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Is primary tumour resection associated with survival improvement in patients with colorectal cancer and unresectable synchronous metastases? A pooled analysis of individual data from four randomised trials ☆,☆☆

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Abstract ***Objective:*** To evaluate the impact on survival of primary tumour resection in patients with unresectable synchronous metastases from colorectal cancer (CRC).
Summary background data: Primary tumour resection in this setting remains controversial.
Patients and methods: We retrieved individual data of 1155 patients with metastatic CRC included in four first-line chemotherapy trials: Fédération Francophone de Cancérologie Digestive (FFCD)-9601, FFCD-2000-05, Actions Concertées dans les cancers COloRectaux et Digestifs (ACCORD)-13, and ML-16987. Patients with unresectable synchronous metastases were eligible for this study. We used univariate and multivariate analyses (Cox models stratified on the trial) to assess the impact of primary tumour resection and other potential prognostic variables on overall survival (OS) (the primary endpoint).
Results: Amongst the 1155 patients, 810 patients met the inclusion criteria and 59% ($n = 478$) underwent resection of their primary tumour, prior to trial entry (resection group). Compared

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to patients in the non-resection group ($n = 332$ [41%]), those in the resection group were more likely to have a colonic primary, lower baseline carcinoembryonic antigen (CEA) and alkaline phosphatase levels, and normal white-blood-cell count ($p < 0.001$ each). Primary tumour resection was independently associated to better OS in multivariate analysis (hazard ratio (HR), 0.63 [0.53–0.75]; $p < 0.001$, with a more favourable impact of resection on OS in case of rectal primary and low CEA level. Primary tumour resection was also independently associated to a better progression-free survival in multivariate analysis (HR, 0.82 [0.70–0.95]; $p < 0.001$).

Conclusion: Primary tumour resection was independently associated to a better OS in patients with CRC and unresectable synchronous metastases.

1. Introduction

Colorectal cancer (CRC) accounts for 1,234,000 new cases and 608,000 deaths each year in the world [1]. At the time of diagnosis, 20% of the patients have metastatic CRC (mCRC; stage IV disease). Approximately one-fifth to one-quarter of patients with mCRC can be resected in curative intent (primary tumour and metastases), either immediately or after chemotherapy, and may experience prolonged overall survival (OS) [2]. However, most patients with mCRC will never be amenable to curative-intent surgery. For these patients, the need for resection of the primary tumour remains a matter of debate, because the impact on OS is uncertain. Nevertheless, registry studies in the United States showed that 70% of patients diagnosed with stage IV CRC had undergone resection of their primary – thus mostly, for uncertain reasons, this rate is considerably higher than the rate of complications (e.g. bowel obstruction or perforation) related to the primary, with reported figures ranging from 13% to 20% [3–5].

The aforementioned registry studies both concluded that primary tumour resection was associated with a longer OS [3,4]. However, these registry studies were retrospective and had only access to the data collected in the registries – thus, no adjustments were possible for potential confounding factors. Other data available in the literature consisted mostly of small, retrospective surgical series, or focused on complications related to the primary rather than on the impact of primary tumour resection on OS [6–20].

To date, no trial randomised resection of the primary tumour versus no resection in patients with stage IV CRC. While awaiting the results of such trial, a possible alternative is to use individual data of mCRC patients included in chemotherapy trials to assess OS according to whether the primary tumour has been resected prior to trial entry or not [21]. Recently, we used this method with the individual patient data of the Fédération Francophone de Cancérologie Digestive (FFCD)-9601 trial [22], and found that primary tumour resection prior to trial entry was an independent predictor of longer OS and progression-free survival (PFS) in patients with CRC and unresectable synchronous metastases [23]. Nevertheless, these results were obtained in patients from a single trial, with low-efficacy, single-agent chemotherapy regimens.

The present study has three aims: to confirm the results, obtained in the FFCD-9601 patient population, in patients included in other trials and treated with oxaliplatin- or irinotecan-based chemotherapy with or without bevacizumab; to search for interactions between primary tumour resection and covariates on OS; and to assess the effect of resection on OS in the whole patient population after adjustment for available potential confounders.

2. Patients and methods

2.1. Patients

We collected individual data of patients included in one of four first-line chemotherapy randomised trials we coordinated: the FFCD-9601 trial [22], the FFCD-2000-05 Phase III trial,[24] the Actions Concertées dans les cancers COloRectaux et Digestifs (ACCORD) 13 trial [25] and the ML-16987 trial [26]. Trial characteristics are given in Table 1. All these trials recruited CRC patients with unresectable metastases defined as the inability to perform a R0 liver resection leaving a large enough liver remnant volume (>30% of the normal liver volume) or the presence of non-resectable metastatic sites (brain, bone, distant nodes, etc.) and World Health Organisation (WHO) performance status (PS) lower or equal to 2. All decisions regarding treatment were made by a multidisciplinary board including surgeon, radiologist and oncologist. Patients who had undergone a resection of the primary tumour prior to trial entry formed the resection group, while the others formed the non-resection group. As in all these trials a history of previous palliative chemotherapy was an exclusion criterion, all resections took place before starting first-line chemotherapy.

Patients were eligible for the present study if they had CRC and synchronous metastases, defined as metastases diagnosed less than 100 days after CRC diagnosis. Patients who underwent resection of their primary

Table 1
Characteristics of the four randomised trials.

	FFCD-9601	FFCD-2000-05	ML-16987	ACCORD-13
Accrual period	1997–2001	2002–2006	2003–2004	2006–2008
Line	First-line	First-line	First-line	First-line
Phase	III	III	III	II
Number of patients	294	410	306	145
Primary endpoint	Progression free survival	Progression free survival after second line	Overall response rate	Six months progression free survival
Treatment allocated by randomization (number of patients in this arm)	– LV5FU2 ($n = 74$) – LV5FU2 with low-dose LV ($n = 75$) – Bolus 5FU ($n = 73$) – Raltitrexed ($n = 72$)	– LV5FU2 followed by FOLFOX at progression then third-line FOLFIRI ($n = 205$) – FOLFOX followed by FOLFIRI at progression ($n = 205$)	– FOLFOX ($n = 150$) – XELOX ($n = 156$)	– Bevacizumab + FOLFIRI ($n = 73$) – Bevacizumab + XELIRI ($n = 72$)
More than one metastatic sites	39%	57%	52%	51%
At least one unresectable sites*	35%	41%	42%	28%
Subsequent surgery	4% had surgery	3% curative intent resection	No data available	14% curative intent resection

FU, fluorouracil. LV, leucovorin.
LV5FU2: bolus and infusional FU and LV.
FOLFOX: oxaliplatin plus bolus and infusional FU and LV.
FOLFIRI, irinotecan plus bolus and infusional FU and LV.
XELOX: capecitabine and oxaliplatin. XELIRI: capecitabine and irinotecan.
FFCD: Fédération Francophone de Cancérologie Digestive, ACCORD: Actions Concertées dans les cancers COloRectaux et Digestifs.
* Defined by the presence of metastasis in one of the following sites: bone, retroperitoneal nodes, supraclavicular nodes, brain, pleura, peritoneum.

tumour more than 6 months prior to randomisation in the initial trial were excluded.

2.2. End-points

The primary end-point was OS, measured from the date of randomisation to the date of death. A secondary endpoint was PFS, defined as the time from the date of randomisation to disease progression (according to World Health Organisation [WHO] criteria [27] for FFCD-9601 and FFCD-2000-05 trials, and RECIST 1.0 [28] for ACCORD-13 and ML-16987 trials) or death whatever its cause, whichever came first.

2.3. Statistical analysis

Missing data were handled using multiple imputations by chained equations using predictive mean matching and logistic regression [29]. Estimates in the multiply imputed datasets were pooled according to Rubin's rules [30].

With a first species error rate of 0.05 and the sample size of 604 patients when pooling the three validation trials, the study would have a power of 0.90 to detect at least a hazard ratio of 0.76.

Baseline characteristics of patients in the resection and non-resection groups were compared with the Mantel–Haenszel chi-squared test stratified on the trial for categorical variables, and with a two-way analysis of variance (accounting for the trial effect) for numerical variables. When the normality of the variables could not been assumed, a Monte-Carlo approach [31] was used.

Forest plots of the resection effect across the trials were drawn, and heterogeneity was assessed with the Cochrane's Q statistics [32]. In the absence of heterogeneity, pooled hazard ratios were estimated using the Maentel–Haenzel–Peto fixed effects method [32]. Hazard ratios between the 'initial' (I) trial (FFCD-9601) we analysed in our previous study [23] and the 'validation' (V) trials (FFCD-2000-05, ACCORD-13, and ML-16987) were compared with an interaction test [32]. Interactions between covariates and the effect of primary tumour resection on OS were assessed by comparing the hazard ratio of the resection effect between subgroup as in traditional meta-analyses [32], and confirmed with the method recently proposed by Fisher et al. [33] as a sensitivity analysis. This second method has the advantage of not pooling between-trial and within-trial comparisons.

Survival curves were calculated according to Kaplan–Meier's method and compared with the logrank test stratified on the trial.

Any variable achieving a $p < 0.20$ in the univariate analysis and any significant interaction ($p < .05$) with the history of resection were considered for the multivariate analysis. A Cox proportional hazard model stratified on the trial with backward selection was used to identify the set of independent predictors of survival. Prespecified sensitivity analyses were done to assess the robustness of the results. In these sensitivity analyses,

we excluded the FFCD-9601 trial because it dealt with somewhat outdated chemotherapy regimens, and the ACCORD-13 trial, as it was the only one dealing with targeted, antiangiogenic therapy. We also performed a sensitivity analysis in which we excluded the 'white blood cell count' variable, which accounted for most of the missing variables, and another one in which we used a more stringent definition for synchronous metastases (i.e. metastases diagnosed less than 15 days after CRC diagnosis).

Analyses were done with R 2.13 [34]. All tests were two-sided, and a value of $p < 0.05$ was considered significant.

3. Results

3.1. Patient characteristics

Overall, 1155 patients with non-resectable mCRC were randomised in the four trials, among whom 345 patients (30%) were found ineligible for the present study, mostly because of a metachronous onset of metastases ($n = 334$) (Fig. 1). Thus, 810 patients (70%) were included in the present study. Their median follow-up was 33 months [95% confidence interval (CI), 30–34].

Baseline patient characteristics are presented in Table 2. Among the 810 patients, 478 (59%) have undergone resection of their primary tumour prior to entry in their chemotherapy trial, this proportion varying within the trials: 71% of the patients (146/206) in FFCD-9601, 55% (168/308) in FFCD-2000-05, 62% (59/96) in ACCORD-13 and 53% (105/200) in ML-16987 ($p < 0.001$). Patients in the resection group were more likely to be older ($p = 0.04$), to have lost more weight ($p = 0.008$), to have a colonic primary ($p < 0.001$) and to have lower plasma levels of Carcino Embryonic Antigen (CEA) ($p < 0.001$), Alkalin Phosphatase (AP) ($p < .001$), and White Blood Cell (WBC) ($p < 0.001$) than patients in the non-resection group. The rate of subsequent surgeries and arguments for unresectability across the four trials are given in Table 1.

Missing data were observed for six baseline characteristics (weight, primary tumour location, AP, CEA, and WBC), but accounted for only 5–7% of patients for all but WBC (missing data, 27%). Of note, 93% of

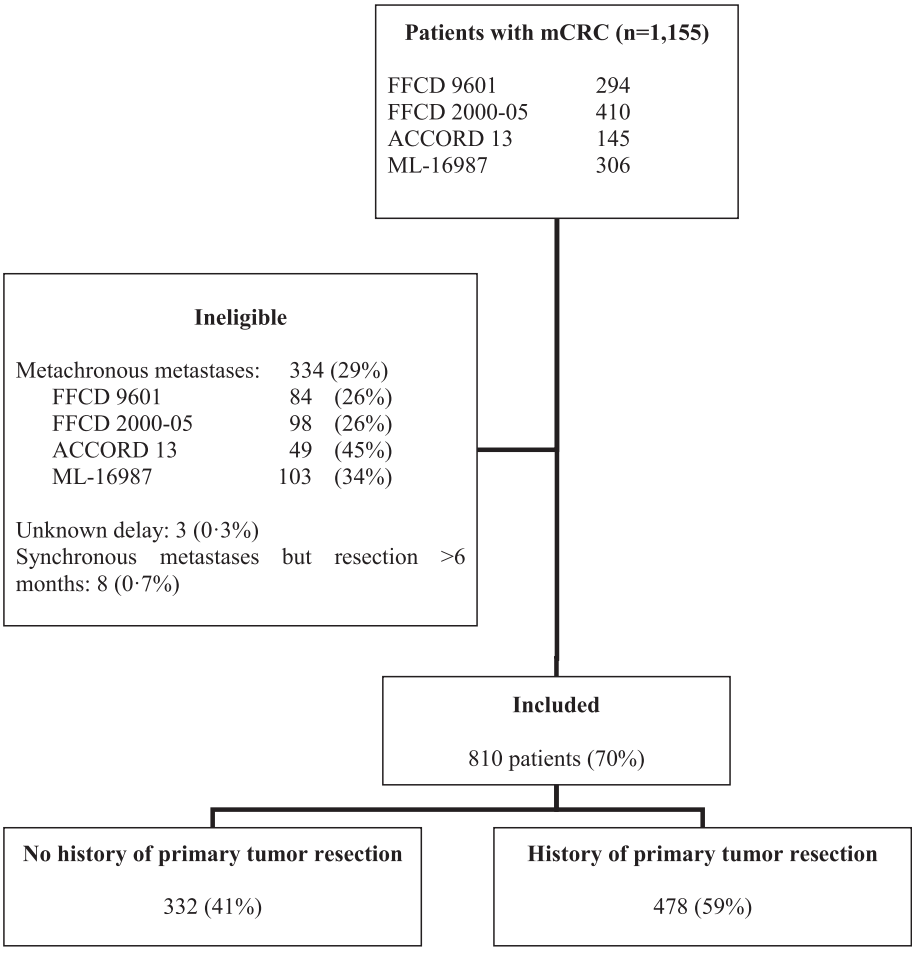

Fig. 1. Study flowchart.

Table 2
Baseline Characteristics.

	Non-resection ($n = 332$)	Resection ($n = 478$)	p^*
Age (years) Mean (SD)	62 (10)	64 (9)	0.04
Sex (%)			0.51
Male	211 (64)	293 (61)	
Female	121 (36)	185 (39)	
Weight (kg) Mean (SD)	70 (14)	67 (14)	0.008
WHO PS (%)			0.20
0	131 (39)	201 (42)	
1	142 (43)	207 (43)	
2	59 (18)	70 (15)	
Primary tumour location (%)			<0.001
Colon	229 (69)	411 (86)	
Rectum	87 (26)	62 (13)	
Missing	16 (5)	5 (1)	
Number of metastatic sites (%)[†]			0.17
1	149 (45)	253 (53)	
2	124 (37)	161 (34)	
3 or more	59 (18)	64 (13)	
CEA (ng/mL) Median (IQR)	190 (39–805)	94 (16–476)	<0.001
0–19 (%)	46 (14)	128 (27)	
20–119 (%)	85 (26)	112 (23)	
120–599 (%)	84 (25)	109 (23)	
⩾600 (%)	91 (27)	95 (20)	
Missing (%)	26 (8)	34 (7)	
AP (UI/L) Median (IQR)	206 (119–341)	171 (99–339)	<0.001
Normal (%)	89 (27)	180 (38)	
1–3 ULN (%)	170 (51)	179 (37)	
>3 ULN (%)	64 (19)	100 (21)	
Missing (%)	9 (3)	19 (4)	
WBC (Giga/L) Median (IQR)	9.5 (7.6–11.5)	8 (6.6–10.1)	<0.001
<10 G/L (%)	155 (47)	237 (50)	
⩾10G/L (%)	112 (34)	84 (18)	
Missing (%)[‡]	65 (20)	157 (33)	

AP, alkaline phosphatases. CEA, carcinoembryonic antigen. IQR, interquartile range. PS, performance status. SD, standard deviation. ULN, upper limit of normal. WBC, white blood cell count. WHO, World Health Organisation.
[*] Mantel–Haenszel test or ANOVA test, stratified on the trial; missing data not taken into account.
[†] Number of metastatic sites corresponds to the number of invaded organs.
[‡] 93% of WBC missing values came from the FFCD-9601 trial.

WBC missing data came from the FFCD-9601 trial in which this parameter was not collected for any patient. The pattern of these missing data is given in the Web-appendix Table 1.

3.2. Univariate analysis

3.2.1. Resection of primary and validation of the FFCD-9601 results

The hazard ratios (HRs) of resection versus no resection for OS (Fig. 2) were not statistically different between the 'initial' (I) trial (FFCD-9601) and the 'validation' (V) trials (FFCD-2000-05, ACCORD-13, and ML-16987) ($HR_I = 0.47$ [95% CI: 0.33–0.67] versus $HR_V = 0.56$ [0.46–0.68]; $p = 0.40$; heterogeneity test, $p = 0.87$). Similar results were found for PFS (Fig. 2) ($HR_I = 0.58$ [0.41–0.82] versus $HR_V = 0.76$ [0.64–0.90]; $p = 0.18$; heterogeneity test, $p = 0.32$). The absence of heterogeneity allowed the use of a fixed effects model to assess the relation between resection and survival, taking into account the other variables and interactions (Fig. 3).

3.2.2. Other variables and interactions

Concerning the other covariables, baseline serum CEA level ($p < 0.001$), PS ($p < 0.001$), number of metastatic sites ($p < 0.001$), AP ($p < 0.001$), and WBC ($p < 0.001$) – were all predictors of OS (Table 3). The same variables, as well as primary tumour location ($p = 0.02$), were also predictors of PFS.

Interaction tests found that the positive impact of resection of the primary tumour on OS was significantly higher in cases of rectal tumour ($p = 0.02$) or lower levels of CEA ($p < 0.001$) or AP ($p = 0.04$). For PFS, only the CEA level showed a significant interaction with resection of the primary (trend test, $p = 0.05$). The corresponding interaction terms were included in the multivariate analysis. These results were confirmed with the second method for assessing interaction [33] with the same variables being significant (data not shown).

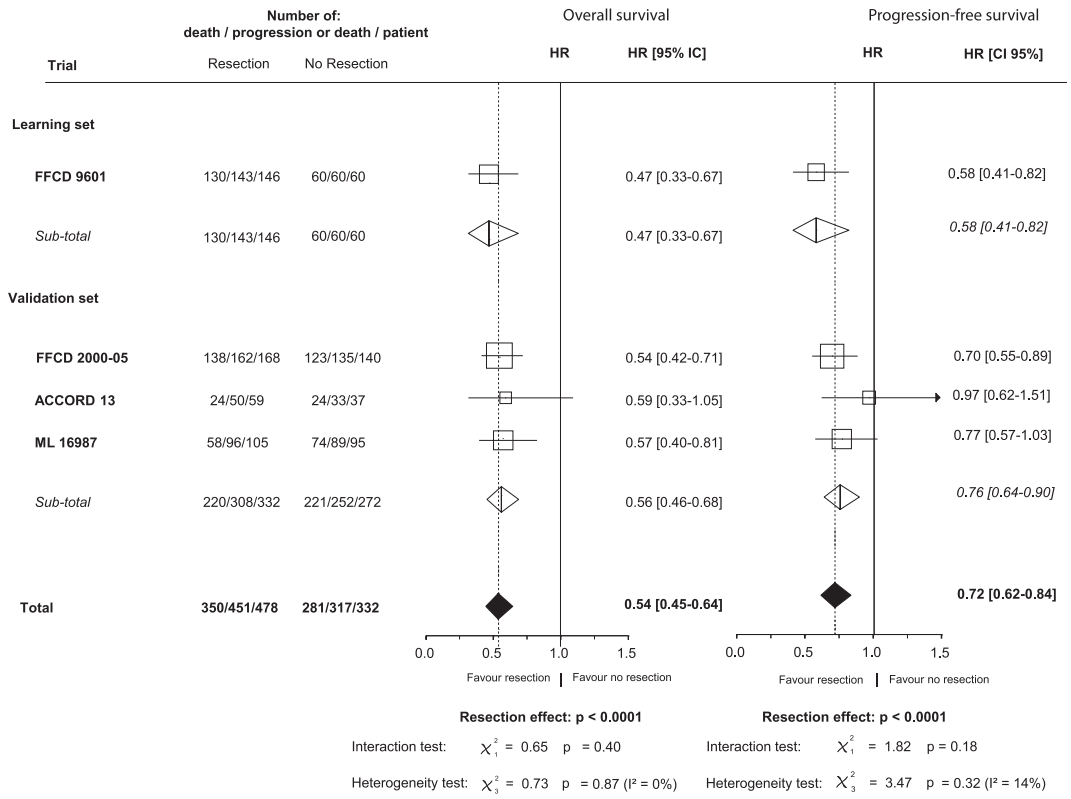

Fig. 2. Forest plot of the impact of primary tumour resection effect on overall and progression-free survival according to trials. CI, confidence interval; HR, hazard ratio.

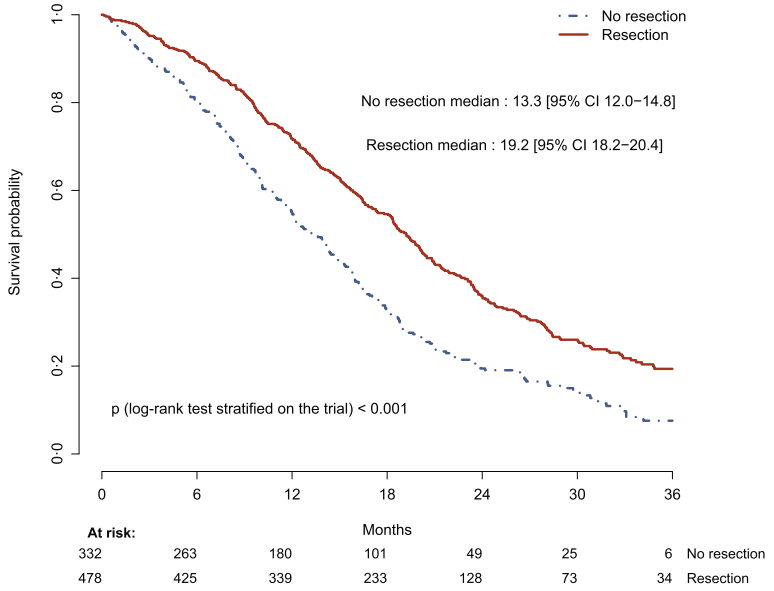

Fig. 3. Kaplan–Meier curves for overall survival according to primary tumour resection status in the overall population.

3.3. Multivariate analysis

Resection of the primary ($p < 0.001$), WHO PS ($p < 0.001$), number of metastatic sites ($p < 0.001$), and CEA ($p < 0.02$), AP ($p < 0.001$), and WBC ($p < 0.001$) levels were all independently associated to OS (Table 4) when interaction between primary resection and either CEA level or primary tumour location (significant in multivariate analysis) were included. The positive impact of resection of the primary on OS was greater in case of rectal primary and lower CEA levels, with an overall (weighted-mean) HR of 0.63 [0.53–0.075] ($p < 0.001$) (Web-appendix Table 2). All these variables but CEA were also independently associated to PFS,

Table 3
Prognostic factor study: univariate analysis.

	Overall survival		Progression-free survival	
	HR [95% CI]	p^*	HR [95% CI]	p^*
Primary tumour resection		<0.001		<0.001
No	1		1	
Yes	0.54 [0.45–0.64]		0.72 [0.62–0.84]	
Age (years)		0.14		0.12
< 55	1		1	
55–64	1.02 [0.81–1.27]		0.97 [0.80–1.19]	
65–69	0.80 [0.63–1.03]		0.93 [0.74–1.16]	
⩾70	1.01 [0.81–1.26]		0.94 [0.77–1.16]	
Weight (kg)		0.18		0.75
< 60	1		1	
60–69	0.86 [0.70–1.10]		0.96 [0.79–1.16]	
70–74	0.86 [0.67–1.10]		0.93 [0.74–1.16]	
⩾75	0.80 [0.65-.98]		0.90 [0.75–1.09]	
WHO PS		<0.001		<0.001
0	1		1	
1	1.21 [1.01–1.44]		1.18 [1.01–1.38]	
2	2.42 [1.93–3.04]		2.42 [1.93–3.05]	
Primary tumour location		0.52		0.02
Colon	1		1	
Rectum	1.07 [0.87–1.31]		1.25 [1.04–1.50]	
Tumour differentiation		0.24		0.17
Well/Moderately	1		1	
Poorly/Absent	1.16 [0.91–1.48]		1.16 [0.94–1.45]	
Number of metastatic sites		<0.001		<0.001
1	1		1	
2	1.30 [1.09–1.56]		1.31 [1.12–1.53]	
3 or more	2.03 [1.62–2.55]		1.61 [1.31–1.98]	
CEA (ng/mL)		<0.001		<0.001
0–19	1		1	
20–119	1.21 [0.97–1.52]		1.24 [1.02–1.52]	
120–599	1.52 [1.21–1.90]		1.41 [1.15–1.73]	
⩾600	1.71 [1.37–2.14]		1.54 [1.26–1.89]	
AP (UI/L)		<0.001		<0.001
Normal	1		1	
1–3 ULN	1.89 [1.56–2.28]		1.48 [1.25–1.75]	
>3 ULN	2.41 [1.92–3.02]		1.76 [1.43–2.15]	
WBC (Giga/L)		<0.001		<0.001
<10	1		1	
⩾10	1.82 [1.50–2.23]		1.54 [1.29–1.84]	

AP, alkaline phosphatases. CEA, carcinoembryonic antigen. CI, confidence interval. HR, hazard ratio. PS, performance status. ULN, upper limit of normal. WBC, white blood cell count. WHO, World Health Organisation.
* Log-rank test stratified on the trial.

as was primary tumour location ($p = 0.03$). No interaction remained significant for PFS in the multivariate analysis (Table 4).

Resection of the primary remained independently associated to better OS, with clinically non-significant changes in the HR, in all the sensitivity analyses performed (i.e. when excluding either the FFCD-9601 or ACCORD-13 trial, WBC data, or when using a more stringent definition of synchronous metastases) (Web-appendix Table 3).

4. Discussion

In this pooled analysis of individual patient data from four first-line chemotherapy randomised trials, we found that, in patients diagnosed with CRC and unresectable, synchronous metastases (unresectable stage IV disease), prior resection of the primary tumour was independently associated with a better OS. Among these patients treated with raltitrexed- or fluorouracil-based single-agent chemotherapy, oxaliplatin- or irinotecan-based doublet chemotherapy, or bevacizumab-based triplet therapy depending on the trial, the effect on OS of resection of the primary was not significantly different across the trials. Prior resection of the primary was one of the strongest predictors of better OS, stronger than major usual OS prognosticators such as WHO PS or the number of metastatic sites. It was also an independent predictor of better PFS, with a lower effect size. Groups were comparable at inclusion regarding major prognostic factors (WHO PS, number of metastatic sites). Differences in CEA, alkaline phosphatase (AP) or weight are hard to

Table 4
Multivariate analysis of the predictors of overall survival and progression-free survival.

Variable	Overall survival		Progression-free survival	
	HR [95% CI]	*p*	HR [95% CI]	*p*
Resection of the primary		<0.001		<0.001
No	1		1	
Yes	0.53 [0.35–0.80]*		0.82 [0.70–0.95]	
Interactions				
Resection * CEA (ng/ml)		<0.02		†
No resection * CEA 0–19	1			
Resection * CEA 20–119	1.04 [0.61–1.65]			
Resection * CEA 120–599	1.38 [0.83–2.30]			
Resection * CEA ⩾ 600	1.90 [1.13–3.17]			
Resection * Primary tumour location		<0.01		†
No resection * Colon	1			
Resection * Rectum	0.57 [0.36–0.89]			
Primary tumour location		0.10		0.03
Colon	1		1	
Rectum	1.29 [0.98–1.69]		1.22 [1.01–1.47]	
CEA (ng/mL)		<0.02		0.10
0–19	1		1	
20–119	0.99 [0.65–1.48]		1.11 [0.89–1.39]	
120–599	1.05 [0.69–1.59]		1.29 [1.02–1.63]	
⩾600	0.80 [0.53–1.80]		1.13 [0.89–1.54]	
AP		<0.001		0.002
Normal	1		1	
1–3 ULN	1.53 [1.25–1.86]		1.29 [1.08–1.54]	
⩾3 ULN	1.94 [1.53–2.47]		1.46 [1.17–1.83]	
WHO PS		<0.001		<0.001
0	1		1	
1	1.16 [0.97–1.39]		1.16 [0.99–1.36]	
2	2.00 [1.58–2.54]		1.61 [1.28–2.02]	
Number of metastatic sites		<0.001		<0.001
1	1		1	
2	1.38 [1.16–1.65]		1.35 [1.15–1.58]	
3 or more	1.90 [1.51–2.40]		1.59 [1.29–1.97]	
WBC (G/L)		<0.001		<0.001
<10	1		1	
⩾10	1.51 [1.23–1.87]		1.31 [1.10–1.56]	

AP, alkaline phosphatases. CEA, carcinoembryonic antigen. CI, confidence interval. HR, hazard ratio. PS, performance status. ULN, upper limit of normal. WBC, white blood cell count. WHO, World Health Organisation.

* Corresponds to the effect of primary tumour resection in a patient with a colonic primary and baseline CEA level comprised between 0 and 20 ng/mL.

† Interaction not significant in univariate analysis. Interaction terms were not included in the multivariate model.

interpret as they can be modified by the resection and can therefore be causes or consequences of the resection. The differences in primary tumour location are most likely due to the fact that rectal surgery has a greater morbidity and frequently requires a diverting stoma, making surgeons reluctant to perform surgery of the primary in a metastatic context.

Our results are in accordance with two American studies based on the S.E.E.R. (Surveillance, Epidemiology and End Results) registry, showing that a history of primary tumour resection was associated with a 7–9 month-OS benefit [3,4]. In 12,239 patients issued from the California Cancer Registry, Lin et al. showed that primary tumour resection was an independent prognostic factor of both OS (HR, 0.42 [0.40–0.44]) and CRC-specific survival (HR, 0.44 [0.42–0.46]) [35]. Nevertheless, their results were only adjusted for tumour histology, patient socioeconomic status, and a few baseline patient characteristics, but not for major confounders such as PS, number of metastatic sites, or serum baseline CEA level. In two recent meta-analysis, a 6-month OS benefit was observed in the resection group [36,37]. However, studies included in these meta-analysis were mostly single-centre, retrospective, and old. In most of them very little to no adjustment were made for potential confounders making results hard to interpret. Karoui et al. reported the outcomes of 208 patients with unresectable stage IV colon cancer treated in six French tertiary hospitals [38]. In this study, patients could have either colectomy followed by chemotherapy or frontline chemotherapy. Indication bias was controlled with propensity score, and results were adjusted for potential confounders. Prior colectomy was associated with better OS (HR, 0.56 [0.38–0.83]) even after

adjustment. However, this is a retrospective study, and chemotherapy regimens and surveillance were not standardised among centres. Finally, apart from our study, only one study to date included a large and homogeneous patient population, and dealt with individual patient data including potential confounders [21]. In this study, Venderbosch et al. assessed the effect of a history of primary tumour resection in 399 and 448 patients included in the CAIRO-1 [39] and CAIRO-2 [40] Phase III trials. In both trials, a history of primary tumour resection was independently associated with a better OS (CAIRO-1: HR, 0.63 [0.43–0.92], $p = 0.016$; CAIRO-2: HR, 0.73 [0.58–0.93], $p = 0.01$). Resection of the primary also tended to be associated with better PFS in univariate analysis (HR, 0.57 [0.30–1.25]; $p = 0.069$), but not in multivariate analysis (HR, 0.84 [0.68–1.05]; $p = 0.13$).

We found significant interactions between the prognostic impact of primary tumour resection and primary tumour location and serum baseline CEA level – the OS benefit associated with primary tumour resection being higher in cases of rectal primary or lower CEA level. A higher CEA level may indicate a more aggressive or extensive disease. Therefore, one can hypothesise that resection of the primary may not significantly benefit such patients. The greater prognostic impact of resection of the primary tumour in patients with rectal primary may indicate that such surgical tumour cytoreduction is of more effect in this subset of patients, perhaps due to differences in intrinsic biological aggressiveness of rectal primaries compared to their colonic counterparts. Alternatively, it could result from an indication bias, if one hypothesises that proctectomy, which is more demanding than colectomy, had been proposed to more selected patients with a better prognosis. Finally, it must be pointed out that the lack of significant interactions with other covariates argues for the internal consistency of our results.

Our study has several limitations. Firstly, although we adjusted for potential confounders, it remains probable that primary tumour resection had been preferably performed in patients with better prognosis and therefore the positive impact of resection is partly a consequence of such a better prognosis. If we could have used them, propensity scores [41] and causal inferences [42] may have been able to circumvent this bias. Unfortunately, baseline characteristics before resection were not recorded. Other prognostic variables (BRAF and RAS mutations) were not available at the time of the trials and have not been adjusted for. Secondly, the prognostic effect of resection of the primary may be due in part to the fact that the resection group consisted of only patients who recovered from surgery sufficiently to be eligible for inclusion in one of the trials. In recent studies, morbidity and mortality are low. In a recently published French study [38], of the 84 patients who had first-line colectomy none of them died postoperatively and only one had performance status deterioration precluding any post-operative chemotherapy. Only a specifically dedicated randomised trial could avoid such indication and selection biases. Thirdly, the mechanisms underlying the positive effect of resection of the primary in patients with stage IV CRC remain elusive. Even if similar results have been found for other cancers, such as renal cancer [43], current concepts of cancer and chemotherapy do not explain why resection of a limited part of the disease burden (more than half of our patients harbouring two metastatic sites or more) could result in such an OS benefit. However, Van der Wal et al. showed very recently that the liver parenchyma adjacent to synchronous liver metastases provides a more prosperous angiogenic environment for metastatic tumour growth in the presence of the primary tumour than when the primary has been resected or in patients with metachronous liver metastases [44].

In conclusion, our pooled analysis of individual patient data from four randomised trials of first-line chemotherapy in patients with non-resectable stage IV CRC strongly suggests that a history of resection of the primary tumour is independently associated with an important OS benefit. These results suggest that these patients may benefit from a primary tumour removal prior to chemotherapy, but need to be confirmed by a multicentre prospective randomised trial like the PRODIGE 30 trial now underway in France.

Conflict of interest statement

MF, AB and JPP have no conflict of interest. DM declared having received consultancy fees from Roche and honoraria from Sanofi-Aventis France, Pfizer, Merck Serono, Novartis, and Amgen and research funding from Amgen, AA and MD declared having received consultancy fees from Roche and honoraria from Sanofi-Aventis France. OB declared having received consultancy fees from Roche.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2014.10.023.

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