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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

# Fong's Score in the Era of Modern Perioperative Chemotherapy for Metastatic Colorectal Cancer: A Post Hoc Analysis of the GERCOR-MIROX Phase III Trial

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## ABSTRACT

**Background.** Despite improvement in colorectal liver metastasis (CLM) treatment, survival after liver surgery remains highly variable. Several clinicopathologic prognostic factors have been reported, but their validity in the era of more effective perioperative chemotherapy remains to be defined. The aim of this study is to analyze the prognostic factors associated with survival after CLM resection.

**Methods.** Clinicopathologic data of patients included in the MIROX phase III trial who underwent surgery for isolated CLMs were analyzed. The primary endpoints were 5-year overall survival (OS) and disease-free survival (DFS). Univariate Cox analysis was performed to identify associations with OS and DFS and select variables for inclusion in a multivariate model to determine their independent prognostic value.

**Results.** A total of 181 patients were analyzed. The median follow-up period was 6.42 years [95% confidence interval (CI) 5.15–8.71 years], and the 5-year OS and DFS rates were 67.1% and 35.4%, respectively. On multivariate analysis, Fong's clinical risk score (CRS) as a categorical variable (CRS 0–1 vs. 2–3 vs. 4–5, $p = 0.036$) and polymorphonuclear neutrophil (PMN) count ($> 6000/mm^3$ vs. $\leq 6000/mm^3$, $p = 0.006$) before chemotherapy were found to be independent prognostic factors for OS. However, only Fong's CRS remained significantly associated with DFS ($p = 0.027$). The final OS model was used to establish a nomogram that allows individual OS estimations at 1, 3, 5, and 10 years.

**Conclusions.** Fong's CRS was independently associated with DFS and poor OS after CLM resection with FOLFOX-based chemotherapy regimen. It could be useful in daily practice and future trials to select patients more accurately.

Surgery is the only potentially curative treatment for resectable colorectal liver metastases (CLMs); however, only 15–20% of metastases are initially resectable.[1] Recently, multimodal treatment strategies have clearly improved the outcome of patients with CLMs. Liver resection can provide significant long-term benefit with 5-year survival rates approaching 40%, but most patients relapse.[2] Due to disease heterogeneity, it is important to identify factors associated with recurrence to identify

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subgroups of patients with different risks of recurrence after surgery for CLMs. Several clinicopathologic prognostic factors associated with survival have been identified, such as number of CLMs, maximum size, lymph node metastases, interval between colorectal cancer (CRC) and CLM detection, preoperative carcinoembryonic antigen (CEA) level, extrahepatic spread, positive resection margin, poor differentiation of CRC, serosal invasion of CRC, hepatic lymph node metastases, and bilobar spread.[3] However, most of these data are historical, and their relevance in the context of more systematic perioperative chemotherapy is not established; For example, Fong's clinical risk score (CRS), the well-known and most validated prognostic model, was established based on a population of operated patients during the 1980s who received only fluorouracil (5-FU) or no chemotherapy.[4] The five parameters of Fong's CRS are primary tumor stage N1 or N2, disease-free interval $< 12$ months, number of metastases $> 1$, preoperative CEA level $> 200$ ng/mL, and metastasis maximal diameter $> 5$ cm.

The aim of this work is to study the factors associated with overall survival (OS) and disease-free survival (DFS) in a large cohort of patients with CLMs treated with both surgery and chemotherapy. We therefore evaluated the outcome after liver resections performed for isolated CLMs in patients included in the MIROX trial.[5] All patients in this study received perioperative or adjuvant homogeneous FOLFOX-based chemotherapy regimens.

## PATIENTS AND METHODS

### *Study Design and Participants*

The MIROX phase III trial (ClinicalTrials.gov identifier: NCT00268398, reporting guidelines in Supplementary Fig. S1), which compared FOLFOX4 chemotherapy (oxaliplatin 85 mg/m$^2$, levofolinate 200 mg/m$^2$, 5-FU bolus 400 mg/m$^2$, and 5-FU infusion 2400 mg/m$^2$) with sequential dose-dense FOLFOX7 (oxaliplatin 130 mg/m$^2$, levofolinate 200 mg/m$^2$, 5-FU bolus 400 mg/m$^2$, and 5-FU infusion 2400 mg/m$^2$) followed by FOLFIRI (irinotecan 180 mg/m$^2$, levofolinate 200 mg/m$^2$, 5-FU bolus 400 mg/m$^2$, and 5-FU infusion 2400 mg/m$^2$) in patients with resectable metastatic CRC, recruited patients from 19 French centers.[5] Patients were eligible if they had histologically confirmed CRC with initially resectable/resected metastases at only one site (liver, lung, ovary, or peritoneum). Synchronous metastatic disease was defined as distant metastases occurring within 6 months from a primary CRC diagnosis, and metachronous metastatic disease was defined as distant metastases beyond 6 months from the primary CRC diagnosis.

Other eligibility criteria are described in the published study.[5] In the present study, all patients included in the MIROX trial and treated by surgery for isolated CLMs were included.

In the MIROX trial, patients were randomized (1:1) using a minimization technique stratifying them by chemotherapy timing (perioperative vs. postoperative), local intervention [surgery vs. radiofrequency ablation (RFA) with/without surgery], and Fong's CRS (0–1 vs. 2–3 vs. 4–5).[4] Patients received either 12 FOLFOX4 cycles or 6 FOLFOX7 cycles, followed by 6 FOLFIRI cycles, 1 cycle every 2 weeks. Chemotherapy timing was decided by the institutional tumor board including a hepatobiliary/thoracic surgeon. Simple/complex surgical procedures were authorized. RFA was authorized if there were $\leq 3$ liver metastases with diameter $\leq 35$ mm. For perioperative chemotherapy, four to six preoperative cycles were recommended. For patients operated before inclusion, R0 resection was required. The biological parameters including PMN count, alkaline phosphatase (ALP), lactic dehydrogenase (LDH), and CEA were assessed at baseline, before the start of chemotherapy. Computed tomography scan and CEA measurement were performed before surgery, at the end of chemotherapy, every 3 months for 2 years, and every 6 months thereafter. Positron emission tomography scan was optional. Intraoperative ultrasound was recommended.

The study protocol was approved by an ethics committee responsible for all the centers and was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. All patients provided written informed consent before registration in the MIROX trial.

### *Statistical Analysis*

Continuous and categorical variables are expressed as median [interquartile range (IQR)] and frequency (percentage), respectively. Medians and proportions were compared using Student's *t* test and the Chi square test (or Fisher's exact test, if appropriate), respectively.

OS was calculated from date of randomization to date of death from any cause. Survival data were censored at last follow-up date. DFS was calculated from date of randomization to date of relapse or death from any cause, or date of last follow-up, at which point data were censored. OS and DFS were estimated using the Kaplan–Meier method. Follow-up duration was calculated using a reverse Kaplan–Meier estimation.

Cox proportional hazards models were performed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for factors associated with OS and DFS. The association of baseline parameters with OS and DFS was first assessed using univariate Cox analyses, then parameters

with $p < 0.05$ were entered into a final multivariable Cox regression model, after considering collinearity among variables with a correlation matrix.

For continuous variables in the Cox model, a potential nonlinear relationship between predictors and OS or DFS was first investigated using the fractional polynomial method to determine the best transformation for continuous variables then validated by the restricted cubic spline method with graphical evaluation. The assumption of proportionality was checked by plotting log-minus-log survival curves and using cumulative martingale process plots. The accuracy of the final model was verified for discrimination and calibration.

The final OS and DFS models were used to establish a nomogram for predicting individual OS and DFS probabilities at 1, 3, 5, and 10 years post-randomization.

## RESULTS

### *Demographics and Histopathology*

A total of 284 patients were included in the MIROX trial, of whom 181 (63.7%) underwent liver resection for isolated CLMs and were included in this study. There were 129 men (71.3%) and 52 women (28.7%) (Fig. 1). The overall median follow-up period was 6.42 years (range 5.15–8.71 years). Median age at inclusion was 61.7 years

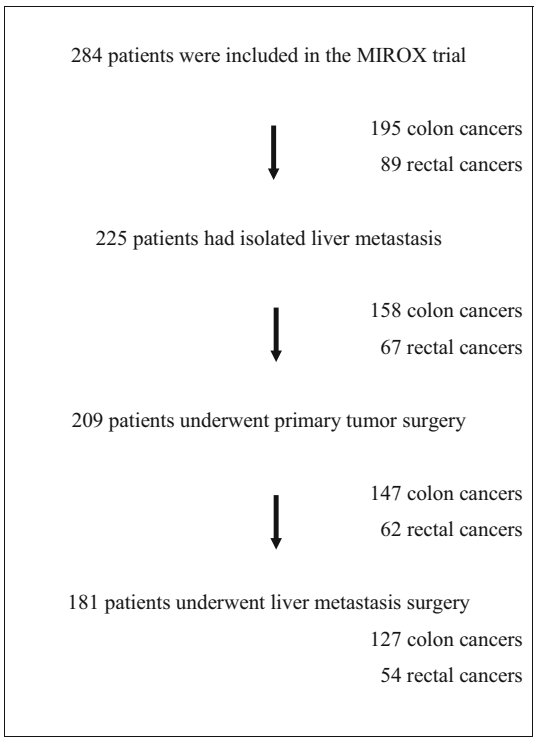


**FIG. 1** Flowchart of the study

**TABLE 1** Patient characteristics

| *Characteristic* | |
|---|---|
| Sex | |
| Male | 129 [28.7%] |
| Female | 52 [71.3%] |
| Age | |
| Median [IQR], years | 61.67 [54.63; 69.16] |
| < 65 years | 113 [62.4%] |
| ≥ 65 years | 68 [37.6%] |
| Symptoms | |
| No | 120 [66.7%] |
| Yes | 60 [33.3%] |
| Missing | 1 |
| *Primary tumor characteristics* | |
| Primary tumor site | |
| Rectum | 54 [29.8%] |
| Colon | 127 [70.2%] |
| Right colon | 39 [30.7%] |
| Left colon | 84 [66.1%] |
| Missing | 4 [3.1%] |
| Lymph node status | |
| N0 | 85 [47.2%] |
| N + or N1 or N2 | 95 [52.8%] |
| Missing | 1 [0.5%] |
| *Preoperative factors* | |
| Interval from primary cancer diagnosis to metastases | |
| Median [interquartile ranges], years | 1.2 [0–19.8] |
| Chronology of metastases | |
| Metachronous | 94 [51.9%] |
| Synchronous | 87 [48.1%] |
| Missing | 0 |
| No. of metastases | |
| 1 | 100 [55.6%] |
| > 1 | 80 [44.4%] |
| Missing | 1 |
| Metastasis diameter | |
| Median [IQR], cm | 3.0 [2.0; 4.0] |
| ≤ 5 cm | 147 [82.1%] |
| > 5 cm | 32 [17.9%] |
| Missing | 2 |
| Preoperative CEA level | |
| Median [IQR], ng/mL | 7.1 [2.5; 22.6] |
| Missing | 4 |
| ≤ 200 ng/mL | 168 [93.9%] |
| > 200 ng/mL | 11 [6.1%] |
| Missing | 2 |
| *Chemotherapy for liver metastases* | |
| Chemotherapy timing | |
| Adjuvant | 80 [44.2%] |
| Perioperative | 101 [55.8%] |

**TABLE 1** continued

| *Characteristic* | |
|---|---|
| Treatment arm | |
| A (FOLFOX4 12 cycles) | 82 [45.3%] |
| B (6 FOLFOX7 + 6 FOLFIRI cycles) | 99 [54.7%] |
| Missing | 0 |
| *Operative factors* | |
| Metastasis treatment | |
| Surgery alone | 173 [95.6%] |
| Surgery + RFA | 6 [3.3%] |
| RFA alone | 2 [1.1%] |
| Missing | 0 |
| Resection margins | |
| R0 | 168 [94.9%] |
| R1 | 9 [5.1%] |
| Missing | 4 |
| Follow-up | |
| Median [95% CI], years | 6.42 [5.15; 8.71] |

*CEA* carcinoembryonic antigen, *FOLFIRI* irinotecan 180 mg/m$^2$, levofolinate 200 mg/m$^2$, fluorouracil bolus 400 mg/m$^2$, and fluorouracil infusion 2400 mg/m$^2$; *FOLFOX4* oxaliplatin 85 mg/m$^2$, levofolinate 200 mg/m$^2$, fluorouracil bolus 400 mg/m$^2$, and fluorouracil infusion 2400 mg/m$^2$, *FOLFOX7* oxaliplatin 130 mg/m$^2$, levofolinate 200 mg/m$^2$, fluorouracil bolus 400 mg/m$^2$, and 5-FU infusion 2400 mg/m$^2$, *RFA* radiofrequency ablation

(IQR 54.6–69.2 years). Patient characteristics are detailed in Table 1.

### *Outcomes*

The 5-year OS was 67.11% (100 patients were alive at 5 years, 49 had died, and 32 were lost to follow-up). The 5-year DFS was 35.4% (58 patients had not relapsed at 5 years, 106 had relapsed, and 17 were lost to follow-up). In all patients, the median OS was not reached for a median follow-up of 6.42 years. The median DFS was 2.9 years (95% CI 1.7–4.3 years) (Supplementary Table 1; Supplementary Fig. S2). Survival according to CRS at this point with current chemotherapies were higher than in Fong's study[4] (Table 2).

### *OS Prognostic Factors*

On univariate analysis, the following parameters were significantly associated with poor OS: (1) Fong's CRS as a continuous variable (HR: 1.42, 95% CI 1.14–1.77, $p = 0.0016$) or categorical variable (0–1 vs. 2–3 vs. 4–5, $p = 0.0118$), (2) PMN count at baseline as a continuous variable ($p = 0.0183$) or discontinuous variable ($\leq 6000/mm^3$ vs. $> 6000/mm^3$, HR: 3.36, 95% CI 1.65–6.85, $p = 0.0009$), (3) the chronology of metastases (HR = 1.740, 95% CI 1.060–2.858, $p = 0.0286$), (4) the interval from primary tumor diagnosis to metastases as a continuous variable (HR = 0.983, 95% CI 0.967–0.999, $p = 0.0352$), and (5) the number of metastases as a continuous variable ($p = 0.0052$) (Supplementary Table 2). Figure 2a and b show the OS curves according to Fong's CRS and PMN count, respectively. Then, Fig. 2c takes into account the PMN count for the Fong 2–3 subgroup with the largest number of patients; when PMN $> 6000/mm^3$, prognosis was poor.

**TABLE 2** Clinical risk score for tumor recurrence in MIROX cohort with current chemotherapy regimen

| MIROX cohort ($N = 181$) | | Survival | | | | | |
|---|---|---|---|---|---|---|---|
| Score | *N* | 1-Year (%) | 2-Year (%) | 3-Year (%) | 4-Year (%) | 5-Year (%) | Median (months) |
| 0 | 17 | 100 | 100 | 100 | 93.75 | 80.77 | NA |
| 1 | 50 | 100 | 98.00 | 98.00 | 93.74 | 86.98 | NA |
| 2 | 66 | 98.48 | 87.83 | 81.55 | 73.58 | 68.15 | NA |
| 3 | 35 | 97.14 | 88.20 | 75.92 | 62.83 | 55.63 | 69 |
| 4 | 12 | 100 | 91.67 | 74.07 | 46.30 | 46.30 | 46 |
| 5 | 1 | 100 | 100 | 100 | 100 | 100 | NA |

The interval between diagnosis of a primary tumor and occurrence of metastases was integrated into Fong's CRS. The above three parameters (chronology of metastases, Fong's CRS, and PMN count) were then studied in multivariate analysis. Only two parameters (Fong's CRS and PMN count) were also independent prognostic factors of OS ($p = 0.036$ and 0.006, respectively) (Table 3).

### *Performance Assessment and Internal Validation of Final Model*

The final OS model was used to establish a nomogram for predicting individual OS probabilities at 1, 3, 5, and 10 years (Fig. 3).

The multivariable model exhibited satisfactory discrimination ability (*C*-index = 0.64). The calibration plots showed good agreement between model prediction and actual observation for predicting OS probabilities at 1, 3, 5, and 10 years (Fig. 4).

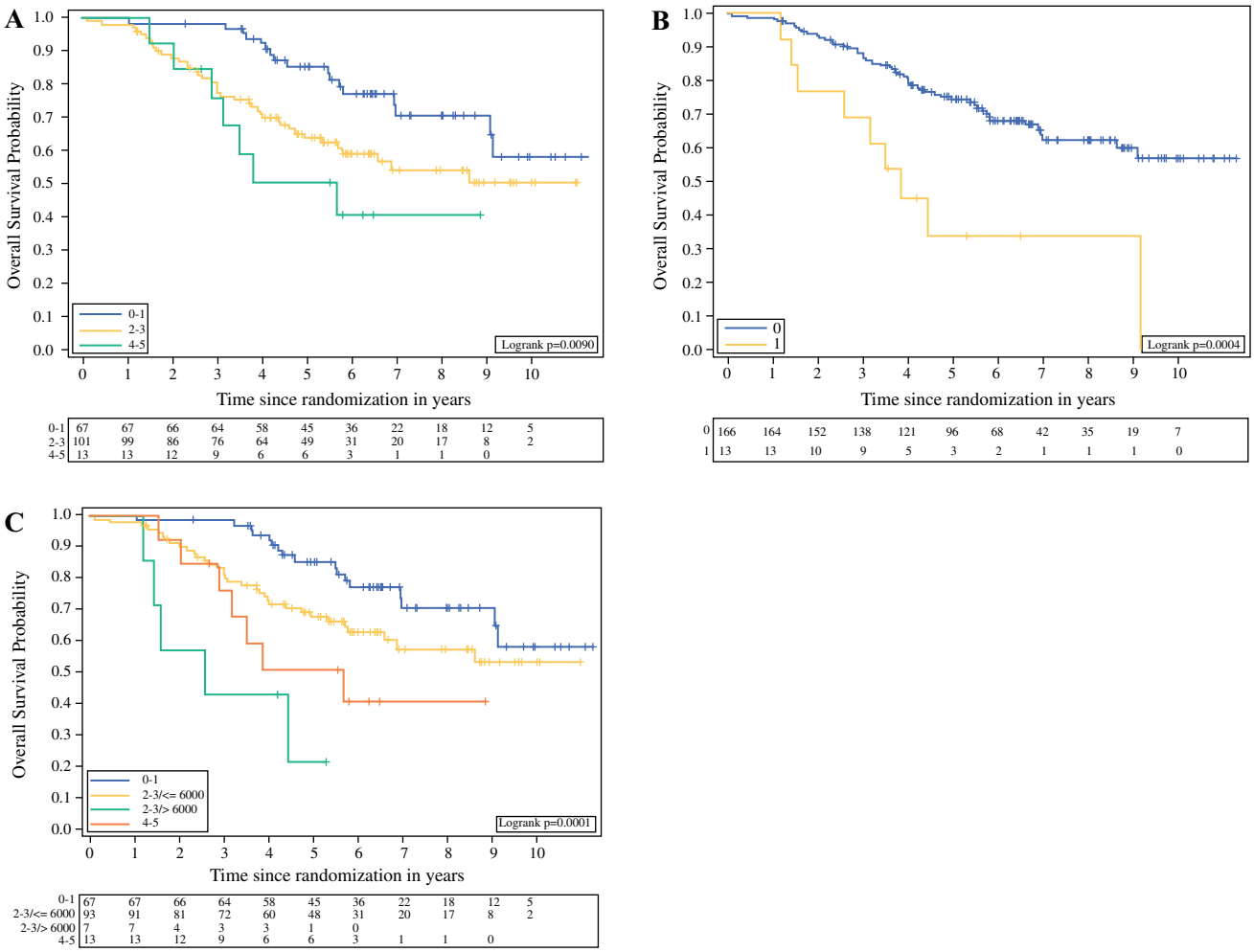


**FIG. 2** OS curves according to **a** Fong's CRS and **b** PMN count (Kaplan–Meier method). Stratification by PMN count (**c**). Fong's CRS: 0–1 versus 2–3 versus 4–5 according to the number of poor prognostic factors. *CRS* clinical risk score, *PMN* polymorphonuclear neutrophils, 0 = PMN $\leq$ 6000/mm$^3$; 1 = PMN $>$ 6000/mm$^3$

### *DFS Prognostic Factors*

On univariate analysis, Fong's CRS as a continuous variable (HR: 1.46, 95% CI 1.22–1.73, $p = 0.0001$) or categorical variable ($p = 0.0002$) was significantly associated with poor DFS.

PMN count $>$ 6000/mm$^3$ (HR: 2.05, 95% CI 1.09–3.84, $p = 0.02$) and ALP level $>$ 3 times the upper limit of normal (HR: 4.57, 95% CI 1.43–14.6, $p = 0.027$) at baseline were also significantly associated with poor DFS (Supplementary Table 3).

DFS curves according to Fong's CRS and PMN count are shown in Supplementary Fig. S3A and S3B, respectively.

On multivariate analysis, only Fong's CRS remained significantly associated with DFS ($p = 0.027$) (Supplementary Table 4).

## DISCUSSION

Identification of robust prognostic scores is useful for selecting patients who may benefit from surgery and for guiding the surveillance strategy in isolated CLMs. This study, with long follow-up ($>$ 6 years), showed that Fong's CRS could still be applicable in the era of effective perioperative chemotherapy. However, the five parameters composing Fong's CRS (i.e., primary tumor stage N1 or N2, disease-free interval $<$ 12 months, number of metastases, preoperative CEA level $>$ 200 ng/mL, and metastasis maximal diameter $>$ 5 cm) when considered individually were not significantly associated with OS, although some were associated with DFS. Notably, the combination of these parameters in Fong's CRS was an independent prognostic factor of poor OS ($p = 0.0118$) and DFS ($p = 0.0002$).

**TABLE 3** Multivariate analysis of OS prognostic factors

| Population | 179 | Multivariate analysis [OS] | | | | | |
|---|---|---|---|---|---|---|---|
| | | Number of patients | Number of events | HR | 95% CI | | *p* |
| Fong's CRS | 0–1 | 66 | 16 | 1 | | | |
| | 2–3 | 100 | 39 | 2.097 | 1.168 | 3.763 | |
| | 4–5 | 13 | 7 | 2.342 | 0.896 | 6.119 | 0.0356 |
| PMN count | $\leq 6000/mm^3$ | 166 | 53 | 1 | | | |
| | $> 6000/mm^3$ | 13 | 9 | 2.951 | 1.355 | 6.427 | 0.0064 |
| | Missing | 2 | | | | | |

*HR* hazard ratio, *PMN* polymorphonuclear neutrophils, *CRS* clinical risk score

Fong's score has already been validated recently but retrospectively, with less information concerning the chemotherapy protocol. Our phase III trial cohort is more homogeneous with a FOLFOX4 scheme of perioperative chemotherapy.[6,7]

PMN count, a marker of systemic inflammatory response, has been reported to predict an adverse outcome in patients with various solid tumors including primary CRC.[8–11] After CLM resection, PMN count $> 6000/mm^3$ has been associated with high relative risk of death and shortened DFS following hepatectomy.[12] In our study, only 13 patients had PMN count $> 6000/mm^3$, and this parameter, measured before the start of chemotherapy, was highly associated with poor OS ($p = 0.0064$). PMN count $> 6000/mm^3$ assessed in our study either after liver surgery ($N = 80$) or before neoadjuvant chemotherapy ($N = 101$) for colorectal cancer with nonoperated liver metastases may be associated with inflammation.

Finally, our final OS model based on Fong's CRS and PMN count was used to establish a nomogram for predicting individual OS probabilities at 1, 3, 5, and 10 years.

Meanwhile, resection margins (R0 vs. R1) were not associated with survival in our study. The prognostic impact of this parameter remains controversial, with some studies considering that the tumor biology of CLMs is a more important survival factor than surgical margin.[13,14]

Other factors, such as primary CRC location, have been associated with prognosis after primary tumor resection.[15] Right colon tumors are generally less well differentiated and more frequently *BRAF* mutated. They are also associated with poor OS. Recently, a single-center study evaluated the prognostic impact of primary tumor location after CLM resection in 475 patients.[15] Right colon primary tumors recurred with more extensive disease (> four lesions, $p < 0.01$), resulting in poorer OS ($p = 0.03$) and poorer survival after recurrence ($p = 0.01$). In our study, we did not demonstrate any prognostic impact of primary tumor location due to a lack of statistical power.

Hepatectomy is the only potentially curative treatment for CLMs, offering 5-year OS rates of 30–50%.[16,17] Our study confirms the benefit of surgery in terms of OS and DFS in patients with isolated CLMs. Interestingly, the long-term OS rate in our study is the highest ever reported in this setting, with a 5-year OS rate of 67.8% versus 51.2% for the EORTC-40983 perioperative chemotherapy arm.

To explain the better OS in our cohort, our hypotheses are the improvement of liver surgery (surgical technique and multidisciplinary team decisions), better selection of patients in a clinical trial, and better management of toxicities of chemotherapy by oncologists.

Meanwhile, chemotherapy timing is another crucial issue. In the MIROX trial, the perioperative schedule was not mandatory, with the chemotherapy timing being decided by the investigator. Patients with synchronous metastases preferentially received perioperative chemotherapy (44.2%), whereas patients with metachronous metastases more often received postoperative chemotherapy (55.8%). Current recommendations advocate perioperative chemotherapy for all patients with resectable CLMs based on the EORTC-40983 study, which compared perioperative chemotherapy with 12 FOLFOX4 cycles versus single surgery.[18] The exception may be surgery for metastases with good oncological criteria and easy resectability,[19] for example, solitary metachronous CLMs.[20] In our cohort, half of the patients had a single metastasis, comparable to the patients in the EORTC-40983 study. In contrast, the number of synchronous metastases was higher in our cohort (48.1% vs. 35% in the EORTC-40983). Despite the overrepresentation of poor prognostic factors in our cohort, the survival rates were higher (Supplementary Table 5). Our study was not designed a priori to compare the impact of postoperative versus perioperative chemotherapy, hence prospective trials are needed to establish the impact of the chronology of chemotherapy on survival.

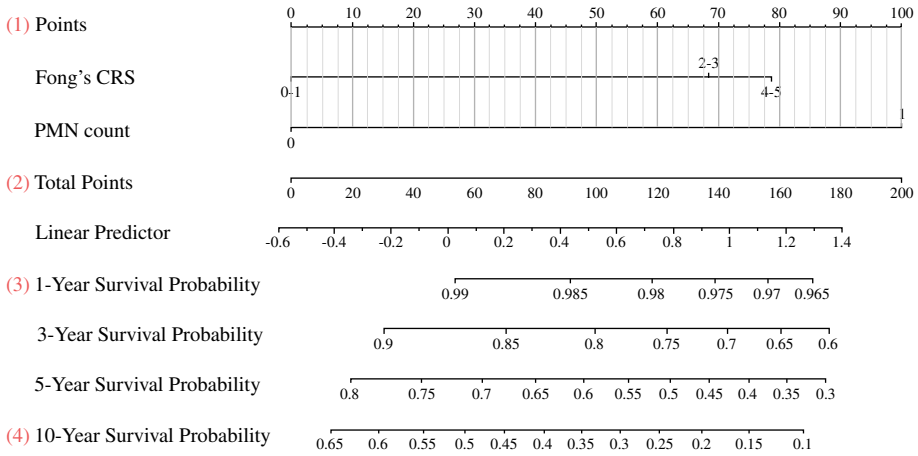


**FIG. 3** Prognostic nomogram for predicting individual OS probabilities after CLM resection. First, points associated with each of the two prognostic factors are obtained via upward vertical translation of the patient's variable value to the line labeled "Points" (1). Next, the points are summed and the corresponding total number is reported as a dot on the line labeled "Total points" (2). A vertical line is then drawn downward from the dot to obtain the OS prediction at the intersection with the "1-," "3-," "5-," and "10-year survival probability" lines (3–4). *CLM* colorectal liver metastasis, *CRS* clinical risk score, *OS* overall survival, *PMN* polymorphonuclear neutrophils

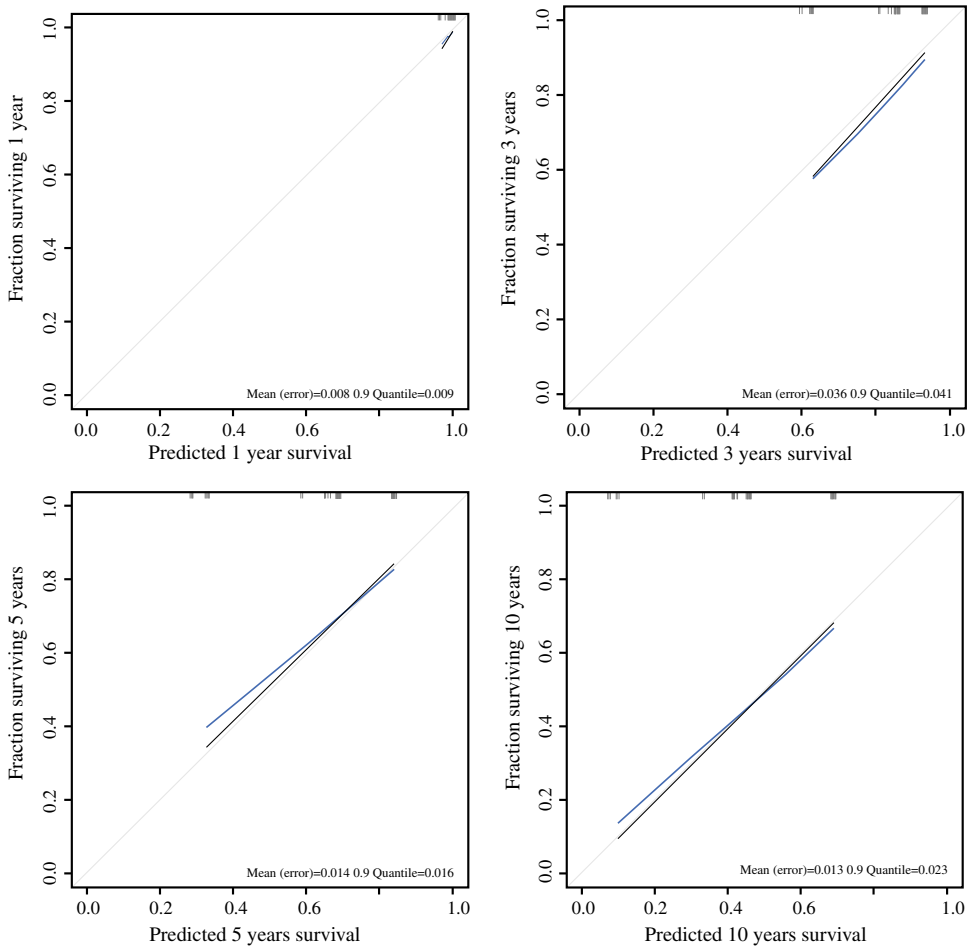


**FIG. 4** Calibration plots at 1, 3, 5, and 10 years for the final multivariate model. Vertical axis is the observed proportion of patients surviving at time of interest. Black line = observed; Grey line = ideal calibrated model; Blue line = bootstrap-corrected estimates (optimism corrected). $B$ = 20 repetitions for bootstrap

Other limitations of our study include the small number of patients with PMN count > 6000/mm$^3$; however, this study had sufficient statistical power to highlight its important negative prognostic impact. Furthermore, response to neoadjuvant chemotherapy and other potentially predictive parameters currently used in clinical routine, such as *RAS* and *BRAF* status, have not been evaluated, but not every center runs *BRAF* mutations, so comparing results and using them become very difficult. Additionally, significant changes in clinical practice occurring during the MIROX trial enrollment period that lasted > 6 years might have influenced OS, such as anti-epidermal growth factor receptor (EGFR) treatment in RAS wild-type tumors.

Nowadays, according to European Society for Medical Oncology (ESMO) guidelines, if there are poor surgical criteria (technical) or poor oncological criteria, conversion to the best systemic therapy [i.e., intensified protocol with doublet or triplet chemotherapy associated with targeted therapies with vascular endothelial growth factor (VEGF) or EGFR inhibitors] is recommended.[19] FOLFOX-based chemotherapy is a good option for metastases of colorectal cancer with low technical difficulties and poor oncological criteria.[19] In MIROX, patient selection was not based on prognostic oncological criteria or technical difficulties. Therefore, our results need to be confirmed in an external validation cohort and in prospective studies to determine the applicability of the prognostic factors in clinical routine.

We highlight the significant heterogeneity in survival of operated patients and hence the necessity to identify groups at risk of recurrence after surgery. This study revealed that Fong's CRS could still be a relevant prognostic factor in the era of more homogeneous perioperative chemotherapy and could be useful in future trials that evaluate liver surgery strategies in metastatic CRC.

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