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Updated long-term survival for patients with metastatic colorectal cancer treated with liver resection followed by hepatic arterial infusion and systemic chemotherapy:

Survival for resected liver metastases

Nancy E. Kemeny, MD¹, Joanne F. Chou, MPH², Taryn M. Boucher, BA¹, Marinela Capanu, PhD², Ronald P. DeMatteo, MD³, William R. Jarnagin, MD³, Peter J. Allen, MD³, Yuman C. Fong, MD^{3,4}, Andrea Cercek, MD¹, and Michael I. D'Angelica, MD³

¹Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York

²Department of Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York

³Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, New York

⁴Department of Surgery, City of Hope, Duarte, California

Abstract

Background and Objectives—Patients who undergo liver resection for metastatic colorectal cancer (mCRC) have reported 5-year survivals ranging from 25-50%. The current study updated long-term survival for patients with resected liver metastases treated with adjuvant hepatic arterial infusion (HAI) and systemic (SYS) chemotherapy.

Methods—Updated survival and recurrence free survival for patients treated on four consecutive adjuvant protocols with HAI and SYS from 1991 to 2009. Patients were divided into two groups: those treated on protocols before 2003 and after 2003. Median follow-up for all patients was 11 years.

Results—All 287 patients enrolled in four prospective protocols after liver resection are included. Patients treated before 2003 had a median follow-up of 15 years, 5 and 10-year survivals of 56% [95% CI: 49%-64%] and 40% [95% CI: 32%-47%], respectively, and median survival of 71 months. Patients treated after 2003 had a median follow-up of 9 years, 5 and 10-year survivals of 78% [95% CI: 70%-84%] and 61% [95%CI: 51%-70%], respectively, and median survival has not been reached.

Correspondence to: Nancy Kemeny, MD, Address: 300 East 66th Street, 10th Floor, New York, New York 10065, Tel: (646) 888-4180, Fax: (646) 888-4541, kemenyn@mskcc.org.

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Author Contributions: Conception and design: Nancy Kemeny, Michael D'Angelica, Marinela Capanu

Provision of study materials or patients: Michael D'Angelica, William Jarnagin, Peter Kingham, Peter Allen, Ronald DeMatteo

Collection and assembly of data: Marinela Capanu, Joanne Chou, Taryn Boucher

Data analysis and interpretation: Nancy Kemeny, Michael D'Angelica, Peter Allen, Marinela Capanu, Joanne Chou, Taryn Boucher

Manuscript writing: Nancy Kemeny, Taryn Boucher

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Conclusions—Survival is improving for patients with mCRC who undergo liver resection. These data support the durability of long-term survival in patients who undergo resection followed by adjuvant HAI and SYS therapy.

Synopsis for Table of Contents

The 5-year survival after liver resection for metastatic colorectal cancer is approximately 25-50%. This report suggests an increase in 5- survival of 78% can be obtained for patients who undergo adjuvant hepatic arterial infusion and systemic chemotherapy after liver resection.

Keywords

colorectal cancer; liver metastases; adjuvant therapy; hepatic arterial infusion; survival

Introduction

In the last two decades there has been a significant improvement in survival for patients with metastatic colorectal cancer, with 5-year survivals increasing from 25-39% to approximately 40-50% [1-3]. This improvement is due to many factors, including the development of new systemic chemotherapy agents, such as irinotecan [4] and oxaliplatin [5], and molecular targeted agents including vascular endothelial growth factor (VEGF) inhibitors [6], and epidermal growth factor receptor (EGFR) inhibitors [7,8], as well as improvement in surgical technique [9,10]. However, most patients will recur after hepatic resection, and the majority of these recurrences will be in the liver [11,12].

Hepatic metastases derive blood supply from the hepatic artery, whereas normal liver cells derive blood supply from the portal vein [13]. Infusion of chemotherapy via hepatic arterial infusion (HAI) directly into the hepatic artery exposes the metastases to high drug concentrations [14]. Treatment with HAI after liver resection increased progression free survival (PFS) and hepatic PFS in three of four randomized studies that compared HAI plus systemic (SYS) to SYS chemotherapy alone or to surgery alone [15-19]. In one study where the end-point was 2-year survival, HAI plus SYS versus SYS alone produced a 2-year survival of 85% versus 69% ($p=0.02$), and a 2-year hepatic PFS of 85% and 50% ($p=0.001$), respectively [15,19]. We now report a 20-year follow-up on this study [15] as well as an update on three additional prospective trials [20-22] using adjuvant HAI and SYS therapy. To compare our results with other reports in the literature and to determine whether survival has improved over time, patients were divided into two groups: before and after 2003.

Materials and Methods

After approval by the Institutional Review Board (IRB), a pooled analysis of patients enrolled onto four consecutive prospective adjuvant protocols using HAI and systemic after liver resection was conducted. Patients were enrolled from October 1991 to September 2009 at Memorial Sloan Kettering Cancer Center (MSKCC). Patients who enrolled onto protocols initiated after 2009 were not included because of the limited follow-up time.

All patients signed MSKCC IRB approved informed consent before initiation of protocol treatment. Eligible patients had histologically confirmed CRC with resection or ablation of all liver metastases, a Karnofsky performance status $\geq 60\%$ and must have met the following lab values: WBC $\geq 3,000$ cells/ μL , platelets $> 100,000$ cells/ μL , serum total bilirubin < 1.5 mg/dL. Exclusion factors included presence of extrahepatic disease, prior regional therapy and prior hepatic radiation. Prior systemic chemotherapy was permitted provided the last dose was given more than three weeks before trial entry. Prior bevacizumab had to be more than six weeks before trial entry.

Contrast enhanced computed tomography (CT) scans of the chest, abdomen, and pelvis were required within six weeks of liver resection and hepatic pump placement. Hepatic arterial supply was studied pre-operatively in all patients. Surgical guidelines for pump placement have been previously reported [21,23]. Patients were evaluated after resection according to clinical risk score: positive margins after hepatic resection, number of liver metastases, presence of positive lymph nodes in the primary tumor, size of liver tumors, and elevated pre-operative CEA value [2,24].

Chemotherapy Administration

Patients commenced chemotherapy four to five weeks after surgery. On Day 1 of a five-week cycle, HAI with floxuridine (FUDR) (Bedford Laboratories, Bedford, OH) was infused at a dose of $0.12 \text{ mg} \times \text{kg} \times \text{pump volume (30 mL)}$, divided by pump flow rate (supplied by the pump manufacturer; Codman and Shurtleff, Raynham, MA) for a 14-day infusion. In the first protocol [15], the dose of FUDR was $0.14 \text{ mg} \times \text{kg} \times \text{pump volume}$; all other protocols used FUDR 0.12 mg [20-22]. Dexamethasone (dex) was administered concurrently with FUDR [25]. In all protocols, patients received HAI FUDR/dex on Day 1 of each cycle for 14-day infusion.

On Days 15 and 29 of each cycle, SYS chemotherapy was administered and the pump was refilled with 30 mL heparinized saline. The different SYS chemotherapies used with HAI FUDR/dex on the four protocols have been previously published and are shown in Table 1 [15,20-22]. The first protocol used fluorouracil administered as an intravenous bolus of 325 mg/m^2 , preceded by an infusion of leucovorin (LV) at 200 mg/m^2 for five consecutive days [15]. The second phase I/II protocol used irinotecan (CPT) alone with a starting dose of 60 mg/m^2 and escalation to 200 mg/m^2 [20]. The third protocol used oxaliplatin 85 mg/m^2 to 100 mg/m^2 (2-hour infusion) given concurrently with LV 400 mg/m^2 via a Y-connection, followed by 5-fluorouracil (5-FU) $2,000 \text{ mg/m}^2$ delivered via an external pump for a 48-hour infusion [21]. In the fourth protocol, patients who had not had prior oxaliplatin received oxaliplatin 85 mg/m^2 (2-hour infusion) concurrently with LV 400 mg/m^2 via a Y-connection, followed by 5-FU $2,000 \text{ mg/m}^2$ delivered via external pump for a 48-hour infusion [22]. Patients who had prior oxaliplatin received CPT 150 mg/m^2 (over 30 minutes) with the same doses of 5-FU and LV. Patients were randomized to receive bevacizumab at 5 mg/kg given on the days of SYS chemotherapy.

Follow-up scans were performed every three months for the first two years, then every four months for the next two years, then every six months for the fifth year, and then yearly thereafter. Patient outcomes, toxicities, and accrual goals of recurrence-free survival and

overall survival were monitored throughout the study by the MSKCC Data and Safety Monitoring Committee.

KRAS Molecular Genotyping

KRAS testing became the standard of care at MSKCC in 2009, and consequently, we only have KRAS information on 106 patients. Description of technique and microdissection of tumor are described in previous manuscripts [26,27].

Statistical Analysis

Overall survival (OS), recurrence free survival (RFS) and hepatic RFS were calculated from the time of liver resection and pump placement until the time of death (for OS) or until the first recurrence or death, whichever came first. Patients who were alive and did not experience the event of interest were censored at the date of last follow-up. Log-rank test was used to compare survival distributions between treatment era (prior to 2003 vs after 2003) and KRAS status. Patients were divided according to the date they entered protocol: those before 2003 and those after 2003. The year 2003 was chosen as the cutoff date because new drugs became available after 2003 and two protocols started after 2003. OS and RFS were estimated according to clinical characteristics, separately for patients treated before 2003 and for patients treated after 2003, using Kaplan-Meier method and survival distributions between clinical characteristics were compared using log-rank test [28,29]. Chi-square test and Wilcoxon Rank-Sum test were used to examine the clinical/pathological characteristics between patients treated prior to 2003 and those treated post-2003. Multivariate Cox regression model was used to examine the survival outcomes (OS and RFS) between patients treated before or after 2003 adjusting for known risk factors such as age, number of lesions (1 vs 2-4 vs 5-7 vs 8), clinical risk score (0-2 vs 3-5), surgical margin (0 vs 1 cm vs >1 cm), tumor size (<5 cm vs 5 cm), positive lymph nodes, synchronous tumor, and prior chemotherapy. All *p* values were based on 2-tailed statistical analysis and *p*-value <0.05 was considered to indicate statistical significance. All analyses were performed with SAS version 9.3 (SAS Institute, Cary, North Carolina).

Results

All 287 patients included were enrolled in one of four consecutive trials using adjuvant HAI and systemic therapy after liver resection from October 1991 to September 2009. Patients were planned to receive six months of adjuvant HAI and SYS on the protocols shown in Table 1.

Patients were divided into two groups: those who entered protocol prior to January 2003 (n=169) and those who entered after January 2003 (n=118). The median follow-up among the survivors for the entire group was 11 years [Range: 5.3-22.7 years]. Median follow-up for patients treated before 2003 and after 2003 was 15 years [Range: 12-22 years] and 9 years [Range: 5.3-11.9 years], respectively. Toxicities for each treatment regimen have been reported in previous manuscripts [15,20-22]. The most serious toxicity was biliary sclerosis requiring biliary stenting, which occurred in 3% of all 287 patients. Characteristics of patients treated on the four protocols are listed in Table 2.

Overall Survival

The median OS for the entire cohort (n=287) was 100 months [95% CI: 80-170 months]. The median OS for patients treated before 2003 was 71 months [95% CI: 59-89 months] and has not been reached for those treated after 2003 ($p<0.01$) (Figure 1). The 5 and 10-year OS for the entire cohort was 66% [95% CI: 60%-71%] and 48% [95% CI: 42%-54%], respectively. The 3, 5, and 10-year OS for patients treated before 2003 was 73% [95% CI: 66%-80%], 56% [95% CI: 49%-64%], and 40% [95% CI: 32%-47%], respectively. The 3, 5, and 10-year OS for patients treated after 2003 was 92% [95% CI: 85%-95%], 78% [95% CI: 70%-84%], and 61% [95% CI: 51%-70%], respectively.

The influence of various clinical characteristics on OS for patients treated before and after 2003 is shown in Table 3. OS was decreased in patients with known poor prognostic characteristics such as high clinical risk score, positive margins after hepatic resection, number of liver metastases, presence of positive lymph nodes in the primary tumor, and elevated post-operative CEA value [2,24,30].

The differences in characteristics of patients treated before and after 2003 are shown in Table 4. When the group treated after 2003 was compared to the group treated before 2003, there was a greater number of patients with 8 metastases (10% versus 5%, $p=0.02$), a higher percentage with margins 1 cm or 0 cm (70% versus 56%, $p=0.05$), and more patients with synchronous disease (59% versus 42%, $p<0.01$). A lower percentage of patients treated after 2003 were chemotherapy naïve before resection (20% versus 34%, $p<0.01$) but this factor was not significantly associated with survival.

In multivariate analysis, after adjusting for known risk factors for poor prognosis such as age, number of lesions (1 vs 2-4 vs 5-7 vs 8), clinical risk score (0-2 vs 3-5), surgical margins (>1 cm vs 1 cm vs 0 cm), tumor size (<5 cm vs 5 cm), positive lymph nodes, synchronous disease, and prior chemotherapy, patients treated after 2003 still had better OS as compared to patients treated prior to 2003 (HR: 0.4 95%CI: 0.3-0.6, $p<0.01$).

Recurrence Free Survival

The median RFS for the entire group was 20 months [95% CI: 17-27 months], with a 5-year RFS of 38% [95% CI: 32%-43%] and a 10-year RFS of 34% [95% CI: 29%-40%]. Patients treated before 2003 had a median RFS of 19 months [95% CI: 17-28 months] versus 21 months [95% CI: 16-63 months] for patients treated after 2003 ($p=0.20$). The 3 and 5-year RFS for patients treated before 2003 was 41% [95% CI: 34%-48%] and 35% [95% CI: 28%-42%], respectively, while patients treated after 2003 had 3 and 5-year RFS of 42% [95% CI: 33%-51%] and 41% [95% CI: 35%-50%], respectively (Figure 2).

The influence of various clinical characteristics on RFS for patients treated before and after 2003 is shown in Table 5. The same factors associated with OS were also associated with RFS. For instance, a clinical risk score of 0-2 versus 3-5 produced a 10-year survival of 41% versus 17%, respectively, for patients treated before 2003 (<0.001).

In multivariate analysis, after adjusting for known risk factors for poor prognosis such as age, number of lesions (1 vs 2-4 vs 5-7 vs 8), clinical risk score (0-2 vs 3-5), surgical

margin (>1cm vs 1 cm vs 0 cm), tumor size (<5 cm vs 5 cm), positive lymph nodes, synchronous disease, and prior chemotherapy, there was no statistical significant association between treatment era and RFS (HR: 0.8 95%CI: 0.5-1.02, p=0.07).

Hepatic Recurrence Free Survival

The median hepatic RFS for the entire group was 72 months [95% CI: 60-107 months], and the 3, 5 and 10-year hepatic RFS for the entire group was 66% [95% CI: 61%-72%], 55% [95% CI: 49%-61%] and 43% [95% CI: 38%-50%], respectively. The 3 and 5-year hepatic RFS for the group treated before 2003 was 63% [95% CI: 55%-70%] and 51% [95% CI: 43%-58%], respectively. The 3 and 5-year hepatic RFS for patients treated after 2003 was 72% [95% CI: 63%-79%] and 62% [95% CI: 52%-70%], respectively (p=0.054) (Figure 3).

KRAS Data

KRAS information was available on 106 patients. The 3 and 5-year OS for KRAS wild-type patients was 96% [95% CI: 89%-98%] and 86% [95% CI: 76%-92%], respectively, while the 3 and 5-year OS for KRAS mutated patients was 89% [95% CI: 70%-96%], and 67% [95% CI: 47%-81%], respectively (p=0.074) (Figure 4). The 3 and 5-year RFS for KRAS wild-type patients were both 49% [95% CI: 37%-59%], whereas the 3 and 5-year RFS for KRAS mutated patients was 32% [95% CI: 16%-50%] and 28% [95% CI: 13%-45%], respectively (p=0.048) (Figure 5).

Discussion

Colorectal cancer is a major cause of cancer death in the United States [31]. Over 50% of patients with colorectal cancer develop liver metastases, which is a major cause of mortality. In the last 50 years the resection of hepatic metastases has become more prevalent in patients with limited hepatic-only disease. Resection of hepatic metastases is associated with prolonged survival and may lead to cure in some patients [3]. The 5-year survival in the older series have been reported between 27-44% [32-34] and in newer series, approximately 50% [35-39]. In a review of literature reporting 10-year survivals for patients after liver resection, 10-year survivals have been reported in the 20-36% range [32-39] (Table 6). Only studies reporting 10-year survival are included in Table 6, with the exception of Nordlinger et al [36] who reported 8-year survival. Some of these reports used systemic chemotherapy after hepatic resection. In this study, all patients received adjuvant HAI plus SYS chemotherapy. With a median follow-up of 11 years, the 5 and 10-year survivals for the entire group was 66% and 48%, respectively. With a median follow-up of 9 years, patients treated after 2003 had 5 and 10-year survivals of 78% and 61%, respectively (Figure 1).

Patients treated after 2003 had a higher 3-year hepatic RFS than patients treated before 2003 (72% versus 63%, respectively), and both groups had a greater hepatic RFS compared to other reports. Regional HAI therapy may protect the liver, which would allow for a greater OS and hepatic RFS. Our favorable survival (78% alive at five years for those treated after 2003) suggests control of hepatic recurrence is important. After complete liver resection, progression in one small lung metastasis can be treated with surgery or radio-frequency ablation (RFA), and may not have an impact on overall survival [40]. Therefore, in

evaluating results after liver resection, the location of progression and different treatment interventions may be more important.

Recently, knowledge of molecular changes has been shown to impact survival. Patients with KRAS mutation in both the general colorectal population and in patients who have liver resection tend to have higher recurrence rate and decreased survival [41]. This information was available for patients who entered after 2003. In this report, patients with KRAS wild-type or KRAS mutation had a 5-year OS of 86% versus 67%, and 5-year RFS of 47% versus 28%, respectively.

The longer survival after 2003 is unlikely to be related to better patient characteristics, since the patients treated after 2003 had a higher proportion of adverse prognostic characteristics (Table 4). A potential explanation for this improvement in survival could be more options for systemic chemotherapy and more aggressive treatment at recurrence [5-8,42,43]. After 2003, 37% of KRAS wild-type patients received Cetuximab or Panitumumab after recurrence. Other potential reasons for improvement in survival are better imaging, including intraoperative ultrasound, more extensive salvage surgery [44], and improvement and greater use of ablation techniques [40]. Additionally, recurrences are now treated more aggressively, including second liver resections, lung resections, and even lymph node or abdominal resections.

Conclusions

Historically, the presence of liver metastases from colorectal cancer has been associated with extremely poor survival. Today, in patients who can undergo liver resection followed by adjuvant systemic therapy plus HAI, 5 and 10-year survivals as high as 78% and 61% can be achieved. Our favorable results may reflect selection bias, since these patients had no known extra-hepatic disease and may have had other good characteristics. However, if a comparison is made between patients included in this analysis and patients included in previous studies that report 10-year survival after liver resection (Table 6), the number of patients with poor clinical characteristics is comparable [32-39].

These results suggest that adjuvant HAI therapy in conjunction with modern systemic chemotherapy can improve outcomes. Other centers should be encouraged to design clinical trials using HAI plus systemic therapy after liver resection. Patients with resectable disease should be encouraged to undergo liver resection and to be seen by a multidisciplinary group which includes surgeons, medical oncologists and interventional radiologists.

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Figure 1. Overall Survival According to Treatment Period

Figure 2. Recurrence Free Survival According to Treatment Period

Figure 3. Hepatic Recurrence Free Survival According to Treatment Period

Figure 4. Overall Survival According to KRAS Status

Figure 5. Recurrence Free Survival According to KRAS Status

Table 1
Protocol Treatment

Protocol Start Year	HAI Pump	Systemic Chemotherapy
1991 *	FUDR/Dex	5FU/LV
1998	FUDR/Dex	CPT
2003	FUDR/Dex	FOLFOX
2004	FUDR/Dex	FOLFIRI or FOLFOX +/- Bevacizumab

Abbreviations: HAI=hepatic arterial infusion; FUDR= floxuridine; Dex= dexamethasone; 5FU/LV= 5-fluoracil/leucovorin; CPT=irinotecan; FOLFOX=5-fluoracil/leucovorin/oxaliplatin; FOLFIRI=5-fluoracil/leucovorin/irinotecan

* This 1991 study compared patients treated with HAI and systemic therapy to systemic therapy alone. In this analysis, we only included patients treated in the HAI and systemic therapy arm.

Table 2
Patient Characteristics of Four Adjuvant HAI + SYS Protocols

	HAI + 5FU/LV	HAI + CPT	HAI + FOLFOX	HAI + SYS +/- Bev
Characteristic	Total % of Patients (N=73)	Total % of Patients (N=103)	Total % of Patients (N=38)	Total % of Patients (N=73)
Age				
22 – 50	32	23	34	43
51 – 74	64	71	63	56
75	4	6	3	1
Gender				
Male	60	55	68	52
Female	40	45	32	48
# Hepatic Metastases				
1	36	38	31	23
2 – 4	42	48	53	44
5 – 7	19	7	8	22
8	3	7	8	11
Clinical Risk Score				
0 – 2	60	55	63	52
3 – 5	40	45	37	48
Margins				
> 1 cm	45	44	38	25
1 cm	47	52	57	67
0 cm	8	4	5	8
Liver Tumor Size				
< 5 cm	64	73	79	82
5 cm	36	27	21	18
Primary Lymph Node Status				
Negative	42	37	37	44
Positive	58	63	63	56
CEA Post-op				
< 5 ng/ml	71	64	84	79
5 ng/ml	29	36	16	21
Synchronous Disease				
No	58	56	53	36
Yes	42	44	47	64
Chemotherapy Naïve				
Yes	47	25	29	14

Abbreviations: CEA=carcinoembryonic antigen; HAI=hepatic arterial infusion; 5FU=5-Fluorouracil; CPT=Irinotecan; Oxal=Oxaliplatin; Bev=Bevacizumab

Table 3
Overall Survival for Patients According to Treatment Era

		Before 2003 n=169			After 2003 n=118		
		%	% 5-year OS	% 10-year OS	p	% 5-year OS	p
Age					.08		.02
22 – 50		27	61	48		38	73
50		73	55	37		62	81
Gender					.28		.58
Male		57	56	37		58	80
Female		43	58	44		42	76
# Hepatic Metastases					<.01		<.01
1		38	71	57		25	86
2 – 4		46	57	35		47	84
5 – 7		11	26	16		18	67
8		5	13	0		10	50
Clinical Risk Score					<.01		.09
0 – 2		59	64	47		54	84
3 – 5		41	47	30		46	70
Margins (cm)					.08		<.01
> 1 cm		44	66	48		31	91
1 cm		50	52	37		63	77
0 cm		6	50	10		6	38
Margins (mm)					.02		<.01
> 1 mm		84	60	42		86	80
1 mm		10	30	30		8	88

		Before 2003 n=169				After 2003 n=118			
		%	% 5-year OS	% 10-year OS	p	%	% 5-year OS	p	
0 mm		6	50	10		6	38		
Size					.32				.16
< 5 cm		69	58	42		81	80		
5 cm		31	54	35		19	70		
Primary Lymph Nodes					.03				<.01
Negative		40	65	52		40	90		
Positive		60	52	32		60	71		
CEA Post-operative					.05				.07
< 5 ng/ml		68	64	44		80	82		
5 ng/ml		32	43	30		20	63		
Synchronous Disease					.37				.38
No		58	60	40		41	80		
Yes		42	52	39		59	77		
Prior Chemotherapy					.80				.45
No		34	60	42		19	87		
Yes		66	55	38		81	76		

Table 4
Patient Characteristics Before and After 2003

	Before 2003 (n=169)	After 2003 (n=118)	p-value
Characteristics			
Age			0.01
Median (range)	58 (22-80)	54 (27-77)	
Gender			0.77
Male	96 (57%)	69 (57%)	
# Hepatic Metastases			0.02
1	65 (39%)	29 (25%)	
2-4	77 (46%)	56 (48%)	
5-7	19 (11%)	21 (18%)	
8	8 (5%)	12 (10%)	
Clinical Risk Score			0.46
0-2	99 (59%)	64 (54%)	
3-5	70 (41%)	54 (46%)	
Margins (cm)			0.05
> 1 cm	73 (44%)	35 (30%)	
1 cm	83 (50%)	74 (63%)	
0 cm	10 (6%)	8 (7%)	
Margins (mm)			0.84
> 1 mm	143 (84%)	100 (85%)	
1 mm	16 (10%)	9 (8%)	
0 mm	10 (6%)	8 (6%)	
Liver Tumor Size			0.03
< 5 cm	117 (69%)	95 (81%)	
5 cm	52 (31%)	23 (19%)	
Primary Lymph Node Status			0.99
Positive	101 (60%)	70 (60%)	
Synchronous Disease			<0.01
Yes	71 (42%)	70 (59%)	
Chemotherapy naïve			<0.01
Yes	57 (34%)	23 (20%)	

Table 5
Recurrence Free Survival According to Treatment Era

	Before 2003 n=169			After 2003 n=118		
	%	% 5-year RFS	% 10-year RFS	p	% 5-year RFS	p
Age				.19		.26
22 – 50	27	43	37		33	
50	73	33	29		47	
Gender				.84		.94
Male	57	35	37		41	
Female	43	36	44		43	
# Hepatic Metastases				<.001		.07
1	38	51	51		58	
2 – 4	46	34	25		43	
5 – 7	11	5.3	5.3		24	
8	5	0	0		25	
Clinical Risk Score				<.001		.40
0 – 2	59	44	41		44	
3 – 5	41	23	17		39	
Margins (cm)				.14		.001
> 1 cm	44	40	38		60	
1 cm	50	34	30		36	
0 cm	6	30	0		13	
Margins (mm)				.06		.02
> 1 mm	84	37	34		42	
1 mm	10	23	23		55	
0 cm	6	30	0		13	
Size				.95		.16
< 5 cm	69	36	31		44	
5 cm	31	35	33		30	
Primary Lymph Nodes				<.01		.16

	Before 2003 n=169				After 2003 n=118		
	%	% 5-year RFS	% 10-year RFS	p	%	% 5-year RFS	p
Negative	40	47	41		40	49	
Positive	60	28	25		60	37	
CEA Post-operative				.05			.43
< 5 ng/ml	68	38	35		80	43	
≥ 5 ng/ml	32	30	25		20	33	
Synchronous Disease				.08			.47
No	58	40	35		41	46	
Yes	42	30	27		59	39	
Prior Chemotherapy				.47			.95
No	34	37	33		20	43	
Yes	66	33	28		81	41	

Table 6
Patient Characteristics and Survival after Resection of Colorectal Liver Metastases

Study	Year Pts Treated	Pts (n)	Median Follow-up (mos)	Patient Characteristics					Overall Survival	
				Margins < 1 cm (%)	Size > 5cm (%)	Positive LN (%)	> 4 Lesions (%)	Synch disease (%)	% 5-year	% 10-year
Jamison ³⁰	1960 – 1987	280	121	44	47	-	8	-	27	20
Scheele ³¹	1960 – 1992	350	-	58	33*	62	9*	41	39	24
Minagawa ³²	1980 – 1997	235	28	50	29	69	28*	45	38	26
Hamady ³³	1993 – 2001	293	-	47**	32	56	18	50	44	36
Giulianti ³⁴	1992 – 2007	251	37 ⁺⁺	-	24	61	13	41	39	24
Nordlinger ³⁵ +	2000 – 2004	182	36	-	-	55	0	34	51	30
Kemeny	1991 – 2009	287	132	52	23	60	21	49	66	48
Before 2003	1991 – 2002	169	180	47	27	60	16	42	56	40
After 2003	2003 – 2009	118	108	61	16	60	28	59	78	61

Abbreviations: Pts=patients; LN=lymph nodes; Synch=synchronous; OS=overall survival; - = not reported

⁺ only includes 182 patients treated with perioperative chemotherapy (FOLFOX) and not entire group

reported 8-year OS, not 10-year OS

* reported as

** reported as

⁺⁺ reported as mean follow-up