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Original article

Long-term survival of patients with unresectable colorectal cancer liver metastases following infusional chemotherapy with 5-fluorouracil, leucovorin, oxaliplatin and surgery

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Summary

Context: Long-term survival of patients with metastatic colorectal cancer has been achieved only in patients who underwent complete resection of metastases. Such surgery could be performed in a greater proportion of patients if effective chemotherapy could downstage previously unresectable metastases. This approach has been limited by the low tumor response rate achieved with conventional chemotherapy.

Objective: We studied the outcome of patients with initially unresectable liver metastases from colorectal cancer treated with a three-drug chemotherapy regimen followed by liver metastases surgery whenever possible.

Patients and methods: From March 1988 to June 1994, 151 patients with colorectal liver metastases were considered initially unresectable because of large tumor size (> 5 cm), multinodular (> 4) or ill-located metastases. All patients received fully ambulatory chemotherapy with 5-fluorouracil, leucovorin and oxaliplatin (chronotherapy in 83% of them). They were periodically reassessed for surgery by a joint medico-surgical team.

Results: In 151 patients, the size of liver metastases decreased by > 50% in 89 patients (59%) and median overall survival was 24 months (95% confidence interval (95% CI): 19–28 months), with 28% surviving at five years (20%–35%). Surgery with curative intent was attempted in 77 patients (51%), complete resection of liver metastases was achieved in 58 patients (38%). The median survival of the 77 operated patients was 48 months (25–71), with a five-year survival rate of 50% (38–61).

Conclusion: This new strategy of combining effective chemotherapy with surgery apparently altered the natural history of unresectable colorectal cancer metastases.

Key words: chronotherapy, colorectal cancer, liver metastases, oxaliplatin, surgery, survival

Introduction

Long-term survival of patients with metastatic colorectal cancer has only been achieved in those patients who could undergo primary surgical resection of metastases [1–7]. Up to now, chemotherapy has been used merely as a palliative treatment which has both improved quality of life and prolonged survival as compared to non cytotoxic palliative care [8, 9]. 5-Fluorouracil (5-FU) has remained the most active drug against colorectal cancer. Objective response rate ranged from 10% to 25% with an apparent dose–response relationship [10–14].

The diaminocyclohexane platinum complex oxaliplatin (l-OHP) is a third generation platinum complex, which lacks any renal toxicity and displays antitumor activity against colorectal cancer [15, 20]. The combination of 5-FU, leucovorin (LV) and l-OHP has consistently achieved 40% to 67% objective response rates in patients with metastatic colorectal carcinoma especially in the trials where these drugs were given as chronotherapy [21–26].

Thus the adaptation of drug delivery to circadian rhythms has improved tolerability and has enhanced antitumor efficacy against metastases from colorectal cancer [22, 23, 28–30]. The combination of 5-FU, LV and l-OHP was developed at first as a chronomodulated schedule in order to take advantage of the improved tolerability associated with this mode of administration. In the initial phase II study, this three-drug combination was given as a 5 day chronomodulated infusion to 93 patients with unresectable colorectal metastases. A 58% objective response rate and a median overall survival of 16 months were achieved [21]. Two consecutive multicenter phase III studies compared flat *versus* chronomodulated infusion of the same three-drug combination. These trials registered a total of 278 patients with previously untreated and unresectable metastatic colorectal cancer. Chronotherapy was significantly less toxic and more effective (objective response rate 51% vs. 29%, $P = 0.0001$) than constant-rate infusion. In addition the median dose intensity of 5-FU was 22% higher with chronotherapy than with flat infusion ($P < 0.0001$)

Table 1. Different types of treatment for the 389 patients.

Trial	Schedule	No. of pts	Liver as the only metastatic site	Operated patients	References
Phase II	5d q 3 w/ chrono	93	28/93 (30%)	9/28 (30%)	Cancer, 1992 [21]
Phase IIIa	5d q 3 w	42	19/42 (36%)	6/19 (40%)	JNCI, 1994 [22]
	Chrono	21	8	2	
	Flat	21	11	4	
Phase IIIb	5d q 3 w	62	30/62 (42%)	19/30 (63%)	Lancet, 1997 [23]
	Chrono	30	15	9	
	Flat	32	15	10	
Phase II	4d q 2 w chrono	54	20/54 (37%)	9/20 (47%)	Proc ASCO, 1993 [24]
Phase II (intensified)	4d q 2 w chrono	50	24/50 (48%)	15/24 (62%)	J Clin Oncol, 1996 [25]
Phase II (multicentric intensified)	4d q 2 w chrono	88	30/88 (34%)	19/30(63%)	Cancer, 1999 [26]
Total		389	151	77	

Table 2. Characteristics of the patients.

	Liver surgery		All patients
	Yes	No	
Patients	77	74	151
Sex			
Female	28	32	60
Male	49	42	91
Age (in years)			
Median	59	58	58
Range	32–79	27–76	27–79
Colon	52	57	109
Rectum	25	17	42
Initial Dukes' stages			
B1/B2	3/4	8/6	11/10
C	23	16	39
D	47	43	90
Initial performance status (WHO)			
0	52	44	96
1	19	21	40
2/3	6/0	7/2	13/2
First-line chemotherapy	47 (61%)	41 (55%)	88 (58%)
Maximal response to chemotherapy			
Progressive disease	0	13	13
Stabilization	16	28	44
Partial response	59 } 61 (79%)	27 } 29 (39%)	86 } 90 (59%)
Complete response	2 }	2 }	4 }
Interval between inclusion and surgery (months)			
0–6	47	NA	47
>6	30	NA	30
CEA (ng/ml)			
≤10	26 (34%)	14 (19%)	40
>10	46	56	102
Unknown	5	4	9
Liver involvement			
≤25%	48 (62%)	20 (27%)	68 (45%)
>25%	27	45	72
Unknown	2	9	11
Involved lobe unilateral/ bilateral	43/34	ND	ND
Diameter of largest metastasis			
≤5 cm	46	33	79
>5 cm	24	27	51
Unknown	7	14	21
Number of metastases			
1	14	19	33
2–4	38	16	54
>4	20	25	45
Unknown	5	14	19

Abbreviations. NA not applicable: ND not done.

[22, 23]. The high efficacy and the good tolerability of this chronomodulated regimen led us to intensify it further with higher response rates both in chemotherapy-naïve patients and in previously treated ones [24–26].

The achievement of high objective response rates with this three-drug regimen, allowed the surgical resection of metastases in some patients with initially unresectable disease. The surgical aspects of this approach combining chemotherapy and surgery of primary unresectable colorectal cancer liver metastases were previously described with particular emphasis on the causes of unresectability and surgical procedures. In this study, patients with extrahepatic disease were also considered [31].

This retrospective analysis aimed to assess any potential survival benefit resulting from the combination of chemotherapy and surgical resection of metastases in patients with initially unresectable disease strictly confined to the liver. It attempted to characterize which patients mostly benefited from this strategy. The study involved the patients registered at our hospital in one of the above mentioned trials between 1988 and 1994 and treated with infusional 5-FU, LV, l-OHP chemotherapy followed by surgery.

Patients and methods

From March 1988 to May 1994, 389 patients with unresectable colorectal metastases received ambulatory infusional chemotherapy with 5-FU, LV and l-OHP (Debiopharm, Switzerland) at our hospital All patients had histologic proof of metastatic colorectal cancer and the same clinical, laboratory or radiological assessments before treatment onset. Out of 389 patients, 151 had unresectable liver-only metastases which is the population that we have studied. The criteria of unresectability were the number of metastases (>4) and/or their size (diameter >5 cm) and/or their location in both lobes and/or the percentage of liver involvement and/or the invasion of intrahepatic vascular structures (Table 2). These criteria were previously described and were usually multifactorial [31]. The medical and surgical management of all the patients was handled at our hospital. All the patients were treated by the medical oncology team and were operated by the same local surgical team highly specialized in liver surgery.

The patients received one of the three schedules of this novel three drug infusional chemotherapy regimen (Table 1). Treatment was ad-

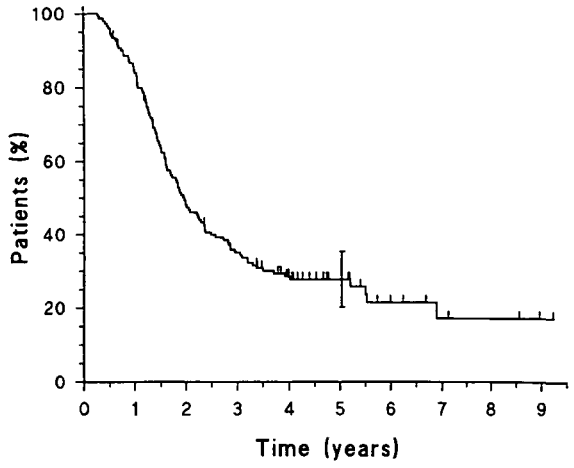

Figure 1 Survival curve of the 151 patients. Median overall survival was 24 months.

ministered in an ambulatory setting with a four channel programmable-in-time pump (Intelliject, Aguettant, Lyon, France). Antitumor activity was assessed according to the World Health Organisation criteria [32]. Initial procedure for study entry included physical exam, routine blood and serum chemistry, liver enzyme tests, carcino embryonic antigen (CEA) serum level, abdominal ultrasound, abdomino pelvic and lung computerized tomography (CT). Each patient had a visit every two or three weeks depending on the protocol he was registered on. Disease status was assessed with thoracic and abdomino pelvic CT scans which were performed every two to three months. Responses were assessed by CT scan rather than ultrasound in order to allow for objective comparisons. The decrease of the CEA level was never considered sufficient to assess an objective response. All patients were followed jointly by oncologists and surgeons. Hepatic resection was reconsidered periodically and was attempted when technically feasible and potentially curative.

All patients had a complete restaging before surgery including liver ultrasound (performed by the same radiology team), lung and abdomino-pelvic computerized tomography, bone scan, colonoscopy (unless performed within the past six months), routine blood and biochemical determinations including liver enzyme tests, and carcinoembryonic antigen (CEA serum levels (ng/ml).

The operative techniques for liver resection were previously described by the surgical team [31]. A complete exploration of the abdomen including intraoperative ultrasound was performed in order to eliminate a peritoneal carcinomatosis, to detect small liver lesions, to confirm the number and the size of liver metastases and to define their relationship with vascular structures. All the histologic slides were reviewed by the same pathologist team who evaluated the margins of liver resection After surgery, all the patients received six to eight additional courses of chemotherapy. Follow up and outcome were documented by clinical visits with liver tests, tumor markers, abdominal ultrasound and abdominal and lung CT scan every three months for the first two years, then every six months as a minimum. In case of liver recurrences, our policy was to apply the same strategy of chemotherapy followed by surgery.

Statistical analysis

Follow-up ranged from 3.5 to 9.5 years (median 5.5 years). Survival time was calculated from the date of protocol registration until death. Progression free survival (PFS) was computed from the date of protocol registration to that of recurrence. Survival curves were generated according to Kaplan–Meier [33]. Prognostic factors of surgery, complete resection, overall survival, and progression-free survival were identified with univariate logistic regression and Cox model. The following factors were examined in univariate analysis in the 151 patients: sex, primary tumor, synchronous metastases (occurrence of metastases within the three months following the diagnosis of primary tumor), diameter of the largest metastasis $\leqslant 5$ cm vs. > 5 cm, percentage of liver involvement $\leqslant 25\%$ vs. $> 25\%$, number of metastases $\leqslant 4$ vs. > 4, performance status (PS, according to the World Health Organisation) upon inclusion in chemotherapy protocol, initial CEA plasma concentration $\leqslant 10$ vs. > 10 ng/ml, previous palliative chemotherapy, maximal response to actual chemotherapy, metastases surgery. Univariate analysis was also performed on the same factors and on the following ones in the 77 operated patients: uni or bilobar location, interval between chemotherapy onset and surgery $\leqslant$ vs. > 6 months, complete vs. incomplete resection. Factors with a level of statistical significance < 0.1 in univariate analysis were selected for multivariate analysis according to the proportional hazard model.

Results

All patients

The characteristics of the 151 patients with liver only disease are listed in Table 2. An objective response was achieved in 90 patients (59%). Median progression-free survival (PFS) was 12 months (95% CI: 10–13 months). Median overall survival was 24 months (19–28 months) with 28% surviving at five years (20–35) and 17% alive at seven years (7%–27%) (Figure 1).

Surgery

A total of 77 patients underwent liver surgery with curative intent. The characteristics of the patients are given in Table 2. An objective response was achieved in 61 operated patients (79%), including two complete responses. Disease was stabilised in 16 patients, 10 of whom displaying a minor response (25% to 49% decrease in tumor size). The interval between chemotherapy onset and hepatic resection ranged from 3 to 21 months with a median of 5.5 months.

Tumor removal remained technically impossible in 19 patients (incomplete resection in 9 patients, no resection in 10 patients) as a result of bilateral liver metastases (13 patients) and/or more than four lesions (8 patients) and/or a diameter of the largest metastasis > 5 cm (9 patients).

Fifty-eight patients had macroscopically complete removal of metastases. Margins of liver resection were tumor-free for forty-eight patients who were thus considered in post surgical complete remission both macroscopically and microscopically. Four of them had a complete histologic response. Tumor free margins were $\geqslant 1$ cm for 18 patients (30%) and were < 1 cm for 26 patients (45%). There was no intraoperative or post operative mortality within the two months following surgery.

Disease recurrence after surgery

Sixty-one of the seventy-seven operated patients (79%) relapsed. Median progression-free survival was 17 months (95% CI: 15–20). Disease progressed in all the patients

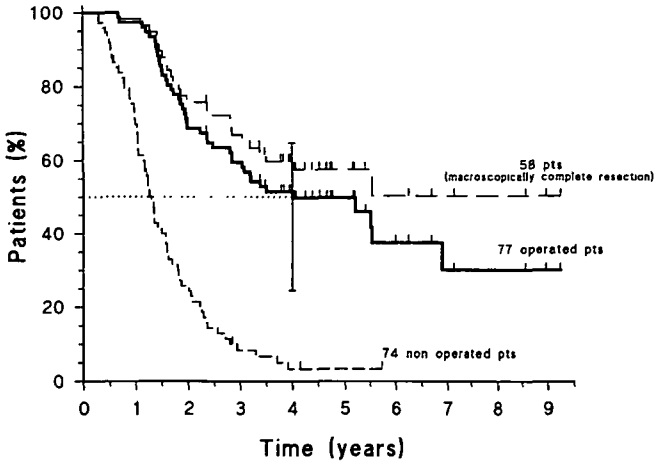

Figure 2. Survival of the 151 patients according to surgery outcome. Median survival was 15.5 months in the 74 non-operated patients and 48 months in the 77 operated patients. In those 58 patients with macroscopically complete resection, median survival has not been reached at five years.

with partial resection or involved margins. Out of the 58 patients who underwent macroscopically complete resection, 42 relapsed (72%) within a median time of 12 months (9–16), mostly in the liver (35 patients). In those 35 patients who relapsed in the liver, margins were involved with tumor in 8 patients. Tumor free margins were ≥ 1 cm in 9 patients and < 1 cm in 17 patients. One of the four patients with histologically- proven complete response relapsed. Twenty-two patients who recurred in the liver underwent again chemotherapy and repeated hepatectomy.

Survival

Fourty-two of the seventy-seven operated patients died (54%). Twenty-five of them (43%) had a complete resection and 17 patients an incomplete one (89%).

Median overall survival was 48 months (95% CI: 25–71). The estimated survival rates of the operated patients at five years and at seven years were respectively 50% (38–61) and 30% (12–48). Median overall survival of the 58 patients in complete resection has not been reached. So far, the estimated survival rates at five and at seven years are respectively 58% (44–71) and 50% (33–68; Figure 2). For comparison, the median overall survival of the 74 non-operated patients was 15.5 months (13.5–17.5).

Prognostic factors of surgery and complete resection following chemotherapy

We subsequently attempted to identify those predictive factors of surgery with curative intent in the 151 patients and the predictive factors of complete resection in the 77 operated patients. Six of the eleven factors tested were predictive of surgery for the 151 patients in an univariate analysis: synchronous vs. metachronous metastases, diameter of the largest metastasis, percentage of liver involvement, number of metastases, maximal response to chemotherapy and CEA level at inclusion. Percentage of hepatic involvement and maximal response to chemotherapy jointly influenced the decision of undertaking surgery as indicated by multivariate regression analysis (Table 3).

Seven of the fourteen potential factors tested in the 77 operated patients predicted for complete resection of metastases in an univariate analysis: initial Dukes' stage, diameter of the largest metastasis, percentage of liver involvement, number of metastases, number of liver lobes involved, interval between chemotherapy onset and surgery and CEA level at inclusion. The number of metastases and the interval between chemotherapy onset and surgery jointly influenced the achievement of a complete resection in multivariate regression analysis (Table 3). Multivariate regression analysis identified two factors which jointly influenced surgery outcome: the extent of liver involvement and maximal response to chemotherapy. Thus, the relative risk of not undergoing metastases surgery was 5.5 times as high in the patients with liver involvement $> 25\%$ as compared to those with $\leq 25\%$ involvement. This relative risk was 8.5 times as high in those without any objective tumor response as compared to the responding patients.

Prognostic factors of progression free survival (PFS) and survival

Univariate analysis was first performed on the data of the 151 patients and showed that surgery for metastases, performance status, percent of liver involvement, number of metastases, diameter of the largest metastasis and CEA at inclusion significantly predicted for both PFS and survival. These factors were entered into a Cox model for multivariate regression as an attempt to identify those which were jointly influential on progression free survival and survival. Number of metastases, CEA at inclusion and surgery of metastases were identified as independent predictors of both survival and PFS (Table 3).

Discussion

Surgical resection is considered to be the sole potentially curative treatment of hepatic metastases from colorectal cancer. About 40% of the operated patients survive at three years and 25% of them are alive at five years [1–7, 34–36]. Repeat liver resections can be performed and still achieve a three-year survival rate of 30% [37–40]. Unfortunately such surgical treatments can only be offered to approximately 10% of the patients who present with metastases from colorectal cancer [41, 42]. The need for an active chemotherapy of unresectable liver metastases is illustrated by the facts that survival rate of these patients is less than 10% at three years and that none is usually alive at five years [31, 36, 41]. The low antitumor activity and/or poor tolerability of most

Table 3. Prognostic factors of surgery, progression free survival and overall survival in the 151 patients, and of complete resection in the 77 operated patients (multivariate analysis).

Variable	Factor	*P*-value	Relative risk	95% CI
Surgery	Percentage of hepatic involvement ($\leq 25\%$ vs $> 25\%$)	0.0003	5.5 ($> 25\%$)	2–14
	Maximal response to chemotherapy	0.0001	8.5 (failure)	3–22
Complete resection	Number of metastases (≤ 4 vs. > 4)	0.011	7.75 (> 4)	2–14
	Interval between chemotherapy onset and surgery (≤ 6 vs > 6 months)	0.0018	16.6 (> 6 months)	3–97
Progression-free survival	Number of metastases	0.008	1.77	1–3
	CEA at inclusion	0.0005	2.27	1–4
	Surgery	0.0001	3.37	2–5
Survival	Number of metastases	0.015	1.78 (> 4)	1–3
	CEA at inclusion	0.0049	2.2 (> 10)	1–4
	Surgery	0.0001	3.7 (no)	2–6

chemotherapeutic regimens has clearly limited the implementation of a strategy combining systemic chemotherapy and surgery [44, 45]. Nevertheless palliative chemotherapy has significantly improved overall survival and quality of life as compared to supportive care in patients with unresectable colorectal metastases [8, 9]. These fluoropyrimidine-based regimens have produced only 10% to 25% objective responses [10–14]. This low response rate explains the lack of any report on combined chemotherapy–surgery in unresectable metastatic colorectal cancer. Response rates close to 50% were achieved with intra arterial hepatic chemotherapy, yet chemical hepatitis, cholangitis, cathether-related complications and/or progression of extrahepatic disease have hampered subsequent implementation of curative surgery [46]. Conversely, systemic chronomodulated chemotherapy with 5-FU, LV and L-OHP has repeatedly achieved both objective response rates exceeding 50% and good tolerability, thus allowing successful curative surgery to be performed since the first phase II trial of this regimen as well as in subsequent multicenter phase III trials [21–26]. In the present series, partial hepatectomy was attempted in 51 % of 151 patients with liver-only disease, which had been, initially considered unsuitable for radical surgery. Curative resection could be performed in 38% of these 151 patients. Such high rate results both from downstaging liver metastases with effective chemotherapy, and from the low toxicity of chronotherapy which permitted to perform hepatic resection with no surgical mortality and acceptable morbidity [31]. We cannot rule out that the characteristics of the patients who were referred to our center could be peculiar. Nevertheless 40% to 50% of these patients had poor prognostic factors such as $> 25\%$ liver involvement (48%) or previous failure to one or more chemotherapy lines (39%).

Surgery attempt was jointly predicted by the characteristics of metastases and the response to chemotherapy. The patients with less than 25% liver involvement and an objective response to chemotherapy respectively had 5.5 and 8.5 higher probabilities of being submitted to surgery after the administration of the three-drug regimen, as indicated by multivariate regression analysis. Both progression-free survival and survival of the 151 patients with liver-only disease, were jointly influenced by the number of metastases, initial CEA level and the ability to perform surgery. These same factors beside surgery jointly predicted for both progression-free survival and survival in the 77 operated patients.

Two recent prospective studies have described the prognostic factors which influence the natural history of metastatic colorectal cancer [48, 49]. In a large series of 524 patients with unresectable liver metastases, eight factors were found to jointly influence survival: performance status, chemotherapy for liver metastases, primary cancer type, presence of extrahepatic disease, and several estimators of liver disease, such as number of involved segments, alkaline phosphatase level and prothrombin time. Twenty five percent of a 'best' prognosis subgroup were alive at two years [48]. In another large series of 484 patients with unresectable colorectal cancer metastases, the overall proportion of patients alive was 7.9% at two years and 2.6% at three years [49]. Median survival expectancy of these unresectable, untreated patients varied from 3.8 to 21.3 months according to the combination of six prognostic factors including percentage of liver involvement, grade of primary tumor, presence of extra hepatic disease, mesenteric lymph node involvement, CEA level, and age [49].

The present study is indeed, to our knowledge the first one which reports a survival rate of 37% at three years and 28% at five years in patients with previously unoperable liver metastases. The estimated five-year survival rate of these 77 operated patients was 50% at five years. Thus, the overall survival of these patients was similar to or even better than that of the patients who usually undergo primary liver surgery for colorectal metastases.

The present study indicates that each patient with primary unresectable liver metastases, who achieves an objective response to chemotherapy should be re-evaluated for liver surgery by a team involving surgeons and oncologists. Moreover, a better outcome is obtained if surgery can be performed within less than six months This strategy is only relevant if the chemotherapy regimen achieves a high proportion of objective responses with good tolerability. In such case, it can effectively translate the antitumor activity of chemotherapy into a long term survival benefit and potential cure. Chrono-

modulated infusion of 5-fluorouracil, leucovorin and oxaliplatin indeed allowed such goal to be met in approximately half of the patients with initially unoperable liver metastases from colorectal cancer.

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