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Improved Long-Term Outcome of Surgery for Advanced Colorectal Liver Metastases: Reasons and Implications for Management on the Basis of a Severity Score

Axel Andres, MD,[1] Pietro E. Majno, MD, FRCS,[1] Philippe Morel, MD,[1] Laura Rubbia-Brandt, MD, PhD,[2] Emiliano Giostra, MD,[3] Pascal Gervaz, MD,[1] Sylvain Terraz, MD,[4] Abdelkarim S. Allal, MD,[5] Arnaud D. Roth, MD,[6] and Gilles Mentha, MD[1]

[1]Unit of Visceral and Transplantation Surgery, University Hospitals of Geneva, 1211, Geneva 14, Switzerland
[2]Clinical Pathology, University Hospitals of Geneva, 1211, Geneva 14, Switzerland
[3]Gastroenterology, University Hospitals of Geneva, 1211, Geneva 14, Switzerland
[4]Radiology, University Hospitals of Geneva, 1211, Geneva 14, Switzerland
[5]Radiation Oncology, University Hospitals of Geneva, 1211, Geneva 14, Switzerland
[6]Oncosurgery, University Hospitals of Geneva, 1211, Geneva 14, Switzerland

Background: The outcome of liver resection for colorectal liver metastases (CRLM) appears to be improving despite the fact that surgery is offered to patients with more-severe disease. To quantify this assumption and to understand its causes we analyzed a series of patients on the basis of a standardized severity score and changes in management occurring over the years.

Methods: Patients' characteristics, operative data, chemotherapies and follow-up were recorded. CRLM severity was quantified according to Fong's clinical risk score (CRS), modified to take into account the presence of bilateral liver metastases. Three periods were analyzed, in which different indications, surgical strategies and uses of chemotherapy were applied: 1984–1992, 1993–1998, and 1999–2005.

Results: Between January 1984 and December 2005, 210 liver resections were performed in 180 patients (1984–1992, 43 patients; 1993–1998, 42 patients; 1999–2005, 95 patients). CRLM severity increased throughout the time periods, as did the use of neoadjuvant chemotherapies, repeat resections, and multistep procedures. While the *disease-free* survival did not improve over time, the 1-, 3- and 5-year *overall* survival rate increased from 85%, 30%, and 23% in the first period, to 88%, 60%, and 34% in the second period, and to 94%, 69%, and 46% in the third period.

Conclusions: Analysis according to the CRS showed that despite the fact that patients had more severe disease, the overall survival improved over the years, mainly thanks to more aggressive treatment of recurrent disease. Management of advanced CRLM should, from the start, take into account the likelihood of secondary procedures.

Key Words: Colorectal cancer—Colorectal liver metastases—Liver surgery—Chemotherapy—Survival.

Adenocarcinoma of the colon and rectum is a common disease in Europe and in the United States, with an incidence of between 15 and 40 per 100,000 people per year. Despite radical removal of their primary tumor, 30% to 40% of the patients will

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Address correspondence and reprint requests to: Gilles Mentha, MD; E-mail: gilles.mentha@hcuge.ch

eventually die from local or distant recurrences. Liver metastases develop in approximately one half of the patients,[1–3] and are the commonest cause of death.

Surgical resection of colorectal liver metastases (CRLM) is a safe and effective treatment,[4–8] with 5-year survival rates ranging from 20% to 40% depending on the pattern of the disease, on operative techniques and on the era of the investigation. The modern picture of the surgical management of CRLM, however, is complex. In the past, surgery was the only effective treatment that could be applied to a minority of patients with a relatively favorable disease pattern or location (10% to 25%). At present, more patients with advanced disease can undergo operations due to improved surgical techniques and neoadjuvant chemotherapies that can downstage initially unresectable disease.[9,10] In addition, a multidisciplinary approach has changed the management and outcome of recurrences after liver surgery, and patients can be offered repeat resections, percutaneous ablation procedures and new chemotherapy regimens.[10–15]

The present study, based on the analysis of 210 liver resections in 180 patients during three time periods, illustrates the results of the modern treatment of CRLM, stratifying patients according to the severity of the disease, and aims to identify the different factors that have changed the outcome of this condition.

PATIENTS AND METHODS

Patient Selection

All patients who underwent a liver resection for CRLM from January 1984 to December 2005 were entered prospectively in a liver resection database. The indication for surgery was a possibility to resect all disease observed by imaging studies (R0 resection), regardless of the number of procedures needed to achieve this goal. Patients 70 years or older were considered as the elderly patient population. Patients with CRLM who did not have liver resections were excluded from the study.

Periods

Three distinct periods could be identified according to the pattern of referrals and to different attitudes in the use of chemotherapy:

- 1984 to 1992: upfront surgical resections in patients with relatively favorable anatomy, disease pattern and operative risk; occasional use of neoadjuvant chemotherapy (12.2%); occasional use of adjuvant chemotherapy (4.7%).
- 1993 to 1998: the majority of patients received neoadjuvant chemotherapy, based on 5-fluorouracil (5FU) and leucovorin (55%); more frequent use of adjuvant chemotherapy (28.6%).
- 1999 to 2005: regular use of irinotecan and oxaliplatin, generally in a neoadjuvant setting. Strategies used in this period included portal vein embolization to prepare the liver for extensive resection,[16] two-step hepatectomies[17,18] and a "reversed" approach for synchronous liver metastases—with neoadjuvant chemotherapy, liver resection and resection of the primary tumor, in that order—as published recently.[19]

Chemotherapy Definitions

Chemotherapy was defined as all the chemotherapeutic cycles delivered, including chemotherapy given after recurrence, with the exception of chemotherapy given as radiotherapy sensitization. Neoadjuvant chemotherapy was defined as the chemotherapy delivered before the liver resection. Adjuvant chemotherapy was defined as consolidation chemotherapy delivered within the year following liver resection. Chemotherapies delivered as treatment of recurrences were not considered as adjuvant.

Data

Data included age, gender, American Society of Anesthesiology (ASA) classification of operative risk, tumor-nodes-metastasis (TNM) classification and the site of the primary tumor, presence of extrahepatic tumor sites, and the chemotherapy given before and/or after surgery. Surgical details included the type of operation, blood transfusions, histology of the resected liver and tumors, resected tumor margins, postoperative complications and outcome. When patients had a nonresectable recurrence, palliative treatment was under the care of the referring oncologist, and data recorded after such a recurrence concerned the type and date of recurrence, the radiofrequency ablation treatment, and the chemotherapy.

Clinical Risk Score

The patients were classified retrospectively according to Fong's classification[20] using a clinical risk score (CRS), validated on large cohorts of patients in the United States and Europe.[20–22] The score is based on five clinical criteria, each one assigned one point: positive lymph node status of the primary tumor, disease-free interval from the resection of the primary to discovery of the liver metastases of less than 12 months, number of liver metastases greater than one, preoperative carcinoembryonic antigen (CEA) level greater than 200 ng/ml, and size of the largest tumor greater than 5 cm. A CRS greater or equal to 3 has been validated as a cutoff defining more severe disease.[20] In the present investigation we modified the CRS by adding the presence of bilateral liver metastases as a new point (abbreviated mCRS in this paper). Bilaterality was associated with more widespread disease and with more complex management (such as two-step operations and portal vein embolization). A recent multicenter study showed that bilaterality was an independent factor of poor outcome in a multivariate analysis ($p < 0.01$).[23]

The purpose of Bilaterality in the mCRS was not to use it as a new prognostic marker but to use the mCRS as a scale of disease complexity, to compare the management of CRLM between different time periods. Bilaterality was not associated with decreased survival in our study.

Imaging Studies

Routine imaging studies before liver resection included an abdominal and thoracic computed tomography (CT) scan. The use of magnetic resonance imaging (MRI) increased after 1997, as well as the positron emission tomography (PET) CT scan. The use of intraoperative ultrasound by liver surgeons has been standard since 1988, and is now considered mandatory in our center.

Surgery

During surgery, a complete exploratory laparotomy was performed. The liver was inspected, palpated and examined by intraoperative ultrasound. Liver resections were classified according to Couinaud and Bismuth, with major hepatectomies defined by the resection of at least three segments.[24] Simultaneous colonic and liver resections were performed in selected circumstances (right colon or < 1–2 segments and left colon), but rectal resections and complex liver resections were not performed during the same operation. When neoadjuvant chemotherapy was used, the resection of all CRLM was planned based not only on the most recent CT scan or MRI but also on the CT scan before chemotherapy was started, to avoid leaving missing metastases behind.

Follow-Up

Follow-up was provided within a dedicated surgical oncology unit, or in collaboration with the referring private oncologist according to the patient's preference.

Statistics

Life-table curves (global survival endpoints, death; and tumor-free survival endpoints, definite tumor recurrence or death) were analyzed with the Kaplan-Meier method and distributions were compared by the log-rank test. In case of simultaneous analysis of more than two populations, statistical differences were assessed by an extension of Gehan's generalized Wilcoxon test, Peto and Peto's generalized Wilcoxon test and the log-rank test algorithms, using the Statistica 5.5 software (Statsoft Inc, Tulsa, OK, US). Continuous data were analyzed by bilateral Student's t test and dichotomous data were analyzed by χ^2 test. P values lower than 0.05 were considered significant.

RESULTS

Demographics

A total of 210 liver resections were performed on 180 patients. In the first period (1984–1992), 43 patients had 45 liver resections; in the second period (1993–1998), 42 patients had 46 resections; and in the third period (1999–2005), 95 patients had 119 resections. The characteristics of the patients for the three periods are summarized in Table 1.

Postoperative Mortality

The postoperative mortality (within 60 days) did not differ during the three time periods, and involved only one patient who died of liver failure 12 days after a repeat hepatectomy in the third time period (overall mortality, 0.5%).

Chemotherapy

During the first period, chemotherapy was delivered to 36.6% of the patients, neoadjuvant chemotherapy was delivered to 12.2% of the patients, and adjuvant chemotherapy was delivered to 4.7% of the

TABLE 1. *Demographic data. Patients' characteristics are listed according to the three different time periods. Statistical analysis between periods is shown for each factor*

	1984–1992	1993–1998	1999–2005	Statistical test		p =
Patients (n)	43	42	95			
Resections (n)	45	46	119			
Sex female/male ratio (n)	23/20	13/29	41/54	χ^2	Period 1–2	0.004
					Period 2–3	0.178
					Period 1–3	0.260
Age: median [range]	61 [37–79]	64 [39–77]	61 [33–81]	t test	1–2	0.184
					2–3	0.227
					1–3	0.769
ASA 1–2/3–4 ratio (n)	36/5	37/5	74/13	t test	1–2	0.871
					2–3	0.405
					1–3	0.840
Overall chemotherapy: yes/no ratio (n)	15/26	35/5	81/8	χ^2	1–2	2.4×10^{-6}
					2–3	0.54
					1–3	5.3×10^{-11}
Neoadjuvant chemotherapy: yes/no ratio (n)	5/36	22/18	74/12	χ^2	1–2	0.00004
					2–3	0.0002
					1–3	1.01×10^{-15}
Adjuvant chemotherapy: yes/no ratio (n)	2/41	12/30	23/72	χ^2	1–2	0.003
					2–3	0.589
					1–3	0.006
Metastases : multiple/solitary ratio (n)	22/21	19/23	59/35	χ^2	1–2	0.058
					2–3	0.056
					1–3	0.200
Primary lymph nodes status: positive/ negative ratio (n)	28/15	23/18	60/30	χ^2	1–2	0.389
					2–3	0.244
					1–3	0.860
Metastases: synchronous/metachronous ratio (n)	18/24	33/9	68/27	χ^2	1–2	0.0008
					2–3	0.391
					1–3	0.001
CEA > 200 at diagnosis: yes/no ratio (n)	1/34	4/32	18/45	χ^2	1–2	0.174
					2–3	0.044
					1–3	0.002
Metastase size > 5cm at diagnosis: yes/no ratio (n)	17/24	13/27	25/47	χ^2	1–2	0.404
					2–3	0.812
					1–3	0.476
CRS: 0–1–2/3–4–5 ratio (n)	23/9	25/9	30/29	χ^2	1–2	0.880
					2–3	0.032
					1–3	0.052
mCRS: 0–1–2/3–4–5–6 ratio (n)	16/8	21/13	24/34	χ^2	1–2	0.702
					2–3	0.059
					1–3	0.037
Liver metastastic involvement: bilateral/unilateral ratio (n)	6/26	15/27	43/51	χ^2	1–2	0.109
					2–3	0.275
					1–3	0.007
Liver resection: major/minor ratio (n)	31/12	25/17	54/41	χ^2	1–2	0.222
					2–3	0.770
					1–3	0.088
Microscopic margins of resected metastases: positive/negative ratio (n)	6/29	8/34	8/73	χ^2	1–2	0.829
					2–3	0.152
					1–3	0.270
Hospital stay after resection (days): median [range]	17 [6–64]	13 [4–59]	11 [4–41]	t test	1–2	0.037
					2–3	0.126
					1–3	0.00002
Follow-up time between resection and last control/death (years): median [range]	1.46 [0.03–15.96]	3.26 [0.36–10.91]	1.69 [0.01–6.32]		See survival curves	

ASA, American Society of Anesthesiology classification of operative risk; CEA, carcinoembryonic antigen; CRS, clinical risk score; mCRS, modified clinical risk score.

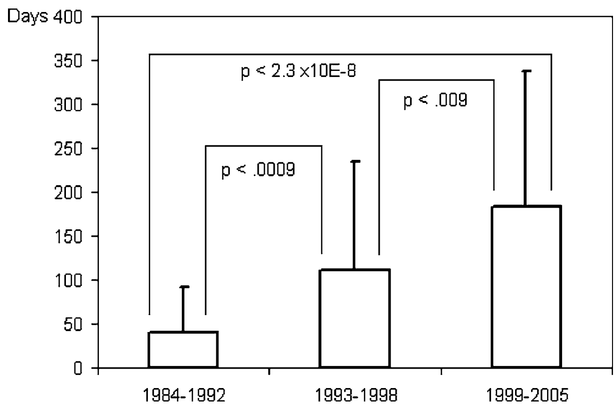

FIG. 1. The time (in days) elapsed between the diagnosis of liver metastases and the R0 liver resection is shown for each period. The delay is statistically longer from the first to the last time period (bilateral Student's *t* test).

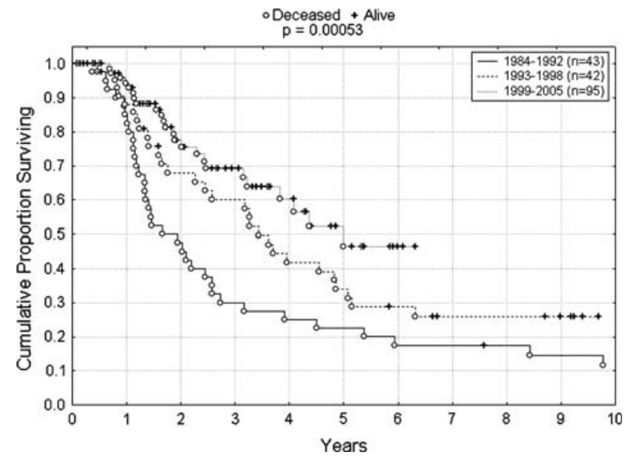

FIG. 2. Overall survival since R0 resection in each period is shown as separated Kaplan–Meier curves. Overall survival significantly increased from the first to the last time period. Numbers in brackets correspond to the patients who underwent operations in each period.

patients (Table 1). No patient during this period underwent a two-stage procedure or a portal vein embolization.

During the second period, chemotherapy was delivered to 88% of the patients, mostly 5FU-leucovorin. In contrast to the first time period, the majority of patients received neoadjuvant chemotherapy (55%), and the proportion of patients who received adjuvant chemotherapy significantly increased (Table 1). A two-step procedure was performed in one case and portal embolization was never used.

During the third time period, when compared to the second, the number of patients who received neoadjuvant chemotherapy increased significantly (Table 1), with 5FU, oxaliplatine, and irinotecan (CPT11) as the main drugs. The proportion of patients who received chemotherapy, and in particular adjuvant chemotherapy, remained similar to those in the second time period (Table 1). Patients with bilobar CRLM had, when appropriate, a two-stage procedure ($n = 13$) or a portal vein embolization prior to surgery ($n = 11$).

During the last time period, seven patients underwent radiofrequency ablation treatment for recurrence.

Survival

For the 180 patients operated between 1984 and 2005, overall 1-, 2-, 3- and 5-year survival rates were 95%, 74%, 58% and 40%, respectively, from the time of the liver metastases diagnosis, and 90%, 66%, 55% and 36% from the time of the liver resection.

The delay between the diagnosis of the metastases and liver resection increased significantly from the first to the third time period. This reflected the use of longer neoadjuvant treatments, as well as procedures to prepare for R0 resection such as portal embolization, or unilateral resection of the metastases and contralateral portal vein ligation (Fig. 1).

The overall survival at 1, 2, 3, and 5 years increased significantly from the first to the third time periods (first period, 83%, 46%, 29% and 22%; second period, 88%, 68%, 60%, and 34%; third period, 94%, 77%, 69% and 46%) (Fig. 2). The 5-year survival rate from CRLM diagnosis also increased from the first (23%), to the second (39%), and to the third time period (50%).

The disease-free survival did not increase significantly from 1984 to 2005 (Fig. 3a) while the difference between the overall and the disease-free survival rates increased from the first to the third time periods (Figs. 3b, 3c and 3d).

CRS and Modified CRS

Patients with a CRS below 3 had a significantly better survival than patients with a CRS equal or greater than 3 (cumulative proportion surviving at 5 years after R0 resection with low vs. high CRS, 44% vs. 21%, $p = 0.031$). Considering a cut-off of 3, more patients had a high CRS in the third time period compared to the two previous periods (Table 1), and the difference was significant for the second and third time periods ($p = 0.032$).

Of the five items included in the CRS, only simultaneity and CEA significantly increased from the first

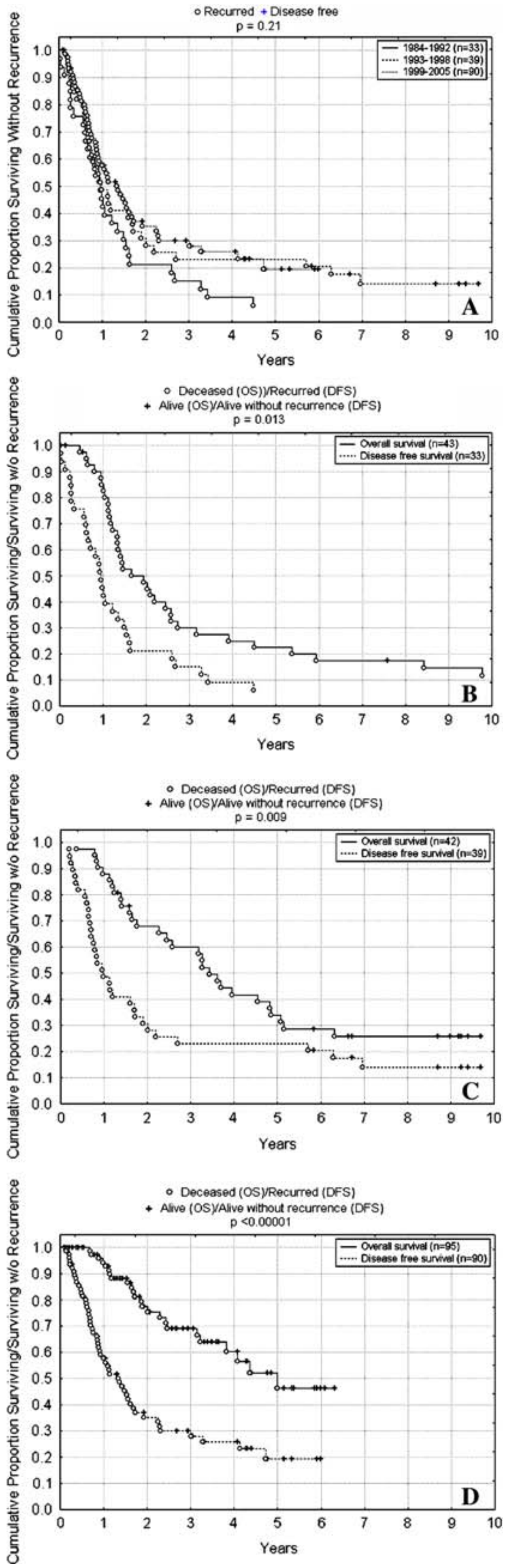

FIG. 3. Disease-free survival in each period and comparison with overall survival. Disease-free survival since R0 resection did not increase with time, as shown by (A) the Kaplan–Meier curve for each period. Although the difference between overall survival (OS) and disease-free survival (DFS) was significant for each period analyzed, the difference increased from (B) the first to (C) the second and to (D) the third period, reflecting a better survival after recurrence.

to the last time periods (Table 1). Multiplicity of metastases increased between periods, although fell short of statistical significance ($p = 0.58$ between the first and second time periods,and 0.056 between the second and third time periods), and the proportion of patients presenting with bilateral metastases increased from the first to the third time period (19% vs. 36% vs. 46%) (Table 1).

Although bilateralism of metastases was not statistically discriminant for better or worse survival per se ($p = 0.26$), it allowed a finer analysis of outcome when added to the CRS (cumulative proportion surviving at 5 years after R0 resection with low vs. high mCRS, 56% vs. 14%, $p = 0.017$).

When survival curves were compared for patients with low mCRS in the different time periods, there was a significant improvement in overall survival (OS) (Fig. 4a) and disease-free survival (DFS) (Fig. 4b) between the first period and the last two periods (OS: first time period at 1, 3 and 5 years, 86%, 46% and 36%; second and third time periods at 1, 3 and 5 years, 95%, 71% and 63%; $p = 0.035$; DFS: first time period at 1, 3 and 5 years, 50%, 16% and 0%; second and third time periods at 1, 3 and 5 years, 58%, 45% and 38%; $p = 0.046$).

For patients with a high mCRS, there was a significant improvement in OS during the last time period as compared to the first two periods (OS: first and second time periods at 1, 3 and 5 years, 90%, 43% and 5.3%; third period at 1, 3 and 5 years, 90%, 60% and 24%; $p = 0.047$) (Fig. 4c), but no improvement in DFS (Fig. 4d).

Young and Elderly Patients

The proportion of elderly patients who had operations increased between time periods (first period, five elderly patients out of 43 patients; second period, eight of 42, third period, 20 of 95), although the increase was not statistically significant.

The DFS remained similar for young and elderly patients between the three periods ($p = 0.51$ for young patients, $p = 0.1$ for elderly patients). In contrast, the overall survival increased between time

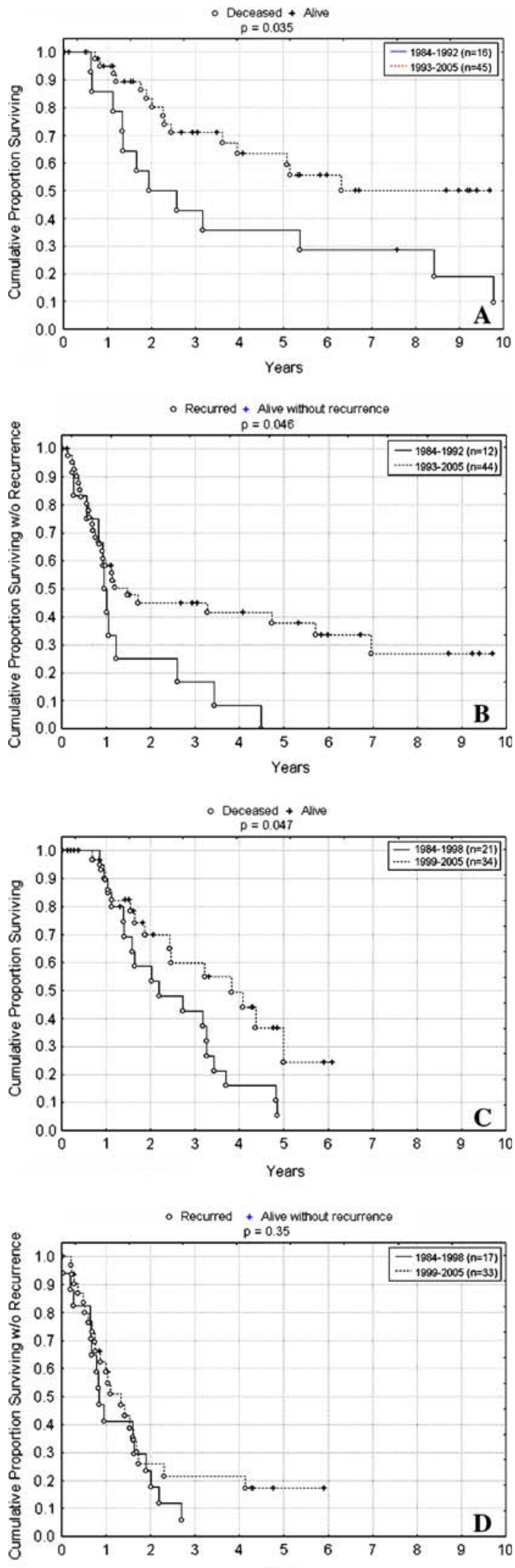

FIG. 4. Survival of patients presenting with low and high mCRS, according to periods. Periods were grouped in order to analyze survival between (A and B) the first time period versus the second and third time periods, and between (C and D) the first two time periods versus the third period. With such cut-offs, overall survival (OS) and disease-free survival (DFS) since R0 were analyzed for patients presenting low and high mCRS. For patients with low mCRS, (A) OS as well as (B) DFS improved significantly from the first period to the last two periods. In contrast, for patients with a high mCRS, (C) OS, but not (D) DFS improved significantly.

periods for young patients ($p = 0.0004$), but not for older patients ($p = 0.48$) (Fig. 5a and 5b).

Among the 33 elderly patients, only one had a second resection for recurrence compared to 16 among the 147 young patients (p = not significant (NS)). No elderly patients had a two-step resection, three had a preoperative portal embolization (vs. 12 young patients, p = NS).

The proportion of elderly patients who had neoadjuvant chemotherapy was similar to the younger population (48% vs. 63%, p = NS), but only 65% of elderly patients received chemotherapy postoperatively, versus 84% of young patients ($p = 0.013$).

DISCUSSION

This study shows that: (1) the severity of CRLM in patients presenting to surgeons, represented by the CRS, increased over the three time periods, and (2) that despite the increasing CRS, the long-term survival improved over these same periods.

Two reasons explain why the severity of the metastatic disease increased over time. The first is that more effective chemotherapy regimens (with response rates as low as 10–20% in the first time period and in the range of 60–70% in the most recent time period) have been applied to the neoadjuvant setting,[25] rendering resectable those patients with previously unresectable disease.[10,11] These patients had by definition a very advanced disease. The second reason is that liver surgery has developed techniques that specifically address the limitations of multiplicity, of a small residual liver and of proximity to major anatomical structures, without compromising safety.[9]

Although the increasing severity of patients operated for CRLM is taken for granted in most specialized centers, this is the first investigation that presents this point as a measurable factor. While the CRS was devised as a prognostic score, it offers a standardized tool and allows appreciation of the severity of the disease, and the difficulty of the surgery that is needed to resect it,[19] especially with the

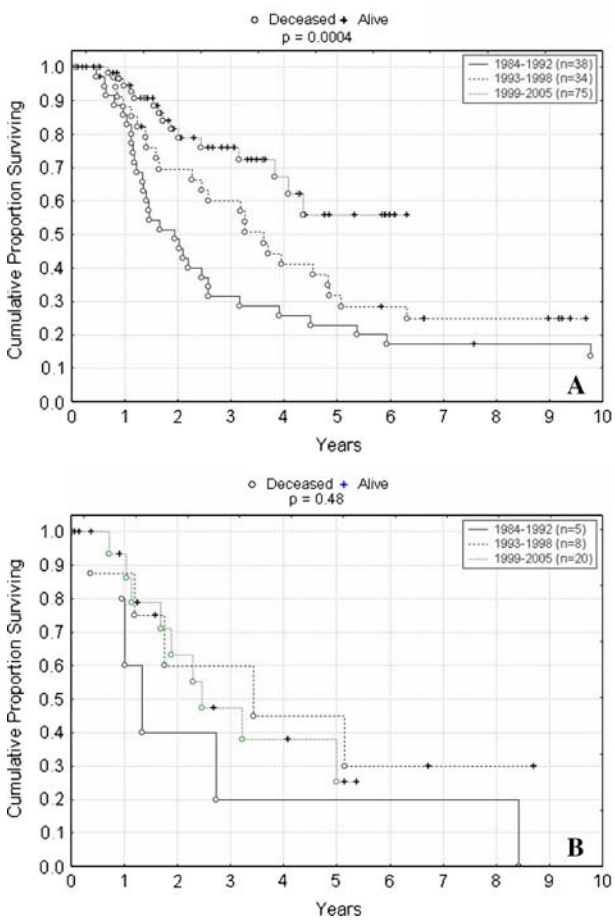

FIG. 5. Overall survival in each period for young and elderly patients. Overall survival since R0 resection of (A) young and (B) elderly patients are shown as separate Kaplan-Meier curves corresponding to the different periods. Young patients are defined by < 70 years old.

additional factoring of bilateral metastases. The stratification of patients using the mCRS allowed us to compare the three time periods and the results of similar patients during the periods. We suggest that the mCRS, the CRS or a similar tool should be used when reporting the results of surgery for CRLM, to offer a common basis for comparison between different treatments and/or different centers.

The stratification of patients in the different risk categories and during different periods allowed us to identify the factors responsible for the improved survival rate over time. The selection of patients with a more favorable risk profile did not play a role, as the proportion of patients with advanced disease increased in the most recent periods. Similarly, factors that are commonly cited, such as lower mortality and better resection techniques, were irrelevant or minor in the present series: the only postoperative death occurred in the most recent period. Surgical progress was indeed important in expanding the limits for safe resection of advanced disease, and in operating safely on patients with chemotherapy-induced liver changes,[26,27] which may impact on postoperative mortality,[28] but these aspects are difficult to quantify.

The more frequent use and the increased effectiveness of chemotherapy appeared to be the two major factors responsible for the increased overall survival rate, affecting the outcome at different levels. From a theoretical point of view, chemotherapy may:

1. Have a systemic effect on undetected extrahepatic metastases. Hematogenous malignant cells have been detected in advanced colorectal cancer, and the manipulation of CRLM may be associated with a high risk of intraoperative tumor cell dissemination.[29–31]
2. Prolong survival after relapse, when the disease is no longer resectable.[32]

Both these mechanisms have probably played a role in our patients, as shown by the reduced incidence of recurrences in patients with a low CRS in the most recent periods.

Another relevant factor, however, emerges from a more detailed analysis of the survival patterns of patients with a higher CRS in the most recent period. The improvement in survival concerned *overall* rather than *disease-free* survival, showing that the gain was due to a better management of recurrences with repeat resections, radiofrequency thermal ablations and new chemotherapy regimens.[33] The corollary of this finding is that while disease-free survival was similar in young and elderly patients in the most recent time period, survival after recurrence was longer in younger patients (patients for whom the overall management can be more aggressive compared to older patients), suggesting a more active treatment of recurrences.[3,34]

Some practical implications can be extracted from our study. The first one concerns reporting. Stratification according to the CRS (especially mCRS, which takes bilateralism into account) is useful to compare different series and to identify the determinants that influence outcome, which would be otherwise masked by the inevitable heterogeneity of the CRLM population.

The second implication is that as more patients with a high CRS present to a surgical team, the likelihood of recurrences has to be integrated into the management program. Since recurrences can be managed aggressively, they have to be taken into account at the initial hepatectomy. Therefore, it seems reasonable to perform conservative radical resections as opposed to large hepatectomies in patients with severe disease at presentation, as further surgery is likely. In CRLM, several studies showed the feasibility of limited resections with safety margins of less than 10 mm without compromising the long-term survival.[35–37] A surgical approach that favors conservative R0 resection, without undue sacrifice of vascular structures or of liver parenchyma is therefore appropriate for most complex cases. Neoadjuvant chemotherapy of high efficacy may play a crucial role in this respect with maximum downsizing of the lesions.

CONCLUSIONS

In conclusion, thanks to the classification according to a standardized severity score, we show in this study that the outcome of patients with CRLM has markedly improved over the last decade. Progress in both surgical techniques and in systemic therapies has contributed to these better results, and patients with more advanced disease can now be treated with a curative intent. Management of recurrences is the new challenge in advanced CRLM and requires a combination of chemotherapy and strategies to economize liver parenchyma that allow for further surgery if necessary.

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