal liver metastases

	N	Median survival (mo)	P
1. Sex			0.8392
Male	41	20	
Female	45	14	
2. Age			0.571
<60 yr	45	17	
>60 yr	41	18	
3. Treatment			0.0076
Liver resection	26	33	
Chemotherapy	39	17	
Palliative treatment	21	5	
4. Site of primary tumor			0.8874
Colon	54	18	
Rectum	32	16	
5. Differentiation			0.5193
Well differentiated	27	18	
Moderately differentiated	44	20	
Poorly differentiated	5	10	
6. T staging			0.0071
T2	10	53	
T3	50	18	
T4	15	5	
7. N staging			0.0293
N0	18	28	
N1	32	15	
N2	20	10	
N3	3	17	
8. CEA			0.569
<5 ng/ml	10	17	
5-100 ng/ml	32	23	
101-200 ng/ml	9	16	
>200 ng/ml	11	18	
9. Liver metastasis			0.0794
Simple	28	28	
Complex	58	14	
10. Extrahepatic metastasis			0.0002
Absence	52	24	
Presence	34	6	
11. Time to diagnosis			0.9701
Synchronous	54	16	
Metachronous	32	20	

Table 5. Multivariate analysis (Cox regression) of prognostic determinants in patients colorectal liver metastases

	Adjusted odd	P value	95% CI
1. Treatment		0.001	
Liver resection	0.058	<0.001	0.0178-0.1914
Chemotherapy	0.231	0.059	0.0813-0.6561
Supportive treatment	1		
2. N staging		0.002	
N0	0.190	0.626	0.044-0.822
N1	0.353	0.148	0.861-1.448
N2	2.001	0.368	0.440-9.093
N3	1		
3. Extrahepatic metastasis	6.214	<0.001	2.238-17.248

In the present study, the highest 3-year survival rate was found in group I. Improvement of imaging quality, surgical techniques and better knowledge of liver anatomy has contributed to better outcome of liver resection. The authors recommend liver resection as the treatment of choice in the patients with colorectal liver metastasis without extrahepatic disease when all liver tumors can be completely resected with free margin and good liver function can be maintained postoperatively. However, in special circumstances, patients with colorectal liver metastasis who have extrahepatic disease such as lung metastasis may undergo surgery if all tumors at both organs can be completely removed [2].

Many reports revealed 25% resectability rate of colorectal liver metastasis [6]. Our resectability rate of 30 % was not different from others. To improve resectability rate, a good surveillance program is mandatory. Blood CEA level is one of the tumor markers which is used to follow up the patients after primary colorectal cancer treatment.

The majority of the patients in group II (82%) and group III (76%) had complex liver metastases in contrast to 38% in group I. This fact explained the unresectability of patients in the chemotherapy and supportive group.

Type of treatment, primary tumor staging (T and N staging) and extrahepatic disease were the factors affecting patients survival by univariate analysis. Primary tumor site, cell differentiation and type of liver metastasis (simple or complex) did not influence the patient's survival. Many reports showed that CEA level and time to diagnose liver metastasis (synchronous and metachro-nous) had strongly affected the patient's long term survival [3,6,8] but the present findings did not support those results.

Conclusion

Survival of patients with colorectal liver metastases depends on the type of treatment. Liver resection is the best treatment which offers long term survival to the patients in selected cases. However, the resectability rate is only 30%. A good surveillance program after primary treatment is mandatory.

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ผลของการรักษามะเร็งตับทุติยภูมิที่เกิดจากมะเร็งลำไส้ใหญ่และทวารหนัก

บุญชู ศิริจินดากุล, ศุภฤกษ์ ปรีชายุทธ

ผู้รายงานได้ศึกษาถึงอัตราการอยู่รอดของผู้ป่วยมะเร็งตับทุติยภูมิที่เกิดจากมะเร็งลำไส้ใหญ่และทวารหนักที่ได้รับการรักษาที่ รพ.จุฬาลงกรณ์ ในระยะเวลา 10 ปี และเปรียบเทียบอัตราการอยู่รอดกับผลของการรักษาแต่ละวิธี ซึ่งได้แก่ การผ่าตัด, การใช้เคมีบำบัด, การรักษาแบบประคับประคอง ผลการศึกษาพบว่ามีผู้ป่วยที่ได้รับการรักษาทั้งหมดจำนวน 86 คน มีผู้ป่วย 26 คน (30.2%) ที่ได้รับการผ่าตัด, 39 คน (45.3%) ที่ได้รับเคมีบำบัด และ 21 คน (24.4%) ที่ได้รับการรักษาแบบประคับประคอง ผู้ป่วยทั้งหมดมีอัตราการอยู่รอดโดยเฉลี่ย 18 เดือน โดยที่อัตราการอยู่รอดโดยเฉลี่ยสูงสุดในกลุ่มผู้ป่วยที่ได้รับการผ่าตัด คือ 33 เดือน ขณะที่กลุ่มที่ได้รับเคมีบำบัด 17 เดือน และการรักษาแบบประคับประคอง 5 เดือน ซึ่งมีความแตกต่างอย่างมีนัยสำคัญทางสถิติ นอกจากนี้ชนิดของการรักษา, ระยะของโรคมะเร็งลำไส้ใหญ่และทวารหนัก และการมีการแพร่กระจายของเนื้องอกนอกตับเป็นปัจจัยที่ผลต่ออัตราการอยู่รอดของผู้ป่วย

อัตราการอยู่รอดของผู้ป่วยมะเร็งตับทุติยภูมิที่เกิดจากมะเร็งลำไส้ใหญ่และทวารหนักขึ้นอยู่กับชนิดของการรักษา โดยที่การผ่าตัดตัดเนื้องอกทำให้ผู้ป่วยมีโอกาสมีชีวิตยืนยาวได้มากที่สุด