Irinotecan (CPT-11)-based chemotherapy as induction treatment for advanced colorectal cancer

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The role of irinotecan-based chemotherapy as induction treatment of non-resectable advanced colorectal cancer (ACRC) is currently being elucidated. The objective of this retrospective study was to determine complete resection (R0), response rate, time to progression (TTP) and overall survival (OS) in patients with non-resectable ACRC after being treated with neoadjuvant irinotecan-based chemotherapy. Thirty-six patients with ACRC were selected, of whom 23 (64%) were treated with irinotecan (250 mg/m^2 on day 1), UFT (300 mg/m^2/day for 14 days) plus leucovorin (45 mg/day for 14 days) every 3 weeks. Another 13 (36%) received the FOLFIRI schedule of irinotecan plus 5-fluorouracil/leucovorin. A total of 214 cycles of irinotecan/UFT/LV (median 8, range 1–15) and 97 cycles of the FOLFIRI schedule (median 9, range 1–30) were administered. The overall response rate was 58% (95% confidence interval 42–74), with six complete and 15 partial responses, whereas seven patients (19%) showed stable disease. Laparotomy was performed in 12 patients, of whom eight (22%) achieved R0 and two (6%) a pathological complete response. Median TTP was 10.0 months and median OS was 38.0 months for all patients. After a median follow-up of 20 months (range 1–49), median TTP in patients with R0 was not reached (mean TTP, 33.1 months), whereas median TTP in non-resected patients was 7.5 months ($p = 0.016$). Toxicity was manageable and no toxic deaths occurred. This retrospective study showed a high resectability rate, and a prolonged TTP and OS in patients with ACRC after induction treatment with irinotecan-based chemotherapy. Both toxicity profile and postoperative complications were acceptable. Nevertheless, the definitive role of irinotecan as induction treatment should be confirmed in future clinical trials. *Anti-Cancer Drugs* 16:31–38 © 2005 Lippincott Williams & Wilkins.

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Introduction

Colorectal cancer (CRC) is a major cause of cancer mortality in Western Europe and represents 10–15% of the new yearly cancer diagnosis cases in such countries [1–3]. During the natural history of the disease, 50–60% of patients develop synchronic (15–30%) [4] or metachronic (15–30%) metastatic disease, usually during the first 3 years after primary tumor diagnosis [5]. The main organ affected by CRC metastasis is the liver (which is the only metastatic site in 30% of patients with stage IV disease) followed by lung, distant lymph nodes, bone and central nervous system.

The chemotherapeutic treatment for stage IV CRC has been revolutionized over recent years. 5-Fluorouracil (5-FU) was the backbone of all standard and experimental regimens for 40 years. The response rates with 5-FU monotherapy in first-line are 10–20%, with symptomatic improvement, but without a clear survival advantage in most cases [6,7]. 5-FU monotherapy evolved through different administration schedules, although it has been demonstrated that the optimal way of administration is as a protracted continuous infusion [8,9] in combination with different modulators like leucovorin (LV) [10]. New cytostatic drugs (e.g. irinotecan and oxaliplatin) in combination with 5-FU/LV [11–13] or oral fluoropyrimidines [14,15] have increased the median survival for stage IV disease to 21.6 months with the sequential administration of FOLFIRI followed by FOLFOX [16]. Evidence favors that either irinotecan or oxaliplatin [17] could be used as first-line treatment of advanced CRC (ACRC). To date, mature results with new agents like bevacizumab or cetuximab are eagerly expected [18,19]. None of these therapeutic alternatives is curative in the metastatic setting, as less than 5% of these selected and treated patients are alive after 5 years. Curative treatment of ACRC implies the complete resection (R0) of all metastases; however, resectability is technically possible only in 10–20% of the cases at the time of diagnosis of stage IV disease [20] and, despite the use of radical surgery in those patients, 70–80% of patients will relapse in the following 5 years, both at a local or a distant level [21]. However, new surgery could be performed in selected patients on a single relapsed site [22]. Complete resection is the main prognostic factor that clearly increases survival. In fact, the survival of patients with

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incompletely resected tumors is similar to that of patients not undergoing surgery [23].

Induction chemotherapy may improve these results by increasing the percentage of patients with resectable disease, and reducing the size and the number of non-resectable metastases. Previous reports suggest that initially non-resectable CRC patients treated with neoadjuvant oxaliplatin-based chemotherapy would show potentially curative resection rates between 13 and 38%, with a survival at 3 years between 30 and 50% [22,24]. However, Gornet *et al.* [25] observed an exacerbation of the oxaliplatin-induced neurosensory toxicity following surgery, and Rubia-Brandt *et al.* [26] found a strong correlation between the use of oxaliplatin as neoadjuvant treatment and the development of severe hepatic sinusoidal obstruction. Accordingly, we performed a retrospective study in order to evaluate the role of irinotecan-based chemotherapy as induction treatment. Patients were initially non-resectable ACRC due to hepatic and/or extra-hepatic involvement. The primary endpoint was to determine the rate of R0 achieved. Secondary endpoints were to evaluate response rate, time to progression (TTP), overall survival (OS) and safety.

Methods

Patients

Patients were selected consecutively between December 1998 and June 2003 at our Hospital. Selection criteria were as follows: (i) histologically confirmed ACRC; (ii) initially non-resectable disease; (iii) induction treatment with irinotecan-based chemotherapy; (iv) age ≥ 18 years; (v) life expectancy ≥ 3 months; and (vi) normal renal, hepatic and bone marrow functions. Unresectability criteria were number of metastases (> 4) and/or their size (> 5 cm) and/or more than one site involved.

Patients were not eligible in case of: (i) previous treatment with any chemotherapy agent on metastatic setting; (ii) high risk of poor outcome due to concomitant non-malignant disease (inflammatory enteropathy, major organ dysfunction, uncontrolled severe infection); (iii) central nervous system metastases; (iv) previous history of cancer (except for resolved carcinoma of cervix uteri or basal cutaneous carcinoma); (v) bowel obstruction and (vi) lactating, pregnant women or patients with reproductive potential not implementing adequate contraceptive measures.

All patients provided their written informed consent before any medical procedure. Pretreatment evaluation consisted of a medical history, physical examination (including assessment of body surface, performance status and tumor size), plasma biochemistry, carcinoembryonic antigen (CEA) and hematological analyses. Computed tomography (CT) scans of the chest and abdominal/pelvic region were performed in all patients at baseline. Cranial CT was only performed when central nervous system involvement was suspected.

Tumor changes were assessed every 3 months by imaging of lesion size, and evaluated by a multidisciplinary team of oncologists and surgeons to determine resectability. Those patients with only hepatic disease were also evaluated with intraoperative ultrasound exploration during the laparotomy. Toxicity was reported every cycle.

Chemotherapy regimen

Two irinotecan-based schedules were used: (A) CPT-11 (250 mg/m^2, 1-h i.v. infusion on day 1) plus UFT (300 mg/m^2/day p.o. days 1–14) and LV (45 mg/day p.o. days 1– 14), repeated every 21 days [27] and (B) CPT-11 (180 mg/m^2, i.v. on day 1) plus 5-FU (400 mg/m^2 bolus and 2400 mg/m^2, 46-h continuous i.v. infusion) plus LV (200 mg/m^2 on day 1), every 2 weeks [12]. The former scheme was administered on a phase II clinical trial context at our center, whereas the latter was considered the standard option. Treatment was administered until non-resectable disease was converted to a resectable disease, or disease progression, unacceptable toxicity or patient withdrawal. Those patients who achieved a complete response (CR) continued treatment for a maximum of 12 cycles.

In all patients, the following guidelines were followed for dose modification: In the event of hematological and/or gastrointestinal grade 2 toxicity, according to National Cancer Institute's (NCI) Common Toxicity Criteria (CTC) [28], the cycle was delayed until recovery (toxicity grade ≤ 1). In the event of grade 3–4 toxicity, the doses were reduced by 75% in the next cycle. In the event of new grade 3–4 toxicity, an additional dose reduction was conducted, but a third grade 3–4 event implied treatment withdrawal.

Prophylaxis for emesis and cholinergic syndrome was allowed. Specific guidelines for the treatment of delayed diarrhea consisted of 2 mg of loperamide every 2 h after the first episode of diarrhea stools until 12 h after the last stool for a maximum of 48 h consecutively. If diarrhea persisted for more than 24 h, an oral prophylactic broad-spectrum quinolone antibiotic was prescribed. If diarrhea persisted for more than 48 h, patients had to be admitted to the hospital for parenteral rehydration. Patients with febrile neutropenia were hospitalized, and treated with antibiotics and specific supportive care. In all cases, symptomatic medication was administered.

Assessment of response and toxicity

Response to treatment was classified according to WHO criteria. Pathological complete response (pCR) was achieved when the histopathological study of the surgical

specimen detected no viable tumor. A resection was considered curative (R0) when complete resection and negative margins were achieved. Other secondary efficacy endpoints were TTP, from the onset of treatment until progression or death, and OS calculated from the start of treatment to the date of death for any reason. All adverse events experienced during the study were recorded and graded according to NCI CTC. All patients were evaluated for adverse events regardless of their relationship to the study drug. All adverse events were graded for severity before each treatment cycle.

Table 1 Characteristics of patients ($n=36$)

Age (years) [median (range)]	60 (34–71)
Gender [*n* (%)]	
male	25 (69)
female	11 (31)
ECOG PS [*n* (%)]	
0	14 (56)
1	20 (56)
2	2 (5)
Primary tumor [*n* (%)]	
colon	24 (67)
rectum	12 (33)
Metastases	
synchronic	22 (61)
metachronic	14 (39)
No. metastatic sites [*n* (%)]	
1	20 (55)
2	14 (39)
>2	2 (6)
CEA (at metastatic diagnosis) >5	25 (69)

Statistical analyses

The statistical analysis was performed by SPSS software (version 11; SPSS, Chicago, IL). Descriptive methods were used to analyze all the study variables. Continuous variables were described with mean, SD, median and range. Qualitative data were described with absolute frequency distributions. TTP and OS were analyzed using Kaplan–Meier curves for each study subgroup and comparisons were made using a two-tailed log-rank test. Objective response rates were calculated with 95% confidence intervals (CIs).

According to Cox's proportional hazards model, a multivariate analysis was performed in order to find each variable independent effect on a survival beyond median OS; age, preoperative CEA, number of metastatic locations and R0 achievement were considered.

Table 2 Metastatic sites and treatment strategy

No.	Metastatic site[a]	Reason for unresectability	Treatment schedule[b]	Clinical response	Surgery (yes/no)	Type of surgery	Results
1	H	bilobar, large size	A	PR	yes	left hepatectomy + segmentectomy	R0
2	O	huge in stomach and pancreas	B	PR	yes	partial gastrectomy + duodenopancreatomy	R0
3	H	bilobar, large size	A	PR	yes	laparotomy	unresectable
4	O	peritoneal carcinomatosis	A	PD	no		
5	H, O	liver and peritoneum	B	PD	no		
6	L, H, O	three sites	A	SD	no		
7	O	large retrogastric mass	A	PR	yes	mass resection	R0/pCR
8	H, O	liver, spleen, peritoneum	A	PD	no		
9	H	six metastases (four >5 cm)	B	CR	no		
10	H, O	liver, pancreas	A	CR	no		
11	O	peritoneum	A	CR	no		
12	H	bilobar	B	PR	yes	extended right hepatectomy	R0
13	H	bilobar	B	PR	yes	laparotomy	unresectable
14	L, H	two sites	B	SD	no		
15	H, O	liver, peritoneum	A	SD	no		
16	O	duodenopancreatic involvement	A	PR	yes	duodenopancreatectomy	R0/pCR
17	H	bilobar	A	CR	no		
18	H	close to porta-hepatic	A	PR	yes	metastasectomy	R0
19	L, H	two sites	B	PD	no		
20	L, H	lung, lymph nodes	B	PD	no		
21	L	both lungs involved	A	PR	yes	thoracotomy	unresectable
22	O	peritoneum	A	PD	no		
23	H, O	liver, retroperitoneum	A	PD	no		
24	L	both lungs involved	A	PR	no		
25	L, H	two sites	B	SD	no		
26	L, H	two sites	A	SD	no		
27	L, O	lung, ovary	B	PR	no		
28	L	large size	A	PD	no		
29	H, O	liver, lymph nodes	A	CR	no		
30	H	bilobar	A	CR	no		
31	H	large size	B	PR	yes	laparotomy	unresectable
32	L	multiple	B	PR	yes	metastasectomy	R0
33	H	6 and 7 cm in size	B	PR	yes	segmentectomy	R0
34	H, O	liver, bladder	A	SD	no		
35	L, O	lung, pancreas, lymph nodes, aorta	A	SD	no		
36	H, O	liver, mediastinum	A	PR	no		

[a]L: lung; H: hepatic/liver; O: other sites.
[b]A: CPT-11/UFT/LV; B: FOLFIRI.

Results

Patient characteristics

Between December 1998 and June 2003, 36 patients with advanced non-resectable CRC in our hospital were treated with irinotecan-based chemotherapy as induction treatment in our hospital. Table 1 shows a summary of the main characteristics of this series. Primary tumor site was colon ($n = 24$, 67%) and rectum ($n = 12$, 33%). All patients who developed metachronic metastases ($n = 14$) had received previous adjuvant treatment (5-FU/LV Mayo regimen for colon cancer and 5-FU/radiotherapy for rectal cancer). The median disease-free interval for these patients was 19.5 months (95% CI 7–96). The remaining patients ($n = 22$) showed metastatic disease at diagnosis.

A detailed description of our series is offered in Table 2. As shown, 10 and four patients had only hepatic and pulmonary involvement, respectively, but were considered initially non-resectable according to selection criteria.

In addition, six patients presented with a single-site, unresectable, non-hepatic, non-pulmonary metastatic disease. Three of them had shown peritoneal disease (two with multiple nodes and one 'omental cake') and therefore they had very little possibilities of subsequent resection without previous induction chemotherapy. The last three patients had single-site metastases (a metachronic metastases disease of a 15-cm adenopathic mass infiltrating the stomach body and pancreas, $n = 1$; a similar condition, but without organ infiltration, $n = 1$; and a synchronous affectation of duodenum and pancreas by a 13-cm mass, $n = 1$).

Sixteen patients had more than one metastatic site affected. Apart from the liver, the lung was also affected in four patients. However, the vast majority of these patients had a non-hepatic non-pulmonary disease (peritoneal disease, $n = 3$; lymph nodes, $n = 2$; pancreas, $n = 1$; pancreas and lymph nodes, $n = 1$; ovaric surface, $n = 1$; bladder infiltration, $n = 1$; spleen, $n = 1$; mediastinum, $n = 1$; and retroperitoneum mass, $n = 1$). Even though curability was highly improbable in the last 16 patients, induction chemotherapy was attempted due to the good initial PS.

Treatment

In Group A, a total of 214 cycles of CPT-11 + UFT-LV were administered during the study. The median number of treatment cycles received per patient was 8 (range 1–15). The dose was reduced in 43 cycles (20%) and seven patients (31%), due to grade 3–4 hematological and/or non-hematological toxicity. Treatment was delayed in 30 cycles (14%) and 13 patients (59%), due to grade 3–4 hematological and/or non-hematological toxicity. The median absolute and relative dose intensity for CPT-11 was 75 mg/m^2/week and 89%, respectively.

In Group B, 97 cycles (median 9, range 1–30) of FOLFIRI were administered. The dose was reduced in 26 cycles (27%) and four patients (28%), mainly due to non-hematological toxicity. Treatment was delayed in 15 cycles (15%) and eight patients (57%), mainly due to non-hematological toxicity. The median absolute and relative dose intensity for CPT-11 was 77 mg/m^2/week and 85%, respectively.

Toxicity

The toxicity profile observed in this study was in accordance with the toxicity described in other irinotecan chemotherapy studies. No toxic deaths were reported in any of the treatment arms.

The median postoperative hospital stay was 11 days and postoperative morbidity was low. Only one surgical wound infection and one transient bilirubin elevation were reported.

One patient died after surgery. He developed a biliary fistula with secondary sepsis by *Enterobacter cloacae*. Fistula never solved, and he died due to a progressive hepatic failure and *Pseudomonas aeruginosa* catheter-related sepsis 4.8 months after laparotomy, without leaving hospital in that period.

Efficacy

All patients were evaluable for response. Six patients (17%) and 15 (41%) patients showed complete (CR) and partial responses (PR), respectively, with an overall response rate of 58% (95% CI 42–74). Stable disease (SD) was observed in seven patients (20%), whereas eight patients (22%) progressed during treatment. Median time to response was 2.2 months (95% CI 1.5–4.1).

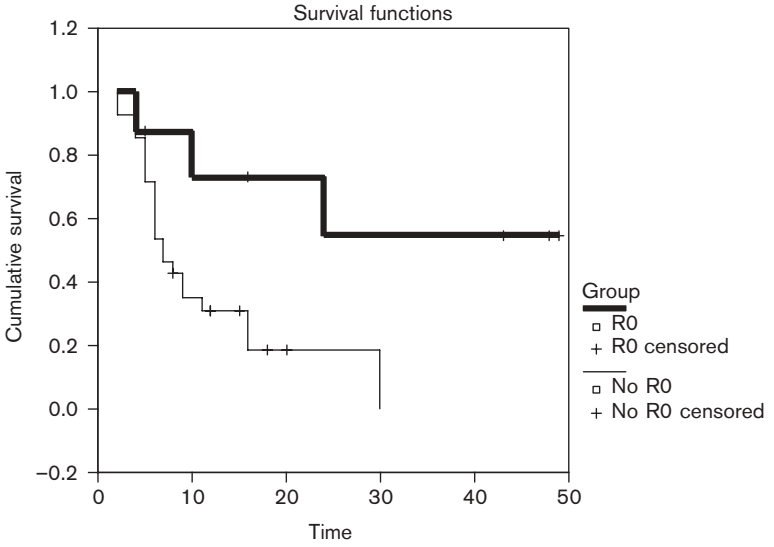
After induction chemotherapy, laparotomy could be performed in 12 patients, eight of whom (22%) achieved R0 and two (6%) showed a pCR. All of them come from

Table 3 Efficacy data on different patient subgroups ($n = 36$)

	R0 ($n = 8$)	NR-CR ($n = 6$)	NR-NCR ($n = 22$)	Overall series ($n = 36$)
TTP [median (months)]	33.1[a]	9.0	6.0	10.0
OS [median (months)]	43.2[a]	38.0	28.0	38.0
OS 2 years (%)	75	66	18	41
Follow-up (months) [median (range)]	40.5 (5–49)	31.0 (12–38)	16.5 (7–45)	20.0 (5–49)

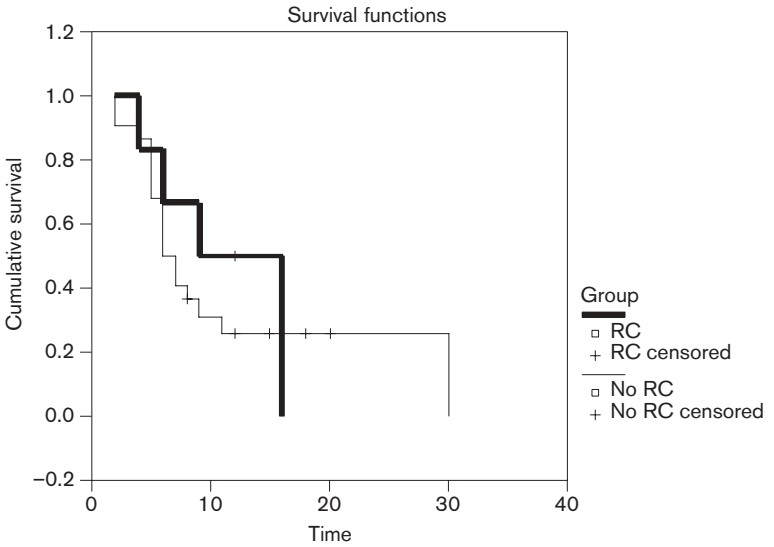
[a]Mean time as follow-up was not enough to reach the median.

Fig. 1



TTP in patients with complete resection (R0) compared to remaining patients.

Fig. 2



TTP in non-resected patients with complete response compared to remaining non-resected patients.

the single-site involvement group. Intraoperative ultrasound exploration showed that resection was not possible in three patients (Patients 3, 13 and 31) due to occult metastases in spite of the fact that the preoperative CT scan suggested potential resectability. In addition, one patient who underwent thoracotomy had a more diffuse lung affectation than that suggested by CT scan.

Apart from four hepatic and one pulmonary R0 resections, we also find it interesting to describe the three remaining cases. Patient 2, who had stomach and pancreas affectation, achieved a PR and partial gastrectomy and duodenopancreatectomy was performed due to tumor infiltration. Patient 7, who presented a large retrogastric mass, showed a PR and a mass excision was practiced without difficulties. Interestingly, while a CT scan

showed a 3-cm tumor, pathologic analysis demonstrated no viable tumor (pCR). Patient 16, who had duodenopancreatic involvement, only showed a slight diminution of his mass; however, surgery was attempted. Surprisingly, no viable tumor was found (pCR). These three patients (and three with hepatic resection) are alive and disease free.

None of the patients with two or more sites involved was suitable for surgery after induction chemotherapy; subsequently, all of them have died or present active disease.

Patients showing a CR were not subjected to surgery, but all those six patients had further PD.

With a median follow up of 20.0 months, the median TTP was 10.0 months and the median overall survival was 38.0 months.

Table 3 shows a comparison of TTP, OS and the 2-year survival rate between patients with complete resection (R0), non-resected with CR (NR-CR), non-resected without CR (NR-NCR) and the complete series. Significant differences (log-rank test, $p = 0.016$) were found in TTP between patients with R0 and the rest of patients (NR-CR plus NR-NCR) (Fig. 1). No significant differences in TTP (log rank test, $p = 0.7$) were found between NR-CR versus NR-NCR (Fig. 2). Only the R0 showed a statistically significant independent effect on survival beyond median OS according to Cox's model [risk ratio 2.57 (95% CI 1.38–4.73); $p = 0.03$; for those achieving R0 being alive beyond median OS with regard to those without R0]. An elevated preoperative CEA showed a clinically negative effect, almost reaching a significant p value [risk ratio –0.0012 (95% CI –0.0008 to –0.0016); $p = 0.07$]).

Discussion

This retrospective study of irinotecan-based chemotherapy as induction chemotherapy in a group of patients with initially non-resectable ACRC showed an overall response rate of 58%, a median TTP of 10. 0 months and a median OS of 38.0 months. Moreover, R0 of disease was performed in eight patients (22%), of which two (6%) of them obtained a pCR.

Other studies where systemic chemotherapy was used to improved resectability have been reported. The first series was published in 1992 and used 5-FU-based chemotherapy [29]. Nevertheless, most publications include the use of oxaliplatin-based chemotherapy as induction treatment to improve resectability. Giaccheti *et al.* [24] described retrospectively the most striking results with curative resections in 77 out of 389 initially non-resectable patients (20%) and a 5-year survival rate of 50% in the resected group of patients. However, this series only included patients with liver involvement. Data closer to clinical practice should include a less selected series of patients, similar to that reported by Adam *et al.* [22] in 701 initially non-resectable patients who achieved a resectability rate of 13.5% and a 5-year survival of 34% in resected patients. None of these two large series [22,24] supported the resection of non-hepatic or non-pulmonary disease sites and series with smaller size showed similar results [30–32].

Irinotecan-based induction chemotherapy has been little studied in small series of CRC patients. One series of 16 patients who achieved resection only showed hepatic metastatic disease [33]. Pozzo *et al.* [34] reported a complete resection rate of 28% in patients treated with FOLFIRI. This series of 40 initially non-resectable patients included patients with more than one metastatic site or extra-hepatic disease as exclusion criteria.

Our series included a population with very poor initial prognostic factors as 69% of patients showed high pre-surgery CEA, 45% had more than one metastatic site, 47% showed at least one non-hepatic or non-pulmonary metastatic site and 11% of these patients showed invaded peritoneum. Despite these poor prognostic factors, we reported a resectability rate of 22%, which is similar to that obtained with other induction chemotherapies.

Another point worth mentioning is that we achieved complete resections not only in patients with hepatic or pulmonary metastases, but also in patients with unique metastatic sites other than liver and lung (Patients 2, 7 and 16). This point suggests that curative intention should not be limited to relapses confined to the liver or the lung. Similar anecdotal reports are available, such as that by Kawasaki *et al.* [35] in one patient with a para-aortic lymph node metastasis.

As expected, multivariate analysis demonstrated independent influence on survival for a R0 achievement (and almost a statistically significant, negative influence, for elevated preoperative CEA, which is a long-discussed topic). However, no independent influence was shown for number of metastatic locations, probably because even though only patients with one location could be resected, many non-resected patients had only one site involved.

Interestingly, the two pCR obtained in our series were in patients where a CT scan showed big lesions—this finding suggests that use of a positron emission tomography (PET) scan should be explored.

In addition, it should be noted that none of the patients with more than one metastatic site achieved the response needed to allow a surgical approach.

The administration of induction chemotherapy did not increase the incidence of post-surgical complications more than expected [20,36]. The toxicity induced by this chemotherapy is well known and was manageable.

When we analyzed efficacy outcomes in different subgroups of patients, we found that after a median follow-up of 49 months, median TTP in patients with R0 was not reached (mean TTP, 33.1 months), whereas median TTP in NR-CR plus NR-NCR patients was 7.5 months ($p = 0.016$). Also, the 2-year survival rate of 75% in the R0 group was very high. On the other hand, no significant differences in TTP were found between NR-CR versus NR-NCR patients (Table 3 and Fig. 2). The former data may suggest that only R0 achievement plays a significant role in OS.

We also would like to discuss the optimum surgery moment. Our series was analyzed retrospectively, but if we intend to conduct a prospective analysis we need to ask ourselves when to make patients undergo intervention. Is it better to operate when PR is achieved? Or, should we continue administering chemotherapy until CR? An excessive early intervention might not allow the surgeon to properly work out the surgical procedure or, if surgery is performed, there may not be enough tissue remaining to preserve hepatic function. In contrast, an excessive wait might result in complete disappearance of the lesions from imaging techniques, thus making it impossible to confirm whether the affected area was resected or not. The last means that patients with CR are not subjected to surgery, but in fact most of them relapse. In our series, six patients showed CR (five of them in the second re-evaluation). Probably, intervention should have been tried in the first re-evaluation, at least in Patients 9, 10, 17 and 30 (see Table 2), and therefore the R0 rate should have been increased up to 30%. Whenever chemotherapy is administered it is hard to stop treatment if tumor response is obtained; however, complete surgery is the only definitive treatment for CRC nowadays. Another approach would be that whenever a CR is achieved, a PET scan should be performed to detect any minimal residual disease in a more accurate way than with conventional diagnostic modalities, like CT [37].

Also note that our series, like others, contained cases of long-term relapse despite R0. To date, there is no randomized data that justify the adjuvant administration of post-surgery chemotherapy in this type of patient, although it seems reasonable to do it.

We must consider some limitations in our series. First, this was a non-randomized retrospective analysis. Second, patients were treated with two different schedules of irinotecan (however, the majority of the previous published studies have similar limitations). Third, the number of patients studied was small, although the results obtained are very good if we consider that these patients were non-selected and other series included only patients with liver and/or lung metastases.

We believe that the data presented here justify a prospective randomized trial in which patient inclusion would not be restricted to those showing liver and/or lung metastases. In order to define the ideal clinical trial with which to evaluate the ability to induce metastases resectability, it should compare oxaliplatin- versus irinotecan-based chemotherapy.

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