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Original Research

Resection of colorectal liver metastases after second-line chemotherapy: is it worthwhile? A LiverMetSurvey analysis of 6415 patients

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KEYWORDS
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Abstract ***Purpose:*** Patient outcome after resection of colorectal liver metastases (CLM) following second-line preoperative chemotherapy (PCT) performed for insufficient response or toxicity of the first-line, is little known and has here been compared to the outcome following first-line.
Patients and methods: From January 2005 to June 2013, 5624 and 791 consecutive patients of a prospective international cohort received 1 and 2 PCT lines before CLM resection (group 1 and 2, respectively). Survival and prognostic factors were analysed.
Results: After a mean follow-up of 30.1 months, there was no difference in survival from CLM diagnosis (median, 3-, and 5-year overall survival [OS]: 58.6 months, 76% and 49% in group 2 versus 58.9 months, 71% and 49% in group 1, respectively, $P = 0.32$). After hepatectomy, disease-free survival (DFS) was however shorter in group 2: 17.2 months, 27% and 15% versus 19.4 months, 32% and 23%, respectively ($P = 0.001$). Among the initially unresectable patients of group 1 and 2, no statistical difference in OS or DFS was observed. Independent predictors of worse OS in group 2 were positive primary lymph nodes, extrahepatic disease, tumour progression on second line, R2 resection and number of hepatectomies/year <50. Positive primary nodes, synchronous and bilateral metastases were predictors of shorter DFS. Initial unresectability did not impact OS or DFS in group 2.
Conclusion: CLM resection following second-line PCT, after oncosurgically favourable selection, could bring similar OS compared to what observed after first-line. For initially unresectable patients, OS or DFS is comparable between first- and second-line PCT. Surgery should not be denied after the failure of first-line chemotherapy.

1. Introduction

Liver resection is the only treatment that currently offers a chance of long-term survival to patients with colorectal liver metastases (CLM). For patients with primarily resectable CLM, especially those with advanced, multiple or borderline resectable disease, perioperative systemic chemotherapy has been given to increase their long-term survival by reducing the risk of recurrence after resection. However, the majority of patients with CLM are not initial candidates for hepatic resection. Without conversion chemotherapy, surgical resection is not possible for 70%–80% of those patients. Encouragingly, the combination of systemic chemotherapy and liver surgery could switch a significant proportion of patients from a palliative to a potentially curative situation, with a reported postoperative 5-year survival of 33% after rescue surgery [1–3]. Recently, an international panel of multidisciplinary experts developed recommendations for the management of patients with CLM, indicating that preoperative treatment to induce resectability should be as short as possible, and that postoperative chemotherapy (POCT) should continue with the same protocol when preoperatively effective [4].

Failure to respond to first-line therapy has frequently predicted poor response rates of subsequent lines of therapy [5–7]. For patients where disease control is the goal, patients should proceed to second-line therapy when there is evidence of disease progression, or toxicity of the first-line [8]. However, the combination of second-line systemic chemotherapy (for neoadjuvant or conversion purpose) with CLM resection has been scarcely described. Its impact on survival is not yet demonstrated, and what kind of patients can really benefit from the resection is so far unknown. In this study, we aimed to analyse the impact of the CLM resection after second-line treatment, in terms of overall survival (OS) and disease-free survival (DFS) in a large international dataset, and to find out the predictive factors of outcomes for such patients. The survival data were also compared to that of the CLM resection following first-line chemotherapy, in the same oncosurgical teams, although the two cohorts were not rigorously comparable.

2. Patients and methods

2.1. Patient selection

LiverMetSurvey is a prospective international internet-based registry, collecting and regularly updating clinical data from all consecutive patients undergoing surgery for CLM, and was designed to assess the efficacy of multimodality treatment of CLM [3]. It accounted on 25th December 2015, with 243 individual patients from 313 institutions worldwide (70 countries). In this study, the data of 6415 consecutive patients were retrospectively analysed. Between January 2005 and June 2013, 5624 patients underwent resection after first-line chemotherapy (group 1) and 791 patients following second-line chemotherapy (group 2), respectively.

Patient eligibility criteria included the completion of hepatic resection with intent to resect all the metastases, irrespective of the initial resectability of CLM and of the

need for specific combined techniques to optimise resectability after first- or second-line preoperative chemotherapy (PCT). In this study, we defined a second-line regimen when the first-line cytotoxic backbone had changed, or when a biological agent had been added. Patients receiving second-line because of intolerable toxicity were included because this situation is not rare in clinical practice, although toxicity does not reflect the tumour response to chemotherapy. The initially unresectable patients in group 1 were classified into subgroup 1, and such patients in group 2 into subgroup 2 for additional subgroup analyses.

Patients, on whom an R2 resection was performed, although considered surgically unsatisfactory, were included in the analysis since we adopted an intent-to-treat policy on such patients, as in real-life situations.

2.2. Preoperative management

Generally, the response to chemotherapy was evaluated every four cycles with computed tomography (CT) according to the Response Evaluation Criteria in Solid Tumours Criteria (RECIST) [9]. In each centre, patients were evaluated from referral by the same local multidisciplinary team, who determined when to start a chemotherapy with neoadjuvant or conversion intent, when to perform liver resection and when to switch to second-line PCT, in case of progression, or insufficient response (stable disease or partial response unable to allow complete or safe resection) or in case of unacceptable toxicity on first-line regimen. Generally, as an accepted clinical practice, for the patients with potentially resectable CLM but with advanced, multiple or borderline resectable disease, neoadjuvant chemotherapy was proposed with the intent to increase survival.

2.3. Hepatic resection

The overall policy of hepatectomy was carried out with the attempt of a complete resection of all lesions by anatomic or wedge resection, sparing the largest amount of hepatic parenchyma but providing as much as possible a safe margin of normal parenchyma from the tumour. Radiofrequency ablation was combined with hepatectomy whenever appropriate in treating unresectable remnant lesions limited in number ($\leq$3) and size ($<$3 cm). Two-stage hepatectomy was reserved for the patients whose disease was deemed unresectable by a single procedure. Other combined techniques including portal vein embolisation were also employed.

2.4. Postoperative chemotherapy

POCT was routinely used after hepatectomy, with the same regimen when preoperatively effective.

2.5. Follow-up

Patients were usually followed one month later after the resection, then every 3–6 months according to the centre policy, with tumour markers (carcinoembryonic antigen and carbohydrate antigen 19.9), clinical examination, thoracic and hepatic imaging (ultrasound and/or CT and/or magnetic resonance imaging). Repeat resection of intrahepatic recurrence or extrahepatic disease was performed by the local surgical team when potentially curative.

2.6. Statistical analysis

Survival was calculated from CLM diagnosis and from hepatectomy to death or to the last available follow-up. Patient survival probabilities were determined by the life-table method and compared in the log-rank test. A multivariate Cox proportional hazard model with a likelihood ratio test was used to identify predictive factors for OS (from CLM diagnosis) and DFS. According to RECIST, tumour responses after first- or second-line chemotherapy were classified into either progression or no progression for multivariate model. Statistical analyses were performed with SAS software version 9.1.3 (SAS Institute Inc., Cary, NC, USA).

3. Results

Overall, 5624 patients (87.7%) and 791 patients (12.3%) received CLM resection after 1 and 2 PCT lines (group 1 and group 2), respectively. The incidences of CLM resection by year following 1 and 2 PCT lines are shown in Supplementary Fig. A1.

3.1. Patient and tumour characteristics

The clinical characteristics of the study population are shown in Table 1, together with comparisons between groups, and between initially unresectable subgroups.

3.2. Chemotherapy data

Supplementary Table A1 presents the PCT regimens used in the two groups. Doublet regimens were administered to 63.4% of the patients in second-line, triplet regimens were used to 3.6%, and monoclonal antibodies were given to 33.0% of these patients. Compared to the first-line PCT in group 1, the second-line PCT in group 2 included more often irinotecan-based regimen and combination with cetuximab or panitumumab.

In group 2, patients received a median of six (interquartile range [IQR], 4–9) cycles of first-line chemotherapy. The causes for switching to second-line were disease progression (22.2%), stable disease (22.7%), insufficient partial response (48.1%) or intolerable toxicity

Table 1
Comparison of clinical features of the study population.

Characteristics	Whole population			Initially unresectable		
	1 PCT line (n = 5624)	2 PCT lines (n = 791)	P-value	1 PCT line (n = 1637)	2 PCT lines (n = 290)	P-value
Female, %	39.2	34.9	0.019	39.5	34.5	NS
Age, mean (SD), year	61.6 (10.7)	61.4 (10.6)	NS	60.5 (11.1)	60.4 (10.2)	NS
Primary tumour localisation, %						
Left including sigmoid	42.6	48.3	0.049	47.0	53.8	NS
Rectum	32.5	29.7		29.6	26.4	
Right	18.0	16.4		16.6	14.6	
Transverse	3.5	2.7		4.0	2.4	
Multiple localisations	3.3	2.9		2.7	2.8	
Metastatic primary lymph nodes, %	67.8	68.4	NS	66.7	66.4	NS
Concomitant extrahepatic disease, %	12.2	16.7	<0.001	14.8	21.7	0.003
Interval between disease diagnosis and liver metastasis occurrence, mean (SD), months	7.1 (18)	5.5 (12.3)	0.002	5.9 (17.6)	4.7 (10.4)	NS
No. of liver metastasis at diagnosis, %						
1–3	69.7	62.9	<0.001	49.0	46.7	NS
4–7	21.9	25.7		30.1	30.3	
>7	8.4	11.3		20.9	23.0	
Metastasis at diagnosis ≤30 mm, %	43.5	38.7	0.023	34.0	28.5	NS
Liver metastases, %						
Synchronous	70.9	73.5	NS	77.2	77.0	NS
Bilateral localisation	46.9	54.1	<0.001	68.0	67.7	
Initially unresectable	32.9	41.8	<0.001	100.0	100.0	
Main causes of non-resectability, %						
Number of metastases	–	–	–	43.7	50.8	NS
Size of metastases	–	–		18.4	15.2	
Vascular ill location	–	–		17.5	13.6	
Extrahepatic disease	–	–		9.9	11.4	
Others	–	–		10.5	9.1	
Preoperative chemotherapy cycles						
1–6 cycles, %	62.9	17.6	<0.001	49.8	12.6	<0.001
No., median [IQR]	6 [4–8]	12 [8–16]	<0.001	7 [5–10]	13 [9–18]	<0.001
Response to PCT last-line, %						
Complete response	5.4	5.0	<0.001	3.9	4.7	<0.001
Partial response	69.0	61.5		81.2	66.1	
Stable disease	19.3	25.1		11.0	22.6	
Progression	6.2	8.4		3.9	6.6	
Limited hepatectomy (<3 segments), %	38.4	33.0	0.004	31.4	26.7	NS
R0+R1 liver resection, %	88.1	82.8	<0.001	76.0	72.7	NS
Hepatectomy not globally curative, %	20.6	26.1	<0.001	35.9	38.4	NS
Combined techniques, %	28.1	37.8	<0.001	56.0	47.2	0.006
Portal vein embolisation, %	14.1	23.8	<0.001	24.9	35.3	<0.001
Radiofrequency ablation, %	11.3	13.4	NS	15.4	15.4	NS
Cryotherapy, %	0.1	0	NS	0.1	0	NS
Two-stage hepatectomy, %	11.2	14.5	0.008	21.7	23.5	NS
Only one hepatectomy, %	83.0	79.4	<0.001	79.3	74.4	0.004
No. of hepatectomies/year ≥50, %	45.3	54.7	<0.001	36.7	49.3	<0.001
POCT, %	58.3	58.2	NS	57.8	56.6	NS
Cycles, median [IQR]	6 [4–8]	6 [4–9]	NS	6 [4–8]	6 [3–12]	NS
90-d postoperative mortality, %	2.7	2.4	NS	3.9	4.3	NS
Postoperative complications, %	29.9	33.5	0.044	35.0	38.7	NS

PCT, preoperative chemotherapy; SD, standard deviation; IQR, interquartile range; POCT, postoperative chemotherapy; NS, not significant.

(7.0%). Progression or intolerable toxicity was the accepted reason for non-operating patients after first-line chemotherapy. In case of stable disease or partial response, the main consideration was better disease control before surgery for initially resectable patients or adequate conversion to allow complete and safe resection for initially unresectable patients. In second-line, these patients received a median of five (IQR, 3–8) preoperative cycles of therapy. Furthermore, 58.2% of group 2 patients received POCT (second-line regimen), and 9.5% received later a third-line for relapse. Conversely, 58.3% of group 1 patients received POCT (first-line regimen), 5.3% received later second-line for relapse and 1.2% a third-line.

In subgroup 2, patients received a median of six (IQR, 4–11) cycles of first-line chemotherapy with 21.5% progression and 56.9% insufficient objective

response. After a median of six (IQR, 3–9) cycles of second-line, this subgroup experienced 6.6% progression and 70.8% objective response ($P < 0.001$).

3.3. Mortality and morbidity

After hepatectomy, the 90-d mortality was 2.4% in group 2 versus 2.7% in group 1 ($P = 0.618$), and the morbidity was 33.5% versus 29.9%, respectively ($P = 0.044$). For the initially unresectable patients, the mortality was similar between the subgroups and so was the morbidity (Table 1).

3.4. Overall survival

After a mean follow-up of 30.1 months, in group 2 ($n = 777$) and group 1 ($n = 5456$), median OS after diagnosis was 58.6 months (95% confidence interval, 52.0–63.2 months) versus 58.9 months (56.0–60.9), 3-year OS rate was 76% (72%–79%) versus 71% (70%–73%) and 5-year OS was 49% (43%–54%) versus 49% (47%–51%), respectively ($P = 0.32$; Fig. 1A). After the first hepatectomy, in group 2 ($n = 785$) and group 1 ($n = 5567$), median OS was 41.4 (39.2–46.8) versus 49.0 months (46.5–51.5), 3-year OS was 60% (55%–65%) versus 62% (60%–64%) and 5-year OS was 35% (29%–42%) versus 43% (41%–45%), respectively ($P = 0.049$; Fig. 1B).

For patients initially unresectable, no statistical difference appeared in OS after diagnosis or after the first hepatectomy (Supplementary Figs. A2 and A3A) between the subgroups of patients resected after first-line and second-line conversion chemotherapy.

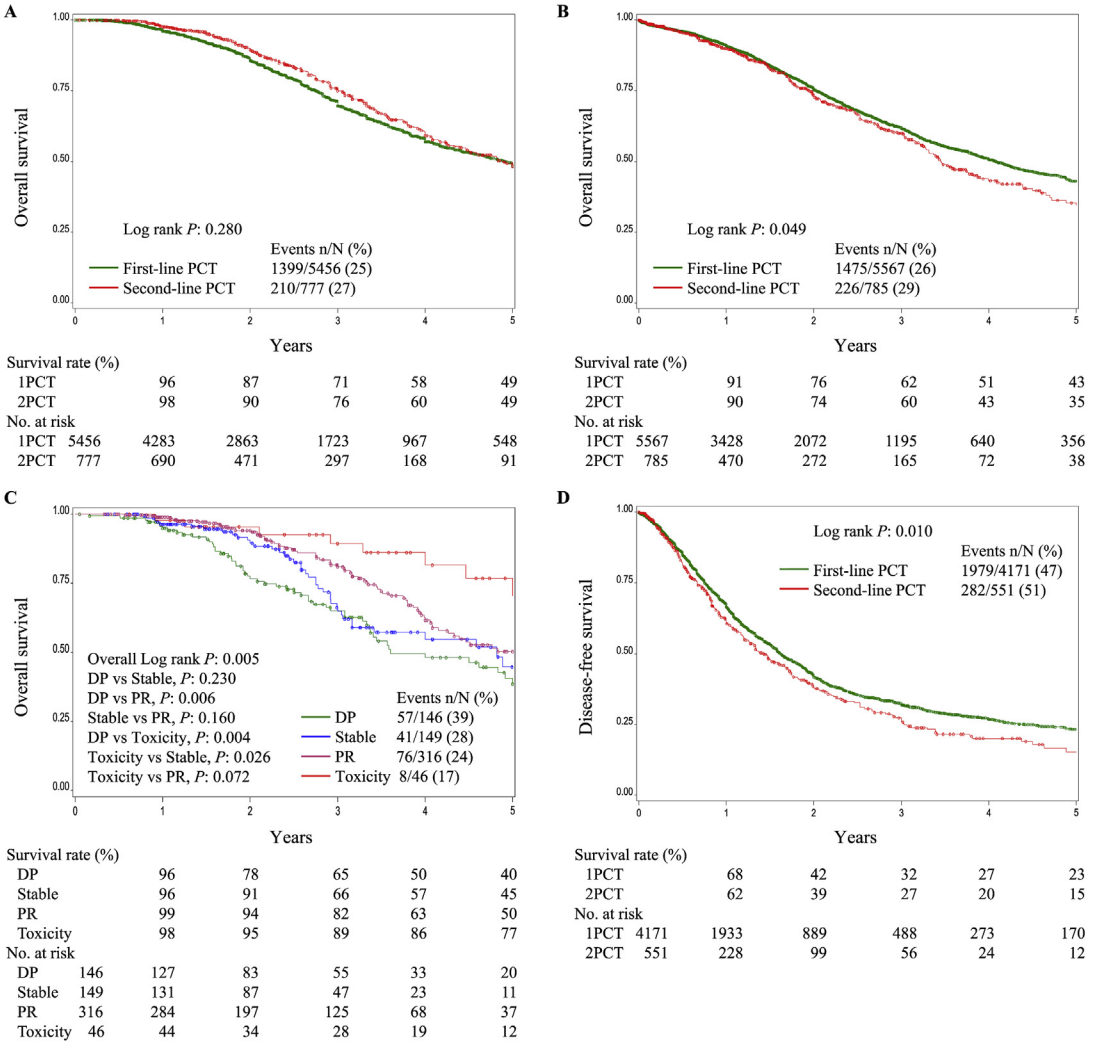

Fig. 1. OS and DFS of CLM patients received liver resection following PCT. OS (**A**) after diagnosis of CLM resected after PCT; OS (**B**) and DFS (**D**) after first hepatectomy of CLM after PCT; OS (**C**) after metastatic diagnosis of CLM resected after 2nd-line PCT according to cause for chemotherapy change. OS, overall survival; DFS, disease-free survival; CLM, colorectal liver metastases; PCT, preoperative chemotherapy; DP, disease progression; PR, partial response.

Regarding the impact of the reasons leading to a second-line regimen, OS of progression was similar to that of stable disease but lower compared to that of insufficient partial response or toxicity. Toxicity seemed to be associated with a higher OS than stable disease but not than partial response. No survival difference existed between stable disease and partial response (Fig. 1C).

3.5. Disease-free survival

Median, 3-year and 5-year DFS after first macroscopically complete hepatectomy were statistically lower in group 2 (17.2 months, 27% and 15%; $n = 551$) than those in group 1 (19.4 months, 32% and 23%; $n = 4171$; $P = 0.01$; Fig. 1D). For initially unresectable patients, no statistical difference in DFS was observed between subgroup 2 and subgroup 1 (median, 3- and 5-year: 18.1 months, 28% and 14% versus 19.7 months, 32% and 22%; $P = 0.09$; Supplementary Fig. A3B).

Concerning the impact of the different causes of second-line inclusion, no statistical difference in DFS was observed (data not shown).

3.6. Analysis of predictive factors

3.6.1. Overall survival

By multivariate analysis, five factors were independently associated with decreased OS (Table 2). Progressive disease on first-line chemotherapy was associated with worse OS after diagnosis at univariate but not at multivariate analysis, in the studied second-line setting (Fig. 1C). For subgroup 2, in the multivariate model, four independent factors were associated with worse OS (Table 2). The separate number (≤6 or >6) of cycles received in first- or second-line did not impact OS in group 2 nor in its unresectable subset (subgroup 2).

3.6.2. Disease-free survival

Among group 2 patients with R0/R1 liver resection, the multivariate analysis showed that metastatic lymph nodes, synchronous and bilateral metastases were associated with decreased DFS. Progression on first-line chemotherapy was not predictive for shorter DFS. In this model for subgroup 2 patients, three factors associated with decreased DFS were bilateral metastases, no POCT and radiofrequency combined with hepatectomy (Table 3).

4. Discussion

In this study, we observed, in a large international and prospective database, that the outcomes of patients with CLM eventually undergoing resection after second-line PCT were mostly similar to those obtained after first-line PCT, although these two cohorts were not strictly comparable because disease was more extensive in the former. Indeed, not surprisingly, these patients had a statistically heavier tumour burden, a poorer response to treatment and more complex surgical treatments, compared to the patients resected after first-line. From first-line to second-line, the switch offered a better tumour control to these patients, allowing a significantly decreased progression rate from 22.2% to 8.4% and an increased objective response rate from 55.1% to 66.5%. Thus, surgery was offered with more stringent criteria of tumour response to patients after second-line

Table 2
Analysis of OS after metastasis diagnosis in 2 PCT lines patients and its initially unresectable subgroup.

Risk factors	All patients with 2 PCT lines ($n = 777$)					Initially unresectable patients with 2 PCT lines ($n = 283$)				
	3 years	5 years	Univariate	Multivariate		3 years	5 years	Univariate	Multivariate	
			P-value	*P*-value	HR (95% CI)			*P*-value	*P*-value	HR (95% CI)
Metastatic primary lymph nodes										
Yes	73%	41%	0.002	0.018	1.54 (1.08–2.19)	69%	44%	0.440	–	
No	83%	63%				76%	48%			
Concomitant extrahepatic disease										
Yes	65%	35%	<0.001	0.016	1.58 (1.09–2.29)	62%	34%	0.009	0.005	2.10 (1.25–3.51)
No	78%	52%				74%	48%			
Second-line tumour progression										
Yes	69%	45%	0.120	0.016	1.75 (1.11–2.77)	65%	55%	0.870	–	
No	76%	49%				72%	44%			
Liver curative resection										
R2	56%	25%	<0.001	<0.001	2.72 (1.86–3.96)	53%	27%	0.011	0.002	2.65 (1.44–4.86)
R0/R1	81%	54%				78%	51%			
No. of hepatectomies/year										
<50	72%	43%	<0.001	0.002	1.67 (1.20–2.33)	68%	39%	0.003	0.004	2.49 (1.35–4.62)
≥50	79%	55%				75%	52%			
Postoperative chemotherapy										
No	70%	47%	0.290	–		66%	35%	0.009	<0.001	2.30 (1.42–3.72)
Yes	79%	49%				80%	55%			

PCT, preoperative chemotherapy; HR, hazard ratio; CI, confidence interval; OS, overall survival.

Table 3
Analysis of DFS in the R0/R1 2 PCT lines patients and its initially unresectable subgroup.

Risk factors	All patients with 2 PCT lines (n = 551)					Initially unresectable patients with 2 PCT lines (n = 167)				
	3 years	5 years	Univariate	Multivariate		3 years	5 years	Univariate	Multivariate	
			P-value	*P*-value	HR (95% CI)			*P*-value	*P*-value	HR (95% CI)
Metastatic primary lymph nodes										
Yes	23%	15%	0.020	0.020	1.39 (1.05–1.82)	24%	9%	0.220	–	
No	40%	19%				36%	18%			
Synchronous metastasis										
Yes	25%	17%	0.033	0.043	1.36 (1.01–1.82)	26%	17%	0.600	–	
No (metachronous)	34%	14%				29%	9%			
Bilateral localisation										
Yes	21%	13%	0.002	0.018	1.36 (1.05–1.75)	21%	–	0.024	0.047	1.60 (1.01–2.55)
No	34%	17%				34%	24%			
Radiofrequency ablation										
Yes	20%	13%	0.009	NS		13%	–	<0.001	0.008	2.09 (1.21–3.61)
No	30%	16%				30%	18%			
Postoperative chemotherapy										
Yes	29%	16%	0.026	NS		32%	16%	0.010	0.024	1.68 (1.07–2.62)
No	20%	10%				15%	–			

PCT, preoperative chemotherapy; HR, hazard ratio; CI, confidence interval; NS, not significant; DFS, disease-free survival.

chemotherapy. Despite less favourable tumour characteristics in such patients, OS from CLM diagnosis was similar, whether hepatectomy was performed after first- or second-line chemotherapy. However, surgery after second-line was associated with a decreased OS and DFS after hepatectomy in comparison to first-line.

Usually patients with CLM receiving second-line chemotherapy and then hepatectomy are expected to have a poorer prognosis, hence the rationale to perform resection is questioned. A retrospective study reported a 5-year OS after hepatectomy following second-line of 22% and a 5-year DFS of only 11% [10]. In our multicentre study, however, such patients (group 2) displayed relatively better results. After hepatectomy, the median and 5-year figures were 41.4 months and 35% for OS and 17.2 months and 15% for DFS, respectively. Moreover, the median and 5-year OS after diagnosis were 58.6 months and 49%, respectively, not significantly different from those observed in group 1. One recent meta-analysis has shown a respective median and 5-year OS of 39.6 months and 37.0% in patients with CLM resected after PCT, most of which were administered as front-line regimen [11]. The survival rates in our patients are consistent with these results.

Compared to chemotherapy alone, a median OS of 58.6 months from diagnosis or 41.4 months from hepatectomy following a second-line regimen is quite promising for patients failing a first-line regimen. A recent Phase III trial reported a median OS from randomisation of 13.5 months in patients receiving second-line therapy of aflibercept added to an irinotecan-based regimen [12]. Another trial combining bevacizumab with irinotecan- or oxaliplatin-based second-line reported a median OS from the start of first-line of 23.9 months [13]. In this context, our results support the indication of CLM resection even after second-line regimen, whenever technically possible.

Furthermore, even though the risk of surgery after second-line chemotherapy was expected to be increased owing to the larger number of cycles and the heavier tumour load, we found that the 90-d mortality in group 2 was similar to that in group 1 (<3%). These results are also consistent with recent data reporting a median 30-d mortality of 2.8% in CLM treated with hepatectomy irrespective of PCT delivery [14]. Compared to that of group 1, the risk appeared nevertheless acceptable, with no increased mortality and with more frequent but tolerable morbidity (33.5% versus 29.9%), further endorsing resection whenever indicated after second-line PCT.

In addition, our rather large sample size allowed the identification of prognostic factors, allowing an even more refined selection of patients in second-line PCT concerning the indication of surgery (Table 2). In the multivariate model of group 2, metastatic primary lymph nodes, concomitant extrahepatic disease, and R2 liver resection were independently associated with a decreased OS. However, the required surgical procedures including major hepatectomy, two-stage hepatectomy or repeat hepatectomies did not emerge as independent prognostic factors. As expected, tumour progression on second-line emerged independently as a negative factor for OS in multivariate model. This suggests that control of the disease, particularly for second-line PCT patients, is essential before surgery to improve outcome, as previously reported by our team in a study on patients with >3 metastases [15]. Additionally, the reason for discontinuation of first-line and switching to second-line was believed to be relevant to the outcome, especially progression as a surrogate for a more biologically resistant and aggressive disease.

Discontinuation for unacceptable toxicity is a common reason for quitting a clinical trial. Even though disease progression is the most frequent cause of discontinuation, basically every oncologist has had experience of switch to second-line for poor tolerance. Therefore, we included such patients receiving second-line because of toxicity. In this study, the causes were exhibited as not only progression (22.2%) but stable disease, insufficient partial response or intolerable toxicity (7.0%). However, the occurrence of progression during the first-line did not independently impact on OS after diagnosis, on the condition that the disease was favourably controlled by second-line PCT, and patients achieved to be resected. This finding proposes an effective treatment of second-line even when the disease appeared chemo-resistant to front-line.

Multivariate analysis showed that metastatic primary lymph nodes, synchronous and bilateral metastases were significantly associated with a decreased DFS in group 2 patients. To our knowledge, no study has yet reported prognostic factors of DFS on such patients. Among all patients with resected CLM, reported DFS predictors include primary lymph nodes, number of liver metastases, resection margin and CA19-9 after hepatectomy [16–18]. We found that the type of regimen, the use of biological agents, the number of cycles and a tumour progression on PCT were not associated with DFS. Moreover, initially unresectable patients did not suffer a poorer OS or DFS than those initially resectable, although the definition of unresectability could have differed from one centre to another.

Among initially unresectable patients with CLM resected after a second-line regimen, encouragingly, OS or DFS was comparable to its counterpart among the patients after first-line. The 3-year OS after diagnosis of 45% in this study compares favourably to that of 10%–44% reported in series of conversion therapies with targeted agents or of hepatic arterial infusion after failure of previous regimens [19–21].

The current study has obviously some limitations. It is a retrospective analysis of surgery-based database with evitable selection bias. By definition the patients who eventually did not undergo resection were not evaluated in LiverMetSurvey. Also, the chemotherapy regimens were decided at the convenience of local oncologists and were consequently diverse, and the treatment algorithms were non-standardised. But on the other hand, this study presents the 'real life' results of a large international cohort, acknowledging that the evaluation of such an approach would be difficult in small series of individual centres and unpractical to be designed within a randomised clinical trial. Furthermore, the heterogeneity of PCT regimens used allowed a comparison among them. Thus, in accordance with previous [7] and more recent [22,23] reports, neither the cytotoxic backbone (oxaliplatin or irinotecan), nor the targeted agent (anti-VEGF or anti-EGFR) used for second-line in this study impacted on clinical outcomes, provided that they were active in downsizing the disease and achieving resectability.

In conclusion, our study demonstrated that CLM resection after second-line chemotherapy, once it is achieved with favourable disease control, even with lesions deemed initially as non-resectable, could offer an estimated survival close to that after first-line and better than what is proved by concomitant data on chemotherapy alone, without a higher risk of perioperative mortality. Hence, we propose liver surgery on the patients whose liver metastases are sufficiently downsized to envisage resection, not only after front-line but also after active salvage chemotherapy.

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Conflict of interest statement

R. Adam received honoraria from Merck, Amgen and Sanofi for oral presentation in congress symposia. LiverMetSurvey benefits from an unrestricted grant from Sanofi.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2017.03.009.

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