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Journal of the Chinese Medical Association 74 (2011) 493–499

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Original Article

A new classification scheme for recurrent or metastatic colon cancer after liver metastasectomy

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Received December 31, 2010; accepted July 5, 2011

Abstract

Background: Metastasectomy is the standard treatment for patients with resectable liver metastasis from colon cancer. This study aimed to determine the impact of initial stage on overall survival (OS) after metastasectomy.
Methods: A retrospective analysis of 2804 patients diagnosed with colon cancer between 1999 and 2008.
Results: Of the cohort, 38.1% of the patients were stage IV or had recurrence after curative surgery, and 131 received liver metastasectomy. The 5-year survival rate for patients after liver metastasectomy was 42.1%. The 5-year survival rates after metastasectomy for initial stage I disease, stage II disease, stage III disease, and stage IV disease were 100%, 82.5%, 31.8%, and 36.9%, respectively ($p = 0.014$). When patients were grouped as initial stage I/II and stage III/IV, the 5-year survival rate after liver metastasectomy differed significantly (83.9% vs. 35.7%, $p = 0.006$). Patients with initial stage I/II disease after liver metastasectomy had a significantly better 5-year progression-free period compared to those with stage III/IV disease (60% vs. 28%, $p = 0.021$), which was due to the lower recurrence rate in the stage I/II group.
Conclusion: Our results suggest that patients who receive liver metastasectomy for metastatic colon cancer should be grouped into two groups: those with initial stages I and II disease, and those with stages III and IV disease, since the progression-free survivals (PFS) and OS after metastasectomy in these two groups differ significantly.

Keywords: colorectal neoplasms; hepatectomy; neoplasm metastasis

1. Introduction

Colon cancer is one of the most common malignancies worldwide, and nearly half of colon cancer patients have either metastatic disease at the time of diagnosis or develop metastases during the course of their disease. The incidence of colon cancer presenting as stage IV disease is approximately 19%.[1] In one multicenter study, the reported 5-year recurrence rates for stage I, II, and III colon cancer were 2.7%, 12.1% and 24.3%, respectively.[2] The liver is the most common site of metastasis, and if left unresected, survival time beyond 5 years is close to zero.[3]

The management of stage IV disease and recurrent colon cancer with liver metastasis has evolved over the past decade, reflecting the integration of new imaging technologies, advanced surgical methods, and new drug regimens. Such

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1726-4901/$ - see front matter
doi:10.1016/j.jcma.2011.09.004

regimens include irinotecan, oxaliplatin, bevacizumab and cetuximab. The standard treatment strategy for resectable metastatic colon cancer is synchronous metastasectomy. For disease that is potentially convertible to resection, the treatment is metachronous metastasectomy after chemotherapy, provided that clear surgical margins can be obtained[4] and adequate residual organ function remains.[5]

Until now, the 5-year survival rate after liver metastasectomy reported in the literature has ranged from 12% to 58%.[4,6–11] The wide range of reported 5-year survival rates is the result of variations in patient selection, criteria of resectability, the use of adjuvant chemotherapy and surgical expertise. However, in recent years, most studies in the literature have focused on overall survival (OS) or progression-free survival (PFS) after metastasectomy, regardless of the initial disease stage at diagnosis. The patients in these studies were usually analyzed statistically as a single population, because the number of patients was often limited to a single institute or surgical case series.

We retrospectively analyzed data from a single institution to examine the impact of initial disease stage on OS after liver metastasectomy in patients with colon cancer. The recurrence pattern after metastasectomy was also examined.

2. Methods

From January 1999 to January 2008, 1783 men and 1021 women were consecutively diagnosed with stage I through IV colon cancer at the Taipei Veterans General Hospital, Taiwan. Disease stage was based on the American Joint Committee on Cancer staging system, sixth edition.[12] All patients with a non-carcinoma tumor histology were excluded. For stage I through III colon cancers, we included only patients who were treated with curative surgery. Patients with rectal cancer were excluded due to the diverse strategies for the application of concurrent chemotherapy and radiation therapy, in locally advanced and low-lying tumors. Informed consent was obtained from all patients prior to enrolment.

Clinical-pathological staging and clinical course were determined by examining a computer database containing detailed information of all histology-proven colon cancer patients. Follow-up information and survival data were obtained from hospital records and the National Cancer Registry. Left colon cancer was defined as malignant in the splenic flexure, descending colon, sigmoid, and/or rectosigmoid colon, and right colon cancer was defined as that occurring in the cecum, ascending colon, hepatic flexure and/or transverse colon. The decision for metastasectomy was made by physicians after considering the extent of the metastatic lesions and condition of the individual patient. Extra-liver metastasis was an absolute contraindication for liver metastasectomy.

Death from any cause was regarded as an event. Patients who remained alive at the end of the follow-up period were censored. OS was defined as the time from metastasectomy to death from any cause. PFS was counted from the date of metastasectomy to the date of confirmation of recurrence. Synchronous metastasectomy was defined as resection of both metastatic and colonic lesions performed at initial hospitalization, and metachronous metastasectomy was defined as resection of metastatic and colonic lesions performed at separate hospitalizations. Surgical mortality was defined as death within 30 days after liver metastasectomy.

The follow-up period in this study ended in January 2009, or at the death of the patient. Patients were followed up for the first 2 years at least every 3 months from time of diagnosis, then every 6 months for 5 years, and then annually until death. Follow-up visits included physical examination, rectodigital examination, carcinoembryonic antigen (CEA) level, chest X-ray, abdominal sonogram and/or abdominal computed tomography (CT) scanning. If recurrence was suspected, further examinations such as chest CT, whole-body bone scan, or whole-body positron emission tomography (PET) scan were performed.

2.1. Statistical analysis

All statistical analyses were performed using SPSS statistical software version 16.0 for Windows (SPSS, Inc., Chicago, IL, USA).[13] Survival curves were computed according to the Kaplan–Meier method and compared by the log-rank test. Formal comparisons across groups were made with the Fisher's exact test (categorical variables). All hypothesis tests were two-sided. Cox regression analyses were performed to assess the independent prognostic significance of different factors. A value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Patient characteristics and 5-year OS

A total of 2804 patients met the inclusion criteria and were analyzed. Patient characteristics are presented in Table 1. The percentages of patients with stages I, II, III, and IV disease were 12.8%, 30.4%, 26.8%, and 30%, respectively. All stage I through stage III patients underwent curative surgical resection with clear histologic margins.

The 5-year survival rate for the entire cohort after diagnosis was 55.1% ($n = 2804$). The 5-year survival rate by stage was 86.9% for stage I disease, 77.8% for stage II disease, 60.6% for stage III disease, and 10.5% for stage IV disease (Fig. 1). For the patients who received liver metastasectomy ($n = 131$), the 5-year survival rate after metastasectomy was 42.1% (Fig. 2).

3.2. Characteristics and OS of metastasectomy according to initial stage

A total of 131 patients received liver metastasectomy. Of these, 77 (58.8%) patients received synchronous metastasectomy and 54 (41.2%) received metachronous metastasectomy. The basic characteristics of the patients who received liver metastasectomy are presented in Table 2. A total of 74/131 patients (56.4%) developed recurrence during follow-up.

Table 1
Patient' characteristics ($n = 2804$).

	Number	%
Gender		
Male/female	1783/1021	(63.6/36.4)
Race		
Chinese	2804	(100)
Age (y)		
Mean	66.5	–
Range	18–102	–
Pathology		
Adenocarcinoma	2734	(97.50)
Carcinoma	24	(0.86)
Mucinous adenocarcinoma	36	(1.28)
Mucinous carcinoma	1	(0.04)
Mucinous cystadenocarcinoma	2	(0.07)
Signet ring cell carcinoma	7	(0.25)
Location		
Right	1134	(40.40)
Left	1670	(59.60)
AJCC stage		
I	359	(12.80)
IIA	767	(27.35)
IIB	86	(3.07)
IIIA	52	(1.85)
IIIB	419	(14.94)
IIIC	280	(9.99)
IV	841	(29.99)

The OS rates after liver metastasectomy in patients with initial stage I, II, III, and IV disease are presented in Fig. 3A. The 5-year survival rate was 100%, 82.5%, 31.8%, and 36.9% in patients with initial stage I, II, III, and IV disease,

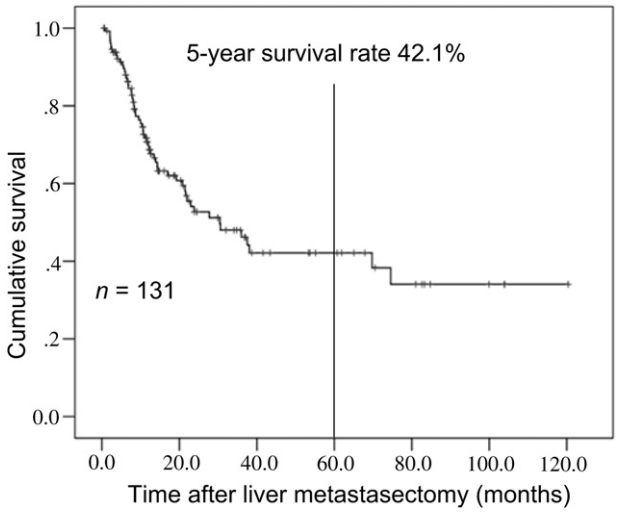
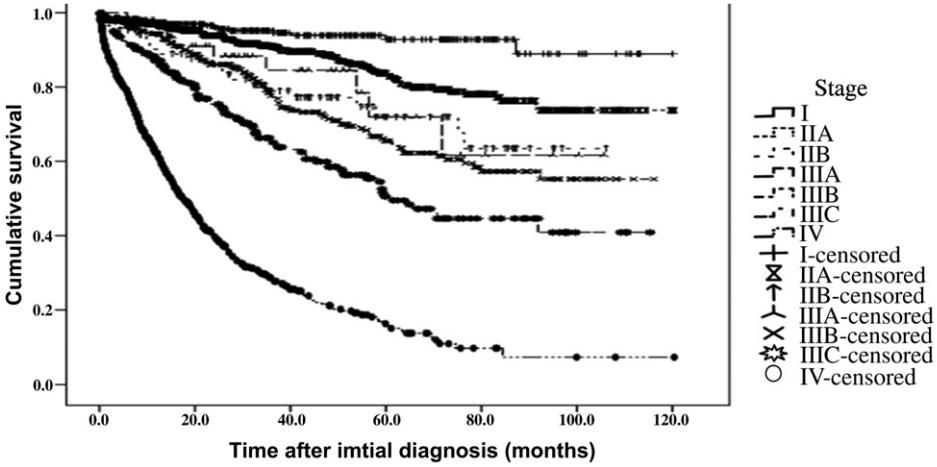


Fig. 2. The overall survival (OS) of all the patients who underwent liver metastasectomy.

respectively, which differed significantly in each stage ($p = 0.014$). As shown in Fig. 3B, it was much lower for patients of initial stages III/IV (35.7 % at 5 years) than for those of stages I/ II (83.9% at 5 years, $p = 0.006$).

3.3. PFS after liver metastasectomy

As seen in Fig. 4A, patients with initial stage I/II disease after liver metastasectomy had a significantly better PFS than patients with stage III/IV disease ($p = 0.021$). Moreover, the 30-month relapse rate was significantly higher in patients with



No. at risk	0 months	12 months	24 months	36 months	48 months	60 months	72 months	84 months	96 months	108 months	120 months
I	359	284	224	160	121	85	64	29	14	9	0
IIA	767	617	457	354	266	187	132	85	45	16	1
IIB	86	70	62	47	35	24	20	11	2	0	0
IIIA	52	45	32	22	19	9	6	3	2	0	0
IIIB	419	357	274	198	154	106	68	40	20	5	0
IIIC	280	217	154	107	85	48	31	20	10	3	0
IV	841	367	161	84	48	25	10	4	3	2	1

Fig. 1. The overall survival (OS) of all patients according to stage.

Table 2
Characteristics of patients who received liver metastasectomy ($n = 131$).

Gender	Number	%
Male/female	82/49	(62.6/37.3)
Race		
Chinese	131	(100)
Age (y)		
Mean	62.0	
Range	25–84	
Pathology		
Adenocarcinoma	128	(97.9)
Carcinoma	1	(0.7)
Mucinous adenocarcinoma	2	(1.4)
Location		
Right	57	(43.5)
Left	74	(56.5)
AJCC stage		
I	1	(0.8)
IIA	13	(9.9)
IIB	1	(0.8)
IIIA	0	(0)
IIIB	15	(11.5)
IIIC	7	(5.3)
IV	94	(71.7)
CEA ng/mL		
Mean	63.1	
Range	1.6–2476	
Surgical margin		
R0	119	(90.8)
R1,R2	12	(9.2)
Relapse pattern ($n = 74$)		
Liver	33	(44.6)
Not liver	41	(55.4)
Frequency of metastasectomy		
1	123	(93.6)
2	7	(5.6)
3	1	(0.8)
Number of liver metastases at operation		
<4	122	(93.1)
≥4	9	(6.9)
Regimen of adjuvant chemotherapy after metastasectomy		
Oxaliplatin-based	33	(25.2)
Irinotecan-based	41	(31.3)
5-FU-based	39	(29.8)
Observation	18	(13.7)
Surgical mortality <30 days	1	(0.7)

CEA = carcinoembryonic antigen; FU = fluorouracil.

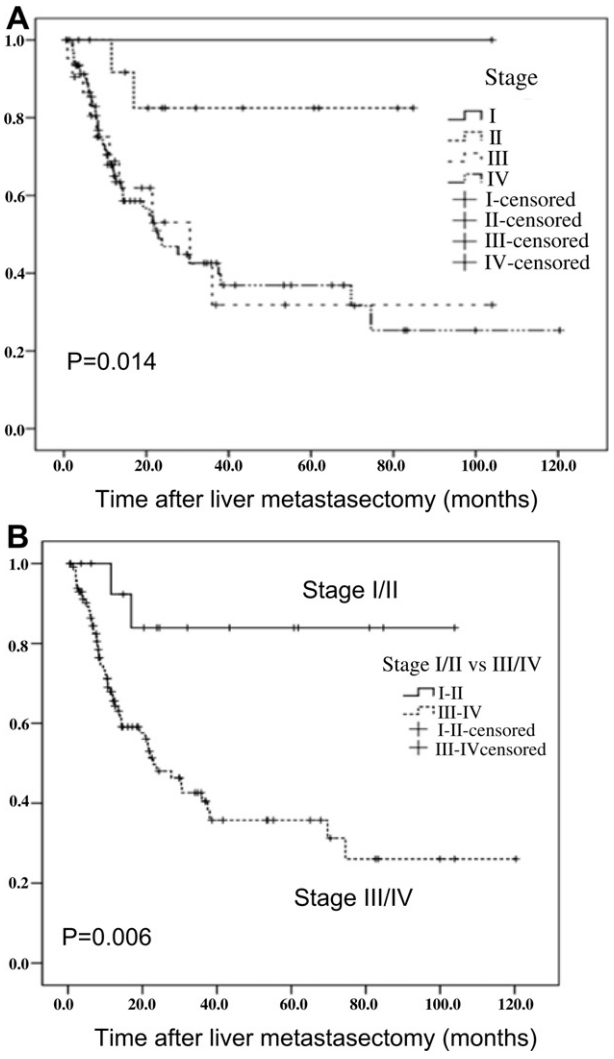


Fig. 3. The overall survival (OS) of the patients with stages I, II, III and IV disease who received liver metastasectomy: (A) OS after metastasectomy of stage I to IV; (B) OS after liver metastasectomy dividing patients to stage I–II and III–IV.

initial stage III/IV disease ($p = 0.006$). As seen in Fig. 4B, regardless of stage, most patients experienced recurrence within 30 months (93.2%, $p = 0.222$).

3.4. Univariate and multivariate analysis of possible prognostic factors associated with OS to liver metastasectomy

Several prognostic factors for liver metastasectomy were analyzed (Tables 3 and 4). Univariate analysis revealed that the primary tumor stage ($p = 0.006$), the number of metastases found in the liver when receiving liver metastasectomy ($p = 0.003$), and the metastatic tumor distribution ($p = 0.038$) significantly affected the OS. Other risk factors such as elevated CEA, diagnosis interval, adjuvant chemotherapy regimens and receipt of adjuvant chemotherapy, were also investigated but did not reach statistical significance for OS. Multivariate analysis showed that primary tumor stage was an independent factor for predicting OS after liver metastasectomy.

4. Discussion

A total of 2804 patients were diagnosed with colon cancer from 1999 to 2008 at our hospital. Among them, 30% were initially diagnosed as stage IV disease. We found that almost 20% of patients who did not have metastatic disease at initial

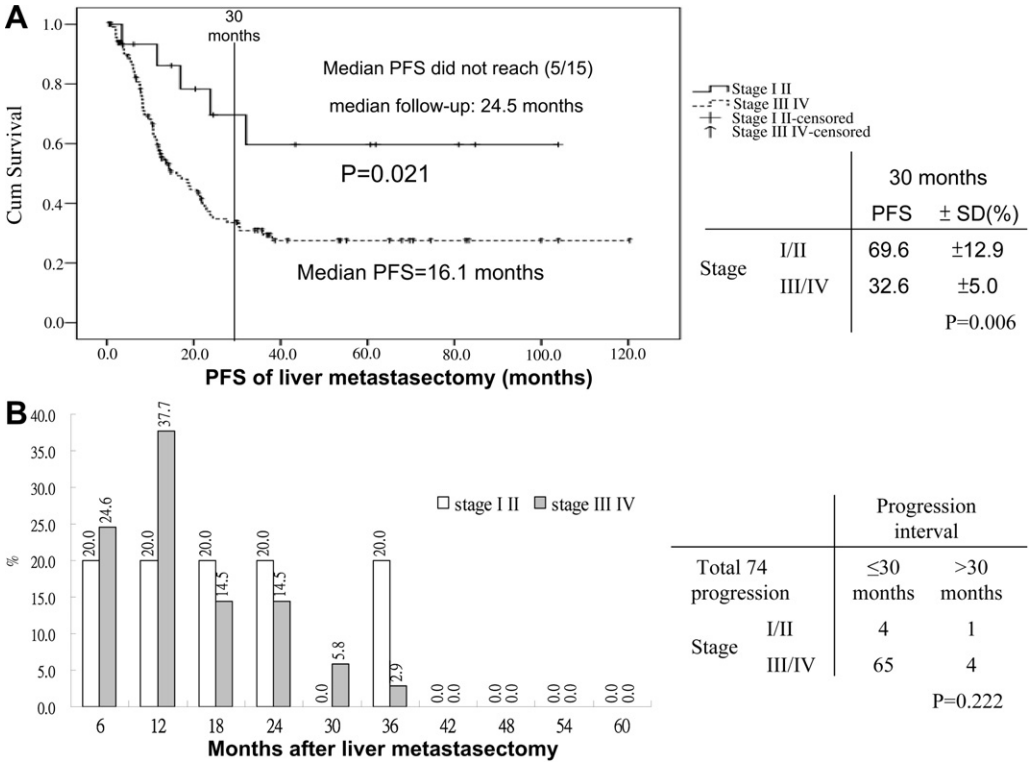


Fig. 4. (A) Progression-free survival (PFS) after liver metastasectomy: stage I/II versus stage III/IV.; (B) Distribution of recurrence after liver metastasectomy, stage I/II versus stage III/IV.

diagnosis eventually developed metastases. Additionally, 38.1% of patients eventually developed stage IV or recurrent disease. Among all colon cancer patients, only 131 (12%) received liver metastasectomy. The 5-year survival rate after liver metastasectomy was 42.1%, which is similar to previous reports.[4,6–11] The relatively low metastasectomy rate was attributed to surgeon preference, as most surgeons only performed resection in patients with ≤4 liver metastases, which is traditionally regarded as the inclusion criteria for metastasectomy.[14]

To date, numerous studies have reported a survival benefit after liver metastasectomy. Most of the published data reported the OS and PFS rates after metastasectomy. The OS rate after liver metastasectomy was significantly different between initial stage I/II and III/IV disease (Fig. 3B). However, in the literature, almost all data was analyzed under the hypothesis that all patients receiving the liver metastasectomy were in the same group. Indeed, we found that they differed according to OS. This difference partially contributes to the wide range of OS after liver metastasectomy reported in the literature. Only a few reviews have indicated the importance of initial disease stage.[15–19] Furthermore, an important issue concerns which factors contributed to significantly better PFS and OS rates after metastasectomy in patients with initial stage I/II disease. We believe this can be partially explained by a lower recurrence rate in initial stage I/II patients, despite the fact that most of them relapsed within 3 years as stage III/IV disease (Fig. 4).

Many clinical features have been suggested as prognostic factors.[20,21] However, results vary considerably from study to study. In our study, parameters including age, sex, primary disease stage, location, metastatic tumor distribution, number of metastasis, CEA, adjuvant chemotherapy and synchronicity were examined (Tables 3 and 4). Adjuvant chemotherapy after liver metastasectomy (neither 5-fluorouracil nor oxaliplatin/irinotecan based) showed no significant survival benefit in our cohort, which was similar to other pooled analyses.[22] The primary tumor stage, the number of metastases in the liver at the time of liver metastasectomy, and the metastatic tumor distribution affected the OS significantly on univariate analysis, but only the initial disease stage was a significant prognostic factor after multivariate analysis. Based on our analysis, we believe that patients who receive liver metastasectomy should be divided into those with initial stage I–II disease and those with stage III–IV disease for analysis.

A total of 74/131 (56%) patients who underwent liver metastasectomy developed recurrence, which is similar to previous reports; this indicated a recurrence rate of 40% to 80%.[23,24] Although few relapses occurred in stage I/II patients, most of the relapse events occurred within 30 months, and none occurred beyond 5 years from the time of diagnosis. Thus, the relapse distribution is similar. In addition, the 5-year progression free interval after liver metastasectomy could be the boundary that distinguishes a cure from a fatal outcome.

Our study was limited in that most of the patients (96.2%) had ≤4 liver metastases at the time of metastasectomy.

Table 3
Factors associated with overall survival after liver metastasectomy in univariate analysis.

	Number of patients	5-y survival (%)	*p* value
Overall survival	131	42.1	
Sex			
Male	82	41.1	0.351
Female	49	43.6	
Age			
≤60	59	37.7	0.455
>61	72	45.1	
Location			
Right	57	36.7	0.139
Left	74	46.4	
Diagnosis interval			
Synchronous	77	37.2	0.419
Metachronous	54	50.5	
Primary tumor stage			
Stage I/II	15	83.9	0.006
Stage III/IV	116	35.7	
Number of metastases			
<4	122	43.3	0.003
≥4	9	25.0	
Metastatic tumor distribution			
Unilobar	83	52.9	0.038
More than unilobar	48	27.7	
CEA ng/mL			
≤20	86	48.1	0.083
>20	45	25.4	0.780
Adjuvant chemotherapy			
Yes	113	40.1	
No	18	52.6	

CEA: carcinoembryonic antigen.

Table 4
Multivariate analysis of possible prognostic factors on overall survival after liver metastasectomy.

	Hazard ratio (95% CI)	*p* value
Primary tumor stage		
Stage I/II	1	0.020
Stage III/IV	5.357 (1.299-22.097)	
Metastatic tumor distribution		
Unilobar	1	0.158
More than unilobar	1.496 (0.856-2.614)	
Number of metastases		
<4	1	0.084
≥4	1.308 (0.964-1.774)	

CI = confidence interval.

Therefore, we could not evaluate the efficacy of more extensive liver metastasectomies.

In conclusion, our results suggest that patients who receive liver metastasectomy for metastatic colon cancer should be grouped into two groups, those with initial stages I and II disease, and those with stages III and IV disease, since the PFS and OS after liver metastasectomy in these two groups differ significantly.

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