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A Preliminary Analysis of Combined Liver Resection With New Chemotherapy for Synchronous and Metachronous Colorectal Liver Metastasis

Wilson Wing Chi Ng, Yue Sun Cheung, John Wong, Kit Fai Lee and Paul Bo San Lai, Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, The Chinese University of Hong Kong, Hong Kong SAR.

OBJECTIVE: To compare the survival between patients with synchronous and metachronous colorectal liver metastases after hepatectomy with new generation of perioperative chemotherapy.
METHODS: From October 2002 to January 2008, patients receiving hepatectomy for synchronous or metachronous colorectal liver metastasis were studied retrospectively.
RESULTS: Fifty-five patients (synchronous group = 35, metachronous group = 20) underwent hepatectomy for colorectal liver metastases. Besides younger age with male predominance, patients in the synchronous group had more tumour multinodularity and bilobe liver involvement. They had received less hepatic curative hepatectomy (81.1% *vs.* 100%) with a higher rate of peri-operative chemotherapy (91.4% *vs.* 50%) and post-operative morbidity (25.7% *vs.* 0%). However both groups had no statistical significant difference in median overall survival (OS) and disease free survival (DFS). Inferior OS and DFS were observed in the synchronous group for patients who had no peri-operative chemotherapy or those showing poor response to chemotherapy. The most favourable OS is observed in both groups after performing globally curative hepatectomy.
CONCLUSION: Synchronous colorectal liver metastasis is not a poor prognostic factor for survival when compared with the metachronous metastasis. Globally curative hepatectomy in combination of new generation of chemotherapy is recommended for the management of resectable colorectal liver metastasis.
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Key Words: chemotherapy, colorectal liver metastasis, metachronous, synchronous

Introduction

About 20–25% of patients have clinically detectable synchronous colorectal liver metastases at the initial diagnosis of colorectal cancer and a further 40–50% develop metachronous liver metastases within 3 years of primary surgery.[1] Although only about 8–23% of colorectal liver metastases are resectable at the time of initial diagnosis,[2–4] curative liver resection remains the only treatment that can offer long-term survival in these two groups of patients. The reported 5-year survival rates range from 35–40% according to large studies.[5–7] However disease relapse is common even after curative liver resection and it occurs in up to 75% of patients.[8] In the era of a new generation of chemotherapeutic agents such as 5-fluorouracil/leucovorin with oxaliplatin (FOLFOX), 5-fluorouracil/leucovorin with irinotecan (FOLFIRI) and targeted therapy (e.g. cetuximab, bevacizumab), the response rates have been increased significantly in recent years. The improved efficacy of chemotherapy not only increases patient survival in palliative settings[9] but also renders the initially unresectable colorectal liver

Address correspondence and reprint requests to Professor Paul B.S. Lai, Department of Surgery, The Chinese University of Hong Kong, Prince of Wales Hospital, 30–32 Ngan Shing Street, Shatin, Hong Kong SAR.
E-mail: paullai@surgery.cuhk.edu.hk • Date of acceptance: 24 August 2009

metastases resectable in a proportion of patients. Adam et al in 2004[4] reported that 12.5% of initially unresectable metastases can be rendered resectable after a newer generation of downstaging chemotherapy, and the overall 5-year survival rate after liver resection can be raised up to 33%. Most importantly, the survival benefit of peri-operative chemotherapy has also extended to eligible and resected colorectal liver metastases and this was confirmed by the recent EORTC 40983 trial.[10]

Although more and more beneficial evidence of new chemotherapy for colorectal liver metastasis has been published in the medical literature, few studies have evaluated the differential benefit of new chemotherapy and liver resection in synchronous versus metachronous liver metastases.[11] The aim of this study is to compare the survival between groups of patients with synchronous and metachronous colorectal liver metastasis after liver resection in the era of new generation of chemotherapeutic agents.

Patients and Methods

From October 2002 to January 2008, a total of 55 patients undergoing liver resection for colorectal liver metastasis in a single tertiary referral centre were identified. The inclusion period started with the introduction of a newer generation of chemotherapy (FOLFOX or FOLFIRI) into our centre. These patients were divided into synchronous group and metachronous group for analysis according to the status of liver metastasis. The liver metastasis was classified as synchronous if the primary colorectal cancer and hepatic metastasis were discovered at the same time or during the colectomy, or if the hepatic metastasis was discovered before the primary tumour, or within 3 months after the colectomy without pre-operative chemotherapy or radiotherapy. Those liver metastases discovered more than 3 months after the primary cancer were classified as metachronous tumours.

Tumour resectability was assessed by the hepatobiliary surgeon, senior radiologist and oncologist at a joint clinic based on the number, size and extent of the liver tumour. The aim of the liver resection was to achieve a macroscopically curative resection with adequate liver reserve. The decision on peri-operative chemotherapy was made by the multidisciplinary team based on individual status. Some of our patients with resectable tumours received neoadjuvant and adjuvant chemotherapy as they were recruited as participants of EORTC 40983 trial.[10] Pre-operative chemotherapy was also given to patients with initially unresectable liver metastasis (downstaging chemotherapy with the intention to shrink the lesions) so that they could be considered for hepatectomy at subsequent re-evaluations. For those patients who had received pre-operative chemotherapy, the same group of specialists would assess the response to chemotherapy and subsequent resectability after three or four cycles of chemotherapy. Follow-up abdominal computed tomography (CT) scans were performed and the response to chemotherapy was evaluated according to the WHO response criteria.[12] Postoperative chemotherapy was also recommended to patients with residual disease after liver resection. Under normal circumstances, patients had to pay for the drug charges of newer chemotherapeutic agents (FOLFOX, FOLFIRI, cepacitabine, cetuximab, bevacizumab). It is a widely adopted practice in the Hospital Authority of Hong Kong.

Patients' medical records were reviewed retrospectively and compared for the following data: demographic data, tumour characteristics, characteristics of hepatectomy, morbidity and mortality, pre- and post-hepatectomy chemotherapy, chemotherapy response rate and survival. All data were recorded in a computerized database to facilitate subsequent analysis.

Statistical analysis was performed by the Statistical Package for the Social Sciences (Windows version 15.0; SPSS Inc, Chicago, IL, USA). The Chi-squared test or Fisher's exact test was used for categorical variables, whereas Mann-Whitney U-test was used for continuous variables. The Kaplan-Meier method was used in calculating survival time from the date of first liver resection to the date of death or the date of last follow-up for those patients who were still alive. Prognostic factors of survival were assessed by log-rank test and Cox Regression in univariate and multivariate analysis respectively. Values of p of less than 0.05 were considered significant.

Results

Demographics and clinical features

A total of 55 consecutive patients had undergone liver resection for colorectal liver metastasis during the study period. The majority (63.6%) of our patients had synchronous colorectal liver metastasis. Compared with the metachronous group, patients in the synchronous group were younger (median age, 55.3 *vs.* 60.0, $p = 0.024$) and

Table 1. Demographics and clinical features of patients in synchronous and metachronous groups

	Synchronous group ($n = 35$)	Metachronous group ($n = 20$)	p
Median age (range) [yr]	55.3 (28–81)	60.0 (49–78)	0.024
Sex (M:F)	24:11	8:12	0.05
ASA classification			0.410
Class 1	24	13	
Class 2	11	6	
Class 3	0	1	
Site of primary colorectal cancer			1.000
Colon	26	15	
Rectum	9	5	
Dukes' staging at resection of colorectal cancer*			< 0.001
Dukes' A	0	1	
Dukes' B	0	5	
Dukes' C	0	12	
Dukes' D	35	1	
Median CEA level at diagnosis of colorectal cancer (range) [ng/mL]	14.1(2–3525)	8.9 (3–51)	0.372
Imaging studies for liver metastases			
CT abdomen only	35 (100%)	20 (100%)	
PET scan	29 (82.9%)	20 (100%)	0.056
Initial liver metastases			
Unilobar	20 (57%)	18 (90%)	0.015
Bilobar	15 (43%)	2 (10%)	0.046
Median number of metastases (range)	2 (1–12)	1 (1–2)	
Median maximal tumour size at diagnosis (range) [mm]	22.5 (3–130)	33 (10–130)	0.566

*One patient in the metachronous group had no detailed record for Dukes' staging.

were predominantly male (Table 1). Moreover, more tumour multinodularity and bilobe liver involvement were observed in the synchronous group. A pre-operative abdominal CT scan was done for all patients in our study. Although less pre-operative whole body positron emission tomography (PET) scans (82.9% *vs.* 100%, $p = 0.056$) were performed in the synchronous group, an additional CT of the thorax was done for most of the patients (four out of six) without PET scans. The median number of liver metastasis for synchronous and metachronous group were two and one ($p = 0.046$) and the median maximal size of tumour in the two groups were 22.5 mm and 33 mm respectively ($p = 0.566$). There was no statistical significant difference in ASA classification, the site of the primary tumour location and the median carcinoembryonic antigen (CEA) level at the diagnosis of the primary tumour between the two groups (Table 1).

Characteristics of hepatectomy

Thirty-five patients in the synchronous group underwent 37 hepatectomies as two patients in this group had two separate hepatectomies for recurrent liver metastasis (Table 2). Another 22 hepatectomies were performed for 20 patients in the metachronous group as one patent had received three separate hepatectomies for the recurrent disease. All the operations were single-stage hepatectomy. Both groups had the same median pre-hepatectomy CEA level (11 ng/mL). Initially, 34.3% of liver metastases in the synchronous and 10% in the metachronous group were unresectable ($p = 0.058$) and the main reason for unresectability was the multinodularity of the tumour (Table 2). Moreover a significant lower rate of hepatic curative hepatectomy (defined as clear resection margin, irrespective of extrahepatic disease) could be achieved in the synchronous group (81.1% *vs.* 100%, $p = 0.039$), but there

Table 2. Characteristics of hepatectomy performed for patients with synchronous and metachronous colorectal liver metastases

Characteristics	Synchronous group ($n=35$)	Metachronous group ($n=20$)	p
Median pre-hepatectomy CEA level (range) [ng/mL]	11.0 (1–800)	11.0 (2–120)	0.530
Total no. of liver resections performed	37	22	0.235
Patients with			
1 hepatectomy	33	19	
2 hepatectomies	2	0	
3 hepatectomies	0	1	
Hepatic curative resection	81.1% (30/37)	100% (22/22)	0.039
Global curative resection	75.7% (28/37)	95.5% (21/22)	0.074
Major hepatectomy (≥ 3 Couinaud segments)	40.5% (15/37)	40.9% (9/22)	1.00
Minor hepatectomy (< 3 Couinaud segments)	59.5% (22/37)	59.1% (13/22)	
No. of laparoscopic hepatectomies	3	1	
Local ablative treatment	9	3	0.151
Concomitant intra-operative RFA	7	1	
Pre-hepatectomy RFA	2	1	
Post-hepatectomy RFA	0	1	
Patients with initial unresectable liver metastasis	12	2	0.058
Main cause of unresectability			
Multinodularity	10	1	
Large tumour size	2	1	
Median resection margin (range) [mm]	5.0 (0–65)	11.0 (1–60)	0.159

was no statistically significant difference in the globally curative resection rate (defined as no residual hepatic disease and no extrahepatic metastasis) between the two groups (75.7% *vs.* 95.5%, $p=0.074$). A small number of patients in the synchronous group with initially unresectable liver metastasis received palliative liver resection after an unfavourable response (no change or progressive disease) to downstaging chemotherapy. This surgery was performed in the hope of benefits from tumour debulking surgery and subsequent palliative adjuvant chemotherapy. Both groups had a similar proportion of major hepatectomy (≥ 3 Couinaud segments) of about 41%. During the study period, we did not perform synchronous liver resections and colectomies during the same operation. Only four laparoscopic minor hepatectomies (< 3 Couinaud segments) were performed in this study. Radiofrequency ablation (RFA) was used in 25.7% of patients in the synchronous group and 10% of patients in the metachronous group ($p=0.151$) and concomitant intra-operative RFA was the most commonly used procedure (Table 2). There was no statistically significant difference in the median minimal clear resection margin for the synchronous and metachronous group (5 mm *vs.* 11 mm, $p=0.159$).

Morbidity and mortality

There was no operation-associated mortality in our series (Table 3). All the postoperative complications (25.7%) were observed in the synchronous group. The majority were wound infections while one patient had an infected intra-abdominal collection, which was treated by ultrasound-guided trans-abdominal drainage and antibiotics. The median hospital stays in the synchronous and metachronous groups were 9 and 8 days respectively ($p=0.48$).

Peri-operative chemotherapy

Nineteen patients (54.3%) in the synchronous group had received a median of 6 cycles of pre-hepatectomy chemotherapy (range, 2–22). Eleven patients had downstaging while eight patients had neoadjuvant chemotherapy. FOLFOX (57.9%) and FOLFIRI (26.35%) were the two most commonly used initial chemotherapy therapies (Table 4). The pre-operative chemotherapy response rate [partial and complete response according to the World

Table 3. Morbidity and mortality for synchronous and metachronous groups

	Synchronous group	Metachronous group	*p*
No. of patients who developed complications	9 (25.7%)	0	0.02
Non infected collection	2	0	
Infected collection with liver failure	1	0	
Wound infection	6	0	
30 days in-hospital mortality rate	0	0	
Median hospital stay (range) [d]	9 (6–31)	8 (4–7)	0.48

Table 4. Summary of chemotherapy use in synchronous and metachronous groups

	Synchronous group (n = 35)	Metachronous group (n = 20)
No. of patients with prehepatectomy chemotherapy	19 (54.3%)	1 (5%)
Downstaging	11	1
Neoadjuvant	8	0
Median cycle of chemotherapy (range)	6 (2–22)	5 (4–6)
Usage of 1st line chemotherapy		
FOLFOX	11	0
FOLFIRI	5	0
Capecitabine	2	0
5-FUFA	1	1
No. of lines		
1	16	0
2	3	1
No. of patients with post-hepatectomy chemotherapy	27 (77.1%)	7 (35%)
Palliative	9	1
Adjuvant	18	6
Median cycle of chemotherapy (range)	2 (2–13)	6 (3–12)
Usage of 1st line chemotherapy		
FOLFOX	15	2
FOLFIRI	0	1
5-FUFA	7	4
Capecitabine	4	0
Targeted therapy	1	0
No. of lines		
1	18	5
2	7	0
≥ 3	2	2
No. of patients receiving pre-hepatectomy chemotherapy	19 (54.3%)	1 (5%)
Response rate*	57.9 % (11/19)	100% (1/1)
No. of patients receiving post-hepatectomy chemotherapy	27 (77.1%)	7 (35%)
Response rate*	37.0% (10/27)	71.4% (5/7)
Total patients receiving peri-hepatectomy chemotherapy	32 (91.4%)	10 (50%)
Overall response rate*	56.3% (18/32)	60.0% (6/10)

*Response rate is based on partial or complete response to chemotherapy according to WHO response criteria.[12]

Table 5. Univariate analysis of prognostic factors of overall survival

	Median overall survival (mo)	*p*
Mode of presentation		0.075
Synchronous	29.7	
Metachronous	47.7	
Location of metastasis		0.003
Bilobed	19.3	
Unilateral	54.9	
Globally curative resection		< 0.001
Yes	48.9	
No	17	
Pre-hepatectomy CEA		0.119
< 50	42.7	
≥ 50	19.3	
Size of metastasis		0.02
< 5 cm	48.9	
≥ 5 cm	29.7	
Resection margin		< 0.001
< 1 cm	14.7	
≥ 1 cm	39.9	
Use of peri-operative chemotherapy		0.822
No	34.6	
Yes	39.9	
Chemotherapy response		0.001
No chemotherapy/unfavourable response	33.8	
Partial/complete response	60.5	

Health Organisation (WHO) response criteria] was 57.9%. Only one patient (5%) in the metachronous group had received pre-operative chemotherapy. The coverage of post-hepatectomy chemotherapy was 77.1% in the synchronous and 35% in the metachronous group (Table 4). A majority of them had received adjuvant rather than palliative postoperative chemotherapy (Table 4). FOLFOX (55.5%) and 5-fluorouracil/leucovorin (26%) were two most commonly used first line postoperative chemotherapy in the synchronous group while 5-fluorouracil/leucovorin (71.4%) and FOLFOX (28.6%) were the favourable first line chemotherapy for the metachronous group. The postoperative chemotherapy response rates were 37% in the synchronous and 71.4% in the metachronous group. Overall the synchronous group had a higher rate of perioperative (pre- or post-hepatectomy) chemotherapy when compared with the metachronous group (91.4% *vs.* 50%, $p = 0.001$) (Table 4). However the overall chemotherapy response rates (partial or complete response to pre- or postoperative chemotherapy) were similar in both groups (synchronous: 56.3%, metachronous: 60%, $p = 0.218$).

Survival analysis

For unilobar liver metastasis, tumour sizes smaller than 5 cm, resection margins of more than 1 cm, globally curative resection, and favourable response to chemotherapy were significant prognostic factors of better overall survival in univariate analysis (Table 5). In multivariate analysis, tumours smaller than 5 cm ($p = 0.002$), global curative resection ($p = 0.013$) and a favourable response to chemotherapy ($p = 0.013$) were significant independent prognostic factors.

The median duration of follow up for the synchronous and metachronous groups were 19.3 and 35.4 months respectively ($p = 0.964$). Although the synchronous group had a shorter median overall survival (OS)

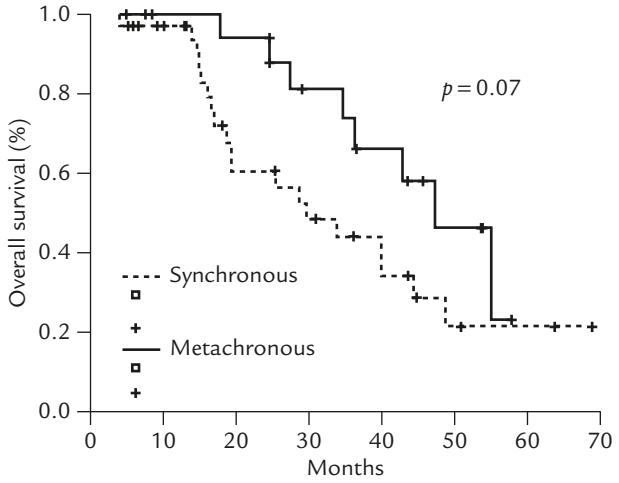

Figure 1. Kaplan-Meier curves of overall survival in synchronous and metachronous groups.

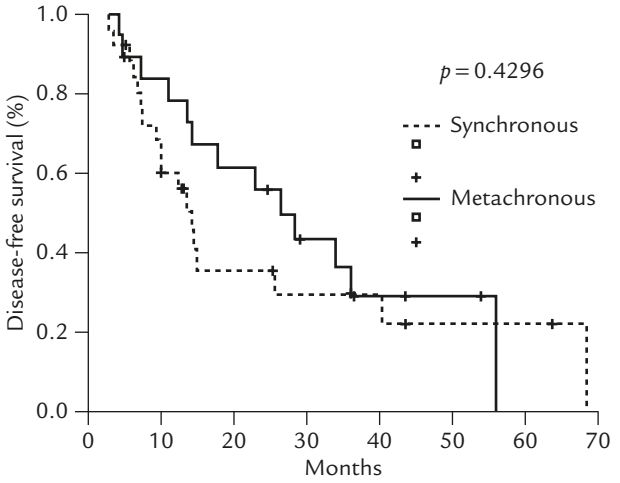

Figure 2. Kaplan-Meier curves of disease-free survival in synchronous and metachronous groups.

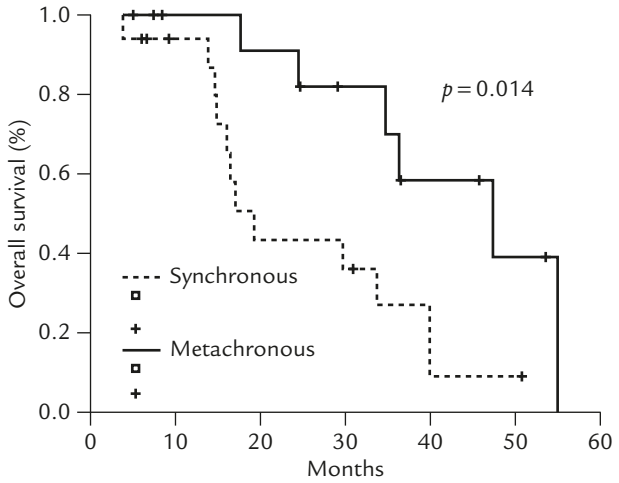

Figure 3. Kaplan-Meier curves of overall survival for patients with no chemotherapy and poor response to chemotherapy in synchronous and metachronous groups.

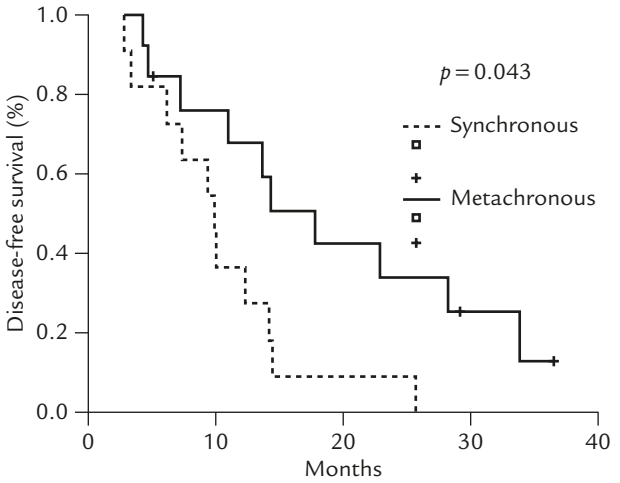

Figure 4. Kaplan-Meier curves of disease-free survival for patients who had no chemotherapy or those showing a poor response to chemotherapy in synchronous and metachronous groups.

[29.7 (95% confidence interval (CI) 17.0–42.4) *vs.* 47.4 (95% CI 37.2–57.6) months] and median disease-free survival (DSF) [10.0 (95% CI 6.5–13.6) *vs.* 26.4 (95% CI 12.4–40.3) months] when compared with the metachronous group, both of the observed differences did not reach a statistically significant level (Figures 1 and 2). Subgroup analysis of survival was also performed in regard to the response to peri-operative chemotherapy between the two groups. In the synchronous group, patients with no chemotherapy or an unfavourable response to chemotherapy (no change or progressive disease according to the WHO criteria) had a poorer overall survival rate [19.3 (95% CI 14.3–24.4) *vs.* 47.4 (95% CI 25.8–68.9) months, $p = 0.014$] and disease-free survival [9.9 (95% CI 6.9–12.8) *vs.* 17.8 (95% CI 10.9–24.7) months, $p = 0.043$] (Figures 3 and 4). On the other hand, for those patients who showed favourable response (partial or complete response) to peri-operative chemotherapy, the OS and DFS were similarly good in both groups (Figures 5 and 6). Moreover the most favourable median overall survival was observed in both groups [synchronous: 44.3 months (95% CI 37.1–51.5), metachronous: 47.4 months (95% CI 37.2–57.6), $p = 0.612$] after globally curative hepatectomy for liver metastases (Figure 7).

Discussion

Traditionally, synchronous colorectal liver metastasis is regarded as one of the poor prognostic factors for survival. Although there is increasing evidence in the

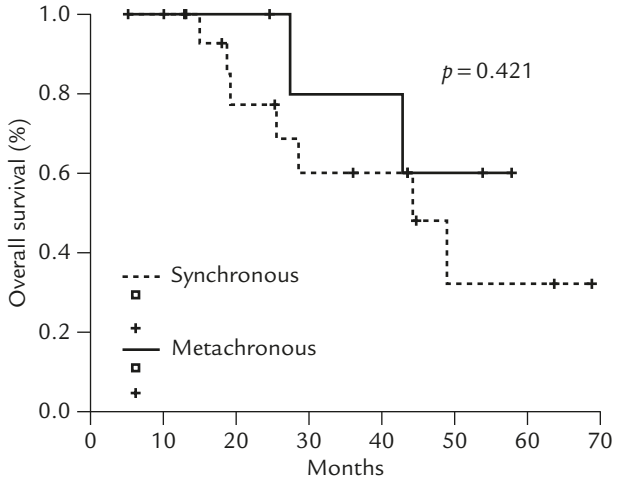

Figure 5. Kaplan-Meier curves of overall survival for patients with a partial or complete response to chemotherapy in synchronous and metachronous groups.

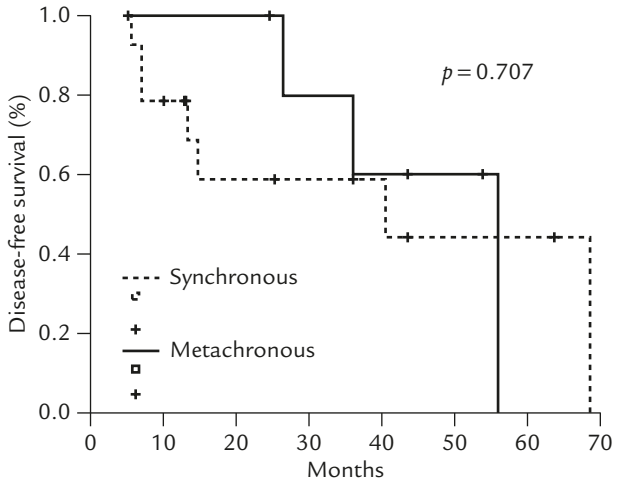

Figure 6. Kaplan-Meier curves of disease-free survival for patients with a partial or complete response to chemotherapy in synchronous and metachronous groups.

medical literature to show the benefit of a newer generation of chemotherapeutic agents for colorectal liver metastasis,[4,9,10] few studies have evaluated the differential benefit of new chemotherapy and liver resection in synchronous versus metachronous liver metastases.[11] This is a retrospective study aimed at comparing the survival between the two groups. Since the duration of follow-up in both groups is relatively short, only the intermediate survival results are available for comparison in this study.

Concerning the patients' demographics and tumour characteristics, the synchronous group has the characteristic of younger age with male predominance. Moreover this group also has more tumour multinodularity and

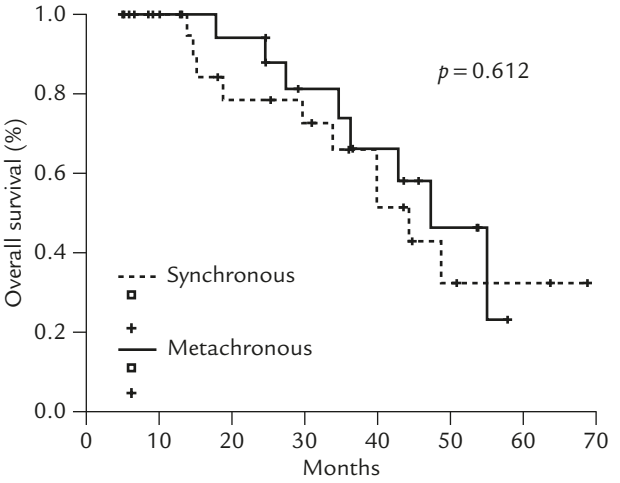

Figure 7. Kaplan-Meier curves of overall survival for patients after globally curative hepatectomy in synchronous and metachronous groups.

bilobe liver involvement. As a result, less curative hepatectomy can be achieved and a higher rate of peri-operative chemotherapy is necessary in this group.

No operation-associated mortality was reported in our study. All the postoperative complications were observed in the synchronous group and the majority of them were due to minor wound infections. Although the synchronous group carries all the unfavourable factors mentioned above, there is no statistically significant difference observed in the OS and DFS between the two groups. The most important factor affecting the survival is the coverage of a newer generation of peri-operative chemotherapy because the OS and DFS were statistically inferior in the synchronous group for those patients who have no peri-operative chemotherapy or those showing an unfavourable response to chemotherapy (Figures 3 and 4). The most favourable median overall survival is observed in the two groups after performing globally curative liver resection (Figure 7). These results showed that performing a globally curative hepatectomy and giving a newer generation of chemotherapeutic agents in colorectal liver metastases could achieve a survival benefit.

There were several limitations in our study. Firstly, there was a relatively small sample size in our study. There was no standardised protocol for chemotherapy and newer generation chemotherapy could not be afforded by all patients. However, before the publication of the European Organization for Research and Treatment of Cancer (EORTC) 40983 trial in 2008,[10] there was no strong evidence to support the use of neoadjuvant and adjuvant chemotherapy for resectable colorectal liver metastasis.

Moreover the role of adjuvant chemotherapy after curative hepatectomy is still controversial as there is a lack of published data on this issue.[13] It is understandable that the metachronous group has a lower rate of peri-operative chemotherapy because most of the tumours are resectable and a higher rate of globally curative hepatectomy can be achieved in this group.

Conclusion

We conclude that synchronous colorectal liver metastasis is not a poor prognostic factor for survival when compared with metachronous colorectal liver metastasis. Resectable synchronous colorectal liver metastasis should not be an obstacle for aggressive treatment including hepatectomy and peri-operative chemotherapy. The strategy of globally curative hepatectomy in combination with a new generation of chemotherapy is recommended for the management of resectable colorectal liver metastasis. More liberal use of peri-operative chemotherapy should be considered for both groups in order to optimise survival.

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