RESEARCH ARTICLE

Survival Outcomes of Liver Metastasectomy in Colorectal Cancer Cases: A Single-Center Analysis in Turkey

Suna Cokmert[1], Hulya Ellidokuz[2], Lutfiye Demir[1,3]*, Mehmet Fuzun[4], Ibrahim Astarcioglu[4], Deniz Aslan[5], Ugur Yilmaz[6], Ilhan Oztop[5]

Abstract

Background: The purpose of this study was to analyze our series of liver resections for metastatic colorectal carcinoma (mCRC) to determine prognostic factors affecting survival and to evaluate the potential roles of neoadjuvant or adjuvant chemotherapy. Materials and Methods: Ninety-nine patients who underwent metastasectomy for liver metastases due to colorectal cancer at the Department of Medical Oncology, 9 Eylul University Hospital between 1996 and 2010 were evaluated in this study. The patients were followed through July 2013. Demographic, perioperative, laboratory, radiological and chemotherapy as well as survival data were obtained by retrospective chart review. Results: In 47 (47.5%) patients, liver metastases were unresectable at initial evaluation; the remaining 52 (52.5%) patients exhibited resectable liver metastases. Simultaneous hepatic resection was applied to 52 (35.4%) patients with synchronous metastasis, whereas 5 (64.5%) patients underwent hepatic resection after neoadjuvant chemotherapy. Forty-two patients with metachronous metastasis underwent hepatic resection following neoadjuvant chemotherapy. R0 resection was obtained in 79 (79.8%) patients. A second hepatectomy was performed in 22 (23.2%) patients. Adjuvant chemotherapy was given to 85 (85.9%) patients after metastasectomy. The median disease-free and overall survivals after initial metastasectomy were 12 and 37 months, respectively, the 1-year, 3-year and 5-year disease-free survival (DFS) and overall survival (OS) rates being 46.5%, 24.3% and 17.9% and 92.3%, 59.0% and 39.0%, respectively. On multivariate analysis, the primary tumor site, tumor differentiation, resection margin and DFS were independent factors predicting better overall survival. Conclusions: In selected cases, hepatic metastasectomy for mCRC to the liver can result in long-term survival. Neoadjuvant chemotherapy did not exert a positive effect on DFS or OS. Adjuvant chemotherapy also did not appear to impact DFS and OS.

Keywords: Liver metastases - colorectal cancer - metastasectomy - survival - prognostic factors

Introduction

Colorectal cancer (CRC) is the third most common diagnosed malignancy in the world and is the second leading cause of cancer death in developed countries (Rebecca et al., 2012). Colorectal cancer is the fourth leading cause of cancer and cancer related deaths among both men and women in Turkey. Distant metastasis is the main cause of death in CRC patients. The liver is the most frequent (approximately 33%) metastatic site (Van Cutsem et al., 2006; Cui et al., 2013). Colorectal liver metastases (CLM) are present in 15% to 25% of cases at the time of diagnosis of the primary tumor (synchronous metastases), and approximately half of the patients undergoing radical resection of CRC will develop metastatic disease

(metachronous metastasis) (Van Cutsem et al., 2006; Dong et al., 2013). Nearly 50%-60% of patients with colorectal cancer will eventually develop metastatic disease during the course of their disease (Van Cutsem et al., 2006; Hsu et al., 2011; Dong et al., 2013).

Over the past 20 years, improvements in systemic chemotherapy and surgical techniques have improved the survival of patients with metastases. Surgical resection remains at the present time the only potentially curative treatment for patients with CLM (Van Cutsem et al., 2006; Dong et al., 2013). Five-year survival after curative resection ranges 30%-40% (up to 60% in selected series), whereas less than 2% of patients are alive 5 years after diagnosis without surgical therapy (Castaing et al., 2009; Hsu et al., 2011). Various factors associated with

¹Department of Basic Oncology, Institute of Oncology, Dokuz Eylul University, ²Department of Preventive Oncology, Insitute of Oncology, School of Medicine, Dokuz Eylul University, ³Department of Medical Oncology, Aydın Atatürk State Hospital, Aydın, ⁴Department of Surgery, School of Medicine, Dokuz Eylul University, ⁵Department of Medical Oncology, School of Medicine, Dokuz Eylul University, ⁶Department of Medical Oncology, Medical Park Hospital, Izmir University, Izmir *For correspondence: demir.lutfiye77@gmail.com

survival after surgery for CRC liver metastases have been identified, including tumor-free surgery margin, TNM stage of primary tumor, disease-free survival, number of metastasis and preoperative CEA level (Gallinger et al., 2013). Recently, with the addition of new chemotherapy drugs and targeted therapies, a positive correlation between the tumor response rate and metastatic complete resection rate has been demonstrated in mCRC patients (Chua et al., 2011). Based on these results, it was expanded the indications for resecting mCRC (Lopez-Gomez et al., 2012).

The aims of our study were to analyze the survival and recurrence of patients with CLM undergoing surgical treatment in our hospital and to determine whether any factor was significantly associated with survival and recurrence. This study provides information from Turkish population that has not been previously reported.

Materials and Methods

Between January 1996 and December 2010, 99 patients undergoing resection of liver metastases of primary colorectal carcinoma at the Dokuz Eylül University Faculty of Medicine Hospital, Izmir, Turkey were retrospectively reviewed using medical records. This study was approved by the institutional review board. Written informed consent was obtained. Patients were followed through July 2013. All patients had preoperative chest and abdominopelvic computed tomography (CT), with liver magnetic resonance imaging for detecting the metastases. The resected specimens (primary tumor or liver metastasis) consist of histologically proven adenocarcinoma.The patients had not undergone prior radiofrequency ablation or cryotherapy for liver metastasis. Patients who underwent primary tumor and metastasectomy surgery were follow-up every 3 months for the first year, every 3 to 6 months for 2 to 5 additional years, and once a year thereafter. In surveillance, physical examination, serum carcinoembryonic antigen (CEA) levels, chest X-ray, and spiral abdominal computed tomography (CT) scan or abdominal ultrasound were performed.

Patients were evaluated for age, gender, location and TNM stage of the primary tumor (Sobin et al., 2009), preoperative chemotherapy, adjuvant chemotherapy, number and largest diameter of liver metastases (when multiple metastases were present, the largest diameter was recorded), existence of unilobar or bilobar liver metastases at diagnosis, type of surgery, surgical margin status and any adjuvant therapy that the patient received following resection to define prognostic factors.

Synchronous metastatic disease in this series was defined as the presence of metastases before, during or within 3 monthsof the time of resection of the primary CRC. Metastases that occurred after a disease-free interval of more than 3 months after primary resection were termed metachronous. The choice of the type of resection was made by the attending surgeon based on patient's tumor number and location and was defined according to the liver segment classification of Couinaud (Couinaud et al., 1954).

All of the patients with synchronous metastases in our series underwent resection of primary colorectal cancer first, and chemotherapy was started within 1 mo of the surgery. In patients who received chemotherapy because of the metastatic disease (neoadjuvant) and in patients who received chemotherapy after the metastasectomy (adjuvant), the response to therapy was evaluated after the first 3 or 4 cycles and every 2 to 3 mo thereafter using serial imaging studies based on tumor diameter changes according to the RECIST criteria (Eisenhauer et al., 2009). Additional follow-up and survival data were determined by telephone.

Overall survival was the primary end-point of our study and was calculated using both the interval from the date of diagnosis of colorectal cancer to the date of last follow up or death from disease progression and from the date of liver resection to the date of death or the last follow-up visit. Disease-free survival the second end-point for patients with metastasectomy, was calculated from the time of first metastasectomy to the observation of any second metastasis. In patients who received neo-adjuvant chemotherapy or underwent metastasectomy, the response to therapy was evaluated using DFS and OS.

Statistical analysis

Categorical variables were compared using the chi-square or Fisher's exact test. Continuous variables were expressed as the mean±SD and compared using Student's t test. When a normal distribution was not present, continuous variables were expressed as the median and the range and compared using the Mann-Whitney U test. Both disease-free and overall survival times were calculated using the method of Kaplan-Meier, and the log rank test was used to compare survival in the univariate analysis. Multivariate analysis was calculated using a Cox regression model. All statistical analyses were calculated by using SPSS for Windows (version 13.0; SPSS Inc., Chicago, IL, USA). Statistical significance was set at $p < .05$.

Results

Patient characteristics

A total of 99 patients who underwent resection of liver metastases from CRC were included in the study. The median follow-up duration from the date of primary tumor diagnosis of all of the patients was 48 months (range: 12-184 months).Of the 99 patients with colorectal cancer, 64 (64.6%) were men, and 35 (35.4%) were women, with an age range of 35 to 82 years (mean age 61) at the time of primary tumor diagnosis. The primary site of the tumor was the colon in 62 (62.6%) patients and the rectum in 37 (37.4%) patients. The CEA serum level was missing in 48 patients and was elevated in 20 of the remaining 51 patients. This parameter was therefore not considered for inclusion in the statistical analysis. In all of the 99 patients, the liver was the only site of metastatic CRC. Fifty-seven patients (57.8%) exhibited synchronous metastases with primary colorectal cancers, whereas the other 42 patients (42.2%) exhibited metachronous metastatic disease. The median liver metastasis size was 2.5 cm. Seventy-three

Survival after Liver Metastasectomy in Colorectal Cancer Cases in Turkey

Table 1. Univariate Analysis of Factors Associated with 1-3-5-year Overall Survival and 1-3-5-year Disease Free Survival

Factors	No	Overall Survival Rate (%)			P	Disease Free Survival Rate (%)			P
		1-year	3-year	5-year		1-year	3-year	5-year	
Total	99	92.9	59.0	39.9		46.5	24.3	17.9	
Gender					0.26				0.78
Male	64	92.2	56.6	34.3		47.2	23.9	15.0	
Female	35	94.3	62.7	48.2		45.7	24.5	21.0	
Age					0.37				0.98
>50	82	91.5	58.1	37.0		47.0	24.8	18.8	
≤ 50	17	-	63.7	54.6		43.9	14.6	14.6	
Location of primary tumour					0.006				0.22
Colon Ca	62	98.4	79.0	62.8		53.3	27.6	19.2	
Rectum Ca	37	97.3	72.1	27.1		34.7	19.1	19.1	
Differentiation of primary tumor					0.008				0.76
Well differentiated	22	-	40.9	13.6		48.9	17.8	15.6	
Moderately differentiated	50	92.0	64.9	49.4		38.8	19.9	17.7	
Poor differentiated	27	88.9	62.4	46.8		45.6	22.6	21.7	
Stage of primary tumour (TNM)					0.41				0.68
2	15	86.7	66.7	58.3		53.5	32.5	21.5	
3	27	96.3	54.7	31.3		36.7	21.9	17.0	
4	57	93.0	58.5	38.0		38.9	26.7	19.8	
Time of first metastasis					0.71				0.60
Synchronous	57	93.0	58.1	36.9		50.1	27.0	18.2	
Metachronous	42	92.9	60.2	43.8		41.1	20.4	17.0	
Size of metastases					0.082				0.97
> 5 cm	14	-	75.0	25.0		48.8	22.8	13.8	
≤ 5 cm	85	98.7	80.0	66.9		39.1	27.9	28.7	
Distribution of metastasis					0.51				0.99
Unilobar	73	93.2	60.0	42.5		49.3	22.7	14.6	
Bilobar	26	92.3	56.3	33.0		38.4	29.9	29.9	
Number of metastasis					0.77				0.18
Solitary	59	93.2	55.4	40.6		44.1	18.3	11.4	
Multiple	40	92.5	64.1	39.7		50.6	34.5	29.6	
Neoadjuvant treatment for metastasis					0.05				0.15
No	52	94.2	67.2	49.9		55.4	30.3	19.3	
Yes	47	91.5	50.4	30.1		36.7	18.0	18.0	
Resection Type					0.37				0.72
Wedge resection	23	95.7	52.4	34.0		47.8	15.3	15.3	
Segmentectomy	39	94.9	65.3	46.0		36.3	16.1	16.1	
Hepatectomy	37	89.2	55.9	36.5		47.8	24.9	20.8	
Resection Margin Status					0.02				0.59
R0 resection	79	94.9	63.5	45.1		50.6	24.4	17.0	
R1 resection	20	85.0	39.8	16.6		29.5	29.5	29.5	
Adjuvant treatment after metastasectomy					0.22				0.82
No	14	-	57.1	33.3		53.6	29.8	29.8	
Yes	85	97.6	79.7	54.3		45.7	23.7	16.5	

patients (73.7%) had unilobar liver metastases, whereas 26 patients (26.3%) had bilobar liver metastases. Fifty-nine (59.6%) patients presented with a single metastasis, and 85 (85.8%) of liver metastases were <5 cm in size. Totally, of 99 patients, 47 (51.8%) exhibited initially unresectable their liver metastases, whereas 52 (48.2 %) patients were initially considered resectable. Of ninety-nine patients, 85 (85.9%) underwent adjuvant 5-FU based chemotherapy after resection. There were no postoperative deaths.

Neoadjuvant therapy before hepatic resection
    A total of 47 (47.4%) patients received neoadjuvant chemotherapy before hepatic resection. Among the 57 patients with synchronous metastases, 5 (8.8%) whose metastases were significantly downstaged by neo-
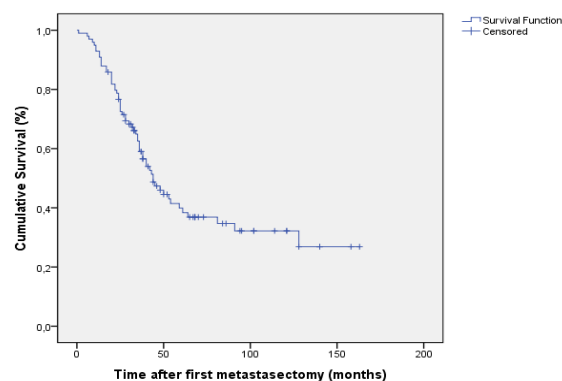

Figure 1. Overall Survival Curve for 99 Patients who Underwent Resection for Hepatic Metastases of Colorectal Cancer

adjuvant chemotherapy underwent hepatic resection and 52 (91.2%) patients underwent hepatic resection within same period. None of 42 patients with metachronous liver metastases underwent hepatic resection directly. Forty-two patients underwent surgery after a median of 3 months of neoadjuvant chemotherapy. A total of 47 records were reviewed, including 9 (19.3%) patients exhibiting complete response, 10 (21.2%) patients with stable disease and 28 (59.5%) patients with a partial response. The most common chemotherapy regimens were FOLFİRİ and FOLFOX-4 and were continued preoperatively for a median of 3 courses.

Table 2. Multivariate Analysis of Factors Significantly Associated with 5-Year Overall Survival (n=99)

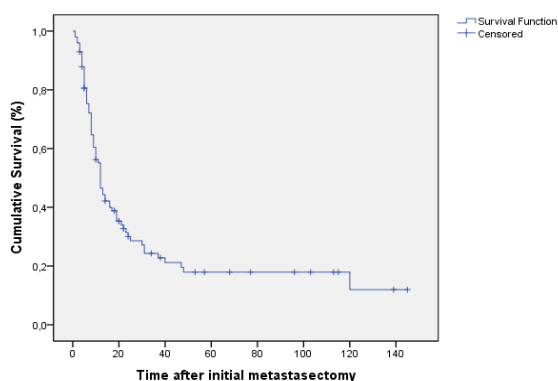|	No	Hazard Ratio (95 % CI)	p value
Colon Location of primary tumour	62	0.500 (0.288-0.867)	0.014
Differentiation of primary tumor			
Well differentiated	22		
Moderately differentiated	50	2.099 (0.999-4.410)	0.050
Poor differentiated	27		
Resection Margin Status			
R0 resection	79	0.191 (0.050-0.723)	0.015
R1 resection	20		
Disease Free Interval			
>12	68	0.513 (0.378-0.976)	0.000
≤12	31		

Figure 2. Disease Free Survival Curve for 99 Patients who Underwent Resection for Hepatic Metastases of Colorectal Cancer
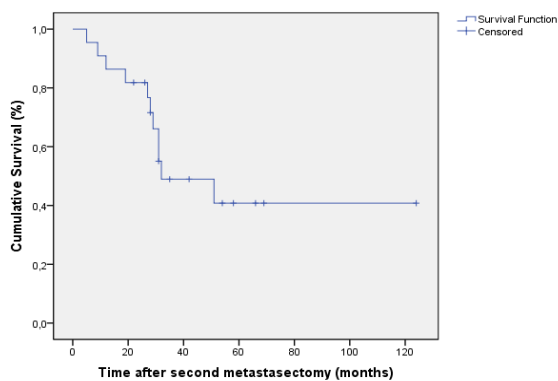

Figure 3. Overall Survival Curve for 22 Patients who Underwent Second Resection for Hepatic Metastases of Colorectal Cancer

Outcomes for surgical treatment of liver metastases:

Segmentectomy was the most common surgical procedure in this study (39 patients, 39.3%), and hepatectomy was the second most common surgical procedure (37 patient, 37.3%). Histopathologic surgical margins were tumor-free in 79 patients (79.7%), and microscopic tumors were observed at the margins in 20 patients (20.3%). Perioperative mortality was not observed.

Adjuvant therapies after hepatic resection

Adjuvant chemotherapy after hepatic resection was performed in 85 patients (85.8%). The most common chemotherapy regimens included FOLFİRİ, FOLFOX-4, FOLFİRİ+Bevacizumab.

Survival analysis

The median follow-up duration from the date of primary tumor diagnosis of all of the patients was 48 months (range: 12-184 months). For the whole group, the median overall survival after metastasectomy was 37 months (range 1-163), and the 1-, 3-and 5-year overall survival rates after liver metastasectomy were 92.9%, 59.0% and 39.9%, respectively (Table 1, Figure 1). The cumulative five-year survival rates were 51.2% after the initial diagnosis for CRC, 39.9% after the first metastasectomy, and 32.8% after the second metastasectomy. In entire group, the median disease-free survival after metastasectomy was 12 months, and the 1-, 3- and 5-year disease-free survival rates were 46.5%, 24.3% and 17.9%, respectively (Table 1, Figure 2). A second resection for recurrent metastases was performed in 22 patients (22.2%), and the 1-, 3- and 5-year survival rates were 83%, 41% and 33%. (Figure 3)

Association between clinicopathologic factors, recurrence and survival

Table 2 summarizes the clinical variables associated with OS and DFS. In univariate analysis, variables significantly associated with higher OS included the following: the colon as the site of the primary tumor, moderate differentiation, R0 resection, and no neoadjuvant chemotherapy. A multivariate analysis revealed that the site of the primary tumor (colon, p=0.014), tumor differentiation (moderately, p=0.05), disease free interval (p=0.000), and the absence of residual disease after surgery (R0 resection, p=0.015) were independent prognostic factors for better survival.

Discussion

The outcomes of surgical management of liver metastases due to colorectal cancers from Turkey have not been described previously. Liver metastases in all of our patients were the first site of metastasis. Ninety-nine patients who underwent metastasectomy for liver metastases due to colorectal cancer were evaluated. The overall, 1-, 3- and 5-year survival rates were 93%, 59% and 39.9%, respectively, and the median survival was 37 months (range 1-163) (Table 1 and Figure 1). Previous studies have reported 5-year overall survival rates of

35% to 58% following the resection of colorectal liver metastases, with a median survival ranging from 33 to 46 months (Castaing et al., 2009; Hsu et al., 2011; Dong et al., 2013). Disease-free survival was 17.9% at 5 years, consistent with the 5-year disease-free survival rates of 15% to 25% reported in the literature (Castaing et al., 2009; Hsu et al., 2011). It has been reported that prolonged disease-free interval (DFI) is one of the most important factors for OS (Sato et al., 1998; Chua et al., 2011). In our study, patients with a DFI of more than 12 months exhibited an independently significant impact on OS versus patients with a DFI < 12 months (64.2 versus 35.5 months) (Table 2).

Despite positive results relating to metastasectomy in the literature, approximately two-thirds of metastatic colorectal cancer patients exhibit no long-term survival benefits. The factors that influence survival include poor tumor differentiation, increasing size and number of metastases, tumor staging, presence of extra-hepatic metastasis, elevated carcino embryonic antigen (CEA) levels and positive nodal status (Chua et al., 2011; Gallinger et al., 2013). The median survival rates depend on the presence or absence of these factors. We were not able to evaluate CEA levels in our study, and none of our patients exhibited extrahepatic metastases. The multivariate analysis demonstrated that the primary tumor site, metastasis size, tumor differentiation and resection margin were independent factors predicting better overall survival.

Metastasectomy is possible in only 20%-30% of mCRC patients (Choti et al., 2007; Pawlik and Choi, 2007; Hsu et al., 2011). Chemotherapy may cause decrease the size and number of metastasis, thus permitting resection in cases initially considered unresectable. Previous studies have demonstrated that 10%-30% of initially unresectable liver metastases can be converted to resectable disease after preoperative (neoadjuvant) chemotherapy (Giacchetti et al., 1999; Nikfarjam et al., 2009). In mCRC patients receiving neoadjuvant chemotherapy, a positive correlation between tumor response rate and resection rate has been reported (Giacchetti et al., 1999). Although studies suggest considerable promise for neoadjuvant chemotherapy in patients with unresectable liver metastases, the role of neoadjuvant chemotherapy is not clear for those patients whose liver disease is already resectable. The EORTC 40983 study, the most important trial in this subject, randomly assigned 364 patients with resectable liver metastases to neoadjuvant FOLFOX chemotherapy or surgery alone. The primary endpoint was 3-year progression free survival. In this study, 301 of 363 patients were resected, and for these patients 3-year PFS was 36.2% in the chemotherapy arm compared with 28.1% in the surgery alone group (Nordlinger et al., 2005). However, the long-term (median follow up of 8.5 years) results of the EORTC 40983 demostrate that the addition of perioperative chemotherapy to surgery led to no significant improvement in OS (Jones et al., 2013). In our study, in the surgery alone group, the 5-year overall survival was superior to the neoadjuvant chemotherapy arm, and the difference was statistically significant (Table 1). Furthermore, we observed that DFS was better in

patients who underwent surgery (unlike the EORTC 40983 trial), but the difference was not statistically significant. This situation may be related to the overall lack of patients and/or more eligible patients for surgery. These findings and the results of our study confirm that surgery may represent the first line treatment for initially resectable liver metastasis.

Relapse within the liver is observed in up to 50% of patients in first 2 years (Jones et al., 2012). Theoretically, post-operative chemotherapy should be effective for microscopic tumor cells in the liver. Therefore, the role of adjuvant systemic chemotherapy after metastasectomy to decrease the incidence of recurrence has been investigated in several studies. Mitry E et al. reported that a pooled analysis of two randomized trials demonstrated a benefit to adjuvant 5-FU based chemotherapy in both DFS and OS (Mitry et al., 2008). The report by Portier et al. represents the first publication of a randomized phase III trial comparing systemic chemotherapy after surgery to surgery alone and patients receiving postoperative systemic FU plus LV exhibited significantly better survival than those receiving surgery alone (24.4 months *vs* 17.6 months, respectively) (Portier et al., 2006) but, the difference did not reach a statistical significance. In two studies including 1100 and 763 patients with resected hepatic metastases of CRC, no significant benefit of adjuvant therapy after metastasectomy could be detected (Fong et al., 1999; Kato et al., 2003). Furthermore, in our study, adjuvant therapy after metastasectomy was not observed to improve overall and disease-free survival (Table 1).

Liver resections were classified as wedge resections, segmentectomy, lobectomy or hepatectomy in our study, and resection type was not a significant influence on disease-free survival and overall survival. Other authors have reported similar results (Ike et al., 2002; Reddy et al., 2004). According to our results, the segmental resection was favorable in terms of overall survival, with less death. However, hepatectomy was more favorable in terms of recurrence compared with wedge resection and segmentectomy. Conversely, the resection margins were important predictors of patient outcomes. Complete R0 resection reportedly results in 5-year survival of up to 24-44% (Jain et al., 2005). Therefore, it has been suggested that the surgery should be performed out with the intention of removing all macroscopic disease with negative margins (R0 resection). In our study, we observed that R0 resection was sufficient to improve overall survival but not disease-free survival (Table 1).

Repeated metastasectomy for hepatic metastases has been reported to contribute to improve prognosis and to have no effect on increase mortality and morbidity (Morise et al., 2006). In our study, there were 22 patients who underwent second metastasectomy, the 5-year survival rate was 33% and the median survival was 31 months (Figure 3).

The limitations of this study include the small number of patients and the retrospective nature of the data analysis. Despite this limitations, our survival rates were consistent with the literature. Although many reports have been published on this subject, there was not a result from Turkey, so far. Furthermore, because

this cohort is one of the largest series of patients with metastases limited to the liver, we believe that this group of patients is representative of the patients likely to benefit from metastasectomy. Further studies needs to address a definition of resectable-nonresectable liver metastasis that may require a multidisiplinary approach. Since no prospective, randomized study has, to date, compared hepatic surgery with the other therapies, our future direction will be to perform the randomized-controlled trials on this issue.

In conclusion, our results suggest that metastasectomy is an effective therapy for hepatic metastases from colorectal cancer. We emphases the importance of R0 resection once again. Adjuvant chemotherapy after liver resection did not confer a survival advantage in our study; therefore we do not recommended adjuvant chemotherapy. In light of the updated results of the EORTC 40983 and according to our results, we believe that chemotherapy is suitable for unresectable liver metastases and patients with liver-limited metastatic colorectal cancer should undergo resection without neoadjuvant chemotherapy.

References

Castaing D, Vibert E, Ricca L, et al (2009). Oncologic results of laparoscopic versus open hepatectomy in two specialized centers. *Ann Surg*, **250**, 849-55.

Chua TC, Liauw W, Koong HN, et al (2011). Surgical therapies in metastatic colorectal cancer with a potential for cure. *Am J Clin Oncol*, **34**, 326-31.

Couinaud C (1954). Anatomic principles of left and right regulated hepatectomy: technics. *J Chir (Paris)*, **70**, 933-66.

Cui YL, Li HK, Zhou HY, et al (2013). Correlations of tumor-associated macrophage subtypes with liver metastases of colorectal cancer. *Asian Pac J Cancer Prev*, **14**, 1003-7.

Dong H, Tang J, Li LH, et al (2013). Serum carbohydrate antigen 19-9 as an indicator of liver metastasis in colorectal carcinoma cases. *Asian Pac J Cancer Prev*, **14**, 909-13.

Eisenhauer EA, Therasse P, Bogaerts J, et al (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*, **45**, 228-47.

Fong Y, Fortner J, Sun RL, et al (1999). Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg*, **230**, 309-18.

Gallinger S, Biagi JJ, Fletcher GG, et al (2013). Liver resection for colorectal cancer metastases. *Curr Oncol*, **20**, 255-65.

Giacchetti S, Itzhaki M, Gruia G, et al (1999). Long-term survival of patients with unresectable colorectal cancer liver metastases following infusional chemotherapy with 5-fluorouracil, leucovorin, oxaliplatin and surgery. *Ann Oncol*, **10**, 663-9.

Hsu Y-N, Lin J-K, Chen W-S, et al (2011). A new classification scheme for recurrent or metastatic colon cancer after liver metastasectomy. *J Chinese Med Assoc*, **74**, 493-9.

Ike H, Shimada H, Togo S, et al (2002). Sequential resection of lung metastases following partial hepatectomy for colorectal cancer. *Br J Surg*, **89**, 1164-8.

Jain S, Sacchi M, Vrachnos P, et al (2005). Recent advances in the treatment of colorectal liver metastases. *Hepatogastroenterology*, **52**, 1567-84.

Jones RP, Jackson R, Dunne DFJ, et al (2012). Systematic review and metaanalysis of follow-up after hepatectomy for colorectal liver metastases. *Br J Surg*, **99**, 477-86.

Jones RP, Malik HZ, Fenwick SW, et al (2013) Perioperative chemotherapy for resectable colorectal liver metastases: where now? *Eur J Surg Oncol*, **39**, 807-11.

Kato T, Yasui K, Hirai T, et al (2003). Therapeutic results for hepatic metastasis of colorectal cancer with special reference to effectiveness of hepatectomy: analysis of prognostic factors for 763 cases recorded at 18 institutions. *Dis Colon Rectum*, **46**, 22-31.

Lopez-Gomez M, Cejas P, Merino M, et al (2012) Management of colorectal cancer patients after resection of liver metastases: can we offer a tailored treatment? *Clin Transl Oncol*, **14**, 641-58.

Morise Z, Sugioka A, Fujita J, et al (2006). Does repeated surgery improve the prognosis of colorectal liver metastases? *J Gastrointest Surg*, **10**, 6-11.

Mitry E, Fields ALA, Bleiberg H, et al (2008). Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials. *J Clin Oncol*, **26**, 4906-11.

Nikfarjam M, Shereef S, Kimchi ET, et al (2009). Survival outcomes of patients with colorectal liver metastases following hepatic resection or ablation in the era of effective chemotherapy. *Ann Surg Oncol*, **16**, 1860-7.

Nordlinger B, Sorbye H, Debois M, et al (2005). Feasibility and risks of preoperative chemotherapy with FOLFOX 4 and surgery for resectable colorectal liver metastases: Interim results of the EORTC Intergroup randomized phase III study 40983. *J Clin Oncol*, **23**, 253.

Pawlik TM, Choti MA (2007). Surgical therapy for colorectal metastases to the liver. *J Gastrointest Surg*, **11**, 1057-77.

Portier G, Elias D, Bouche O, et al (2006). Multicenter randomized trial of adjuvant fluorouracil and folinic acid compared with surgery alone after resection of colorectal liver metastases: FFCD ACHBTH AURC 9002 trial. *J Clin Oncol*, **24**, 4976-82.

Rebecca Siegel, Carol De Santis, Katherine Virgo, et al (2012). Cancer treatment and survivorship statistics, 2012. *CA Cancer J Clin*, **62**, 220-41.

Reddy RH, Kumar B, Shah R, et al (2004). Staged pulmonary and hepatic metastasectomy in colorectal cancer is it worth it? *Eur J Cardiothorac Surg*, **25**, 151-4.

Sato T, Konishi K, Yabushita K, et al (1998). The time interval between primary colorectal carcinoma resection to occurrence of liver metastases is the most important factor for hepatic resection. Analysis of total course following primary resection of colorectal cancer. *Int Surg*, **83**, 340-42.

Stangl R, Altendorf-Hofmann A, Charnley RM, Scheele J (1994). Factors influencing the natural history of colorectal liver metastases. *Lancet*, **343**, 1405-10.

Sobin LH, Gospodarowicz MK (2009). Wittekind Ch Eds. TNM classification of malignant tumors, 7th ed. wiley-blackwell, oxford. 310 pages.

Van Cutsem E, Nordlinger B, Adam R, et al (2006). Towards a pan-European consensus on the treatment of patients with colorectal liver metastases. *Eur J Cancer*, **42**, 2212-21.