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The “reversed” treatment approach for synchronous liver metastases and colorectal cancer. Feasability and first results

Etudiant
Céline Du Pasquier

Tuteur
Prof. Nicolas Demartines
Service de chirurgie viscérale, CHUV

Co-tuteur
Prof. Markus Schäfer
Service de chirurgie viscérale, CHUV

Expert
Dr. Michael Montemurro
Médecin associé, service d’oncologie, CHUV

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Abstract

Background: The « reversed treatment» approach inverts the treatment sequence of advanced synchronous colorectal liver metastases - i.e. the liver metastasis is treated first, followed by resection of the primary tumor. Chemotherapy is performed before and after liver surgery. We recently started to use a reversed treatment approach in selected patients. The aim of this study is to critically assess this new treatment modality.

Methods: Nine patients (7 male, 2 female, mean age 62 years) benefited from this new treatment between November 2008 and May 2010. The data were collected retrospectively.

Results: All patients responded to the neoadjuvant chemotherapy. The median number of liver metastases was 6 (range 1 - 22). The median size of the largest liver metastases was 4.3 cm (range 2.6 – 13 cm). Three patients had portal vein embolization prior to liver surgery. Two patients could not complete the treatment. One had to undergo emergency surgery for occluding colonic tumor. The second one showed liver recurrence before starting the adjuvant chemotherapy. The seven patients who completed the treatment are still alive after a median time of 27 months (range 17 – 37 months). Seven of them had recurrence (1 rectal, 6 liver). The median disease-free survival was 9 months (range 0 – 17 months).

Conclusion: Based on our preliminary experiences, the reversed strategy shows encouraging results for the treatment of advanced synchronous colorectal liver metastases in well selected patients. The treatment was generally well tolerated and long term survival seems to be prolonged.

Key Words: Colorectal cancer, synchronous, liver metastases, reversed treatment, liver-first approach

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Introduction

Colorectal cancer means an important medical issue. In the United States, more than 140'000 patients have been diagnosed in 2010, which represents 10% of all cancer cases.[1] In Europe, it accounts for 13% of all cancer cases, with more than 400'000 new cases in 2008.[2] In those years, more than 50'000 patients died from their colorectal tumors in the US, and approximately 200'000 in Europe.[1,2,3] About 50% of colorectal cancer patients will develop liver metastases during the course of their disease. Colorectal liver metastases (CRLM) may occur simultaneously with the primary tumor (synchronous CRLM) or after resection of the primary tumor as delayed progression of the disease (metachronous CRLM).

The traditional treatment of patients with synchronous CRLM is to remove the primary tumor first to avoid local complications, e.g. obstruction, bleeding, and pain. Resection of liver metastases is performed as a second intervention several weeks later, after full recovery of patients and chemotherapy. Adjuvant chemotherapy aims to reduce local recurrence of the primary tumor as well as to stabilize or even decrease the size and number of CRLM. In addition, non-responders to chemotherapy who reveal a tumor progression can be identified, and unnecessary surgery can be avoided.[4] Simultaneous resection of the primary tumor combined with major liver surgery has been abandoned due to an increased postoperative morbidity.[5] Moreover; no current studies could define a better long-term survival after single versus staged resections.

This aforementioned treatment has been increasingly challenged during recent years since it is known that long-term survival in case of simultaneous CRLM is rather determined by the liver metastases than the primary tumor. The advent of new anticancer drugs and advances in liver surgery are the main factors that initiated the development of new treatment strategies. Irinotecan, capecitabine and oxaliplatin reveal increased tumor response rates up to 40-50% compared to <25% that could

be achieved by using older treatment regimens with 5-fluorouracil (5-FU) and leucovorin (LV). New combinations of these five drugs are able to further raise the response rate to 70%. Most recently, monoclonal antibodies against VEGF (vascular endothelial growth factor), e.g. bevacizumab, and EGFR (epidermal growth factor receptor, e.g. cetuximab have been introduced. Response rates of nearly 100% have been shown.[6,7] Better understanding of liver function, i.e. liver regeneration as well as improved operation techniques, decreased the morbidity and mortality rates of major liver resections. The surgical armamentarium has also been added by modern interventional radiology. Thermal tumor ablation by using radiofrequency, and induction of liver hypertrophy by portal vein embolization are of particular value.[3] For well selected cases, metastasis resection can be done by a laparoscopic approach.[7]

Since primary and metastatic tumor growth can be effectively controlled, the so-called “reversed treatment” of advanced synchronous colorectal liver metastases or “liver-first approach” has been proposed as novel therapeutic approach. As CRLM define the long-term outcome (i.e. survival), it seems sensible to target them first. This approach allows control of the metastases at the same time as the primary, avoiding their progression while treating the colorectal tumor. The aim of this new strategy is to offer to patients with stage IV colorectal cancer a treatment of the primary and the metastases with curative intent to increase survival.[4] Prior to surgical resection of the liver metastasis, patients receive neoadjuvant chemotherapy with the aim to stop further tumor growth or even downsizing liver metastasis. After re-staging, resection of liver metastasis is then performed. Finally, the primary tumor is resected, often requiring a second intervention. It remains optional, whether chemotherapy is continued until the primary tumor will be removed. Actually, only few patients have benefited from this novel approach. *Mentha et al*. studied the effectiveness of this treatment on 30 patients. The survival rates for patients who completed the treatment at 1, 2, 3, 4 and 5 years were 100%, 89%, 60%, 44% and 31%, respectively. The median survival was 44 months. In comparison, the 5-year survival rates of patients undergoing the traditional treatment range between 25% and 58%.[8]

The Department of Visceral Surgery, CHUV, recently started to use the reversed treatment in selected patients. The aim of this study is to critically assess this new treatment in terms of complications, length of hospital stay, mortality and survival.

Patients and Methods

There were nine patients who benefited from a reversed treatment for advanced colorectal liver metastases with curative intent from November 2008 to May 2010. All patients presented a colonic or rectal primary tumor and synchronous liver metastases without further metastases at other sites. Chemotherapy regimens were chosen by the patient's oncologists according to their characteristics. Chemotherapy regimens were documented in the CHUV database if the patient was followed at the Department of Medical Oncology of the hospital. If not, the external oncologist was contacted to get the treatment protocol. Radiological statements were consulted to prove tumor response to chemotherapy.

Patients were identified from prospective databases of the Department of Visceral Surgery. Medical charts, radiological and pathological reports were carefully reviewed to extract patients' data and outcome parameters. Data were retrospectively documented on a separate data sheet developed for each patient; and entered into an electronical database.

The study was approved by our internal Institutional Review Board. All patients signed informed consent prior to liver and colorectal surgery, respectively.

All patients underwent major liver surgery at the CHUV, whereas colorectal surgery was done in part at the CHUV and for some patients in other hospitals. Some documents were to be asked to the patients' surgeon. Surgical treatment of liver recurrence was done at the CHUV, while colorectal recurrence was operated elsewhere.

Postoperative complications were graded according to their severity. A validated therapy-orientated complication score was used.[9] Complications were reported as number of complications, whereby more than one complication per patient was possible.

Overall survival was calculated from first diagnose to death of the patient. Disease-free survival was calculated as time interval between colorectal surgery and tumor recurrence.

Table 1. Patient's characteristics

Number of patients	9
Median age (years, range)	64 (46 - 77)
Gender	
Female	2
Male	7
Median BMI (kg/m^2, range)	22 (17 - 27)
Median ASA (range)	2 (2 - 3)
Co-morbidities	
Arterial hypertension	3
Cardiovascular	2
Pulmonary	0
Chronic renal insufficiency	0
Diabetes mellitus	0
Hepatopathy	0
Others	0

BMI Body Mass Index (kg/m^2)
ASA American Society of Anaesthesiologists

Results

There were nine patients (7 men and 2 women) with a median age of 64 years (range 46 to 77 years), who were treated with the liver first approach. None of them had severe co-morbidities. Patients underwent colonoscopy and imaging control (CT-Scan and Ultrasonography of the liver or/and MRI or/and PET-CT) *(Table 1).*

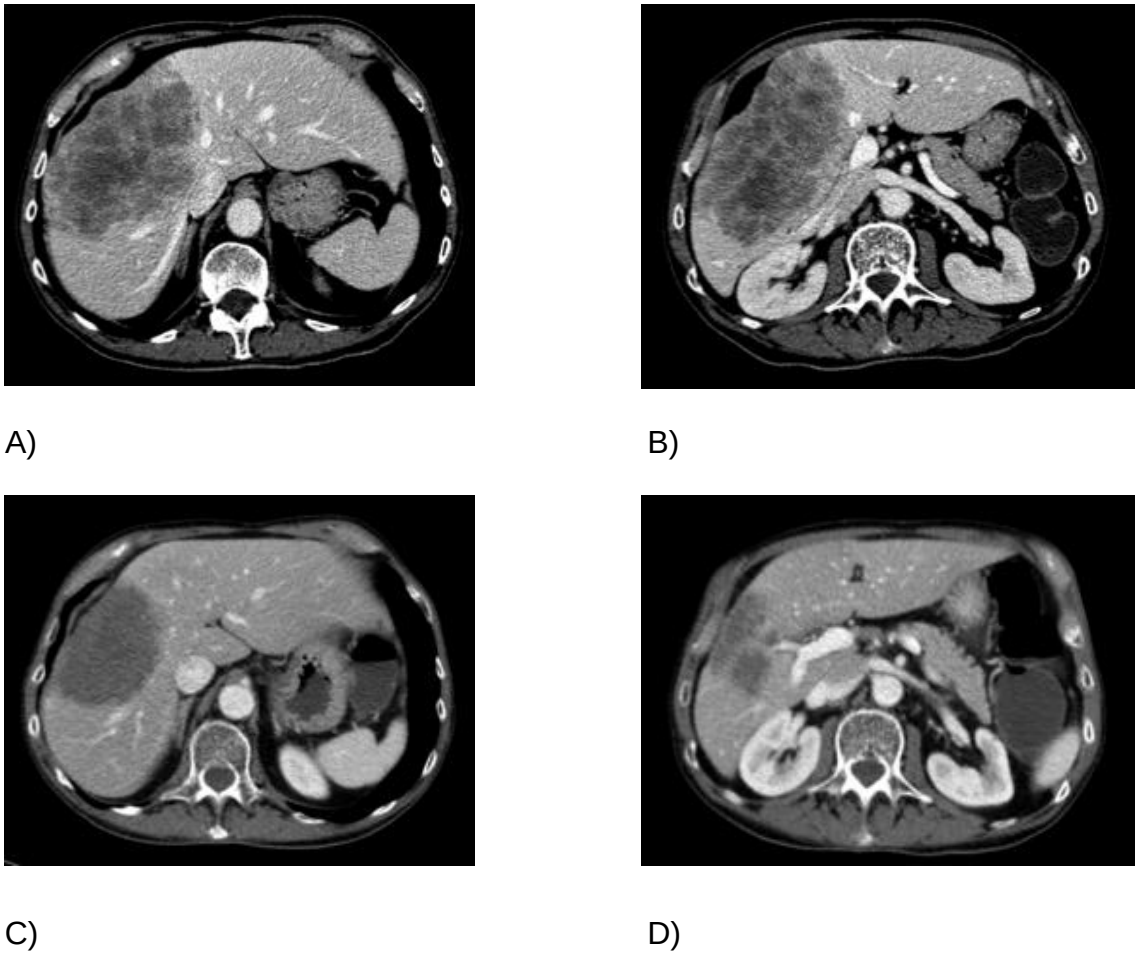
They presented colorectal cancer and synchronous liver metastases with no other metastatic site. Five patients presented adenocarcinoma of the colon, while two patients had a rectal primary. The two others presented both colon and rectum tumor. The median number of liver metastases was six (range 1 – 22). The median size of the largest liver metastasis was 4.3 cm (range 2.6 – 13 cm).

Chemotherapy

All patients were treated with neo-adjuvant chemotherapy prior to surgery. They received 2 to 10 cycles of combination therapy. Three patients were given 8 to 10 cycles of OCFL combination – i.e. oxaliplatin at days 1 and 15, irinotecan (CPT-11) at days 8 and 22, 5-fluorouracil (5-FU) and leucovorin at days 1, 8, 15 and 22. Three patients received 2 to 3,5 cycles of the OCFL-BC regimen – i.e. oxaliplatin at days 1 and 15, CPT-11 at days 8 and 22, 5-FU at days 1, 8, 15 and 22, leucovorin at days 1, 8, 15 and 22 with a weekly infusion of bevacizumab and cetuximab at days 1 and 15. Two patients received 5 to 6 cycles of FOLFOX/Avastin® – i.e. oxaliplatin at day 1, 5-FU as a bolus at day 1 and 2, 5-FU as a continuous perfusion for 24 hours at day 1 and 2, and bevacizumab at day 3. The last patient was given a combination therapy with 6 cycles of oxaliplatin and capecitabine.

Tumor response to chemotherapy was assessed after 2 to 6 cycles of treatment with imaging control, i.e. CT-Scan, MRI or PET-CT, whereby all patients presented radiological shrinkage of both, the metastases and the primary tumor.

(Figure 1). One patient with an occluding sigmoidal tumor that had to be stented, expulsed the stent as the tumor decreased and could restore a normal transit without abdominal pain.



A) B)

C) D)

Figure 1. preoperative CT-Scan of one patient with reverse treatment approach. A) and B) show the initial CT-scan with a big liver metastasis. C) and D) show the same metastasis after 2 months of chemotherapy with the OCFL regimen.

Some complications related to chemotherapy were encountered, but treatment was completed in all patients. Hematotoxicity occurred in three patients but only one developed febrile agranulocytosis and pneumonia. Four patients suffered from mucositis (grade III). Two patients developed a grade I neuropathy on oxaliplatin treatment. Two patients had a mild allergic reaction to oxaliplatin. One patient had recurrent epistaxis. Toxidermitis was encountered in three patients. Five patients

suffered from severe fatigue. One patient developed acute renal failure caused by rhabdomyolysis. Two patients had persistent hiccup. There was no death related to chemotherapy.

Liver surgery

All patients benefited from liver surgery with curative intent, with a median time interval after the last chemotherapy of one month (range 1 – 5 months). Three patients underwent portal vein embolization (PVE) prior to liver surgery to increase the remnant liver volume. The median time interval between PVE and liver surgery was one month (range 1 – 5 months). Liver surgery was based on CT or MRI findings and on intraoperative ultrasonography. Of note, imaging studies that have been performed prior to neoadjuvant chemotherapy were mainly used since metastasis localization after treatment was difficult.

As seen in *Table 2*, all patients underwent major liver surgery. Meticulous inspection of the abdominal cavity was always performed to exclude peritoneal carcinomatosis, which was not found in any patient. One patient received six RBC (red blood cells) and three FFP (fresh frozen plasma) because of major intraoperative bleeding. All other patient had only minor blood loss. There were no other intraoperative complications.

Histological examination of the resected masses showed a median viable cell percentage of 10% (range 1 – 100%). The best histological response to chemotherapy, with 1% remaining viable cells, was obtained with the OCFL-BC regimen. The resection was R0 for seven patients and R1 for the two remaining patients.

Postoperatively, several patients had surgical or/and medical complications. A first patient presented with an intraabdominal abscess that required a laparotomy to drain the abscess, and the abdomen had to be left open. A further operation was needed to close the laparostoma and to introduce a Vacuum Assisted Closure (VAC) therapy. A second patient presented a bilioma, due to stenosis of the left hepatic bile duct. He underwent left hepatectomy, which was complicated by an abscess of the abdominal wall. Conservative treatment with rinsing and gauze plugging was successful to get complete wound healing. The same patient presented a pneumothorax and pleural effusion, which had to be drained. A third patient presented a bilioma with *Staphilococcus epidermidis* infection that was drained by CT-scan control. This patient received antibiotic therapy with Co-Amoxicillin® for 10 days, and developed also a delirium. A fourth patient presented two consecutive bacteriemias, one with *Klebsiella pneumoniae* and one with multi-resistant *Staphilococcus epidermidis* (MRSE). Therefore, the patient received antibiotic treatment with Ciproxine® and Vancomycine® for 14 days. Another patient presented a seroma after discharge but did not consult for it. There was no intraoperative or postoperative death.

Median hospital stay for liver surgery and complications was 15 days (range 8 – 53 days). (*Table 3*).

Table 3. postoperative complications

Case	Liver surgery		Colorectal surgery	
	Clavien score *	hospital stay (days)	Clavien score	hospital stay (days)
1	IIIb	27	IIIa	25
2	-	8	-	6
3	II	20	-	6
4	-	10	II	13
5	IIIa	28	II	10
6	I	15	-	11
7	I	10	-	31
8	-	9	IIIb	33
9	IIIb	53	I	10

* Dindo D, Demartines N, Clavien P-A. Classification of Surgical Complications: A New Proposal With Evaluation in a Cohort of 6,336 Patients and Results of a Survey. *Ann Surg.* 2004; 240: 205–213.

Table 2. Patients undergoing reversed treatment

Case	Age	Sex	TNM	Localization primary tumor	Number of liver mets	Chemotherapy regimen	Tumor response / No of chemotherapy cycles before radiological assessment / Method	PVE prior liver surgery	Time interval between PVE and liver surgery (months)	Liver surgery / time interval after Chemotherapy in months	Colorectal surgery / time interval after liver resection (months)	Recurrence Localization / time interval after last liver surgery (months)	Long-term survival (months after primary diagnosis)	hospital stay for liver and colorectal surgery (days)
1	77	M	pT4 pN2 M1	Colon	6	Folfox 5 cycles / Avastin 3 cycles	Yes / 3 / CT	No	-	Left hemihep + metastasectomy / 1	Enlarged right hemicolectomy / 3	Liver / 2	16	52
2	52	M	pT3 pN1 M1	Colon and rectum	3	OCFL-BC 2 cycles	Yes / 2 / CT, MRI	No	-	Left lobectomy / 1	Left hemicolectomy / 1,5	Rectum / 16	27	14
3	46	F	pT3 pN0 M1	Colon	22	OCFL-BC 3,5 cycles	Yes / 2 / CT	No	-	Left lobectomy, Metastasectomies, RFA / 1	Left hemicolectomy / 1,5	Liver / 12	28	26
4	62	M	PT3 PN1 M1	Rectum	10	OCFL 8 cycles	Yes / 2 / MRI	No	-	Metastasectomies / 1	Proctectomy / 2	Liver / 2	24	23
5	71	M	pT3 pN0 M1	Colon	7	Oxaliplatin and Capecitabine 6 cycles	Yes / 6 / CT, PET-CT	Yes	1	Right hemihep + Segmentectomy / 5	Sigmoidectomy / 5	-	25	38
6	66	M	ypT4 ypN2 M1	Colon	1	OCFL 10 cycles	Yes / 2 / CT, MRI	Yes	1	Right hemihep + part Segmentectomy / 1	Right hemicolectomy (emergency surgery) / 1	Liver / 3	15	26
7	70	F	ypT1 pN0 M1	Rectum	1	OCFL 8 cycles	Yes / 3 / CT, MRI	No	-	Left hemihep + Segmentectomy / 1	Ultra-low anterior resection / 3,5	-	17	41
8	64	M	cT3 cNx M1	Colon and rectum	7	OCFL-BC 3 cycles	Yes / 3 / CT	Yes	5	Right hemihep / 1	Low anterior resection / 1	Liver / 8	37	42
9	57	M	ypT3 ypN2 M1	Colon	6	Folfox-4 / Avastin 6 cycles	Yes / 6 / MRI	No	-	Segmentectomy + metastasectomies and complementary left hemihep (2nd OP) / 1,5	Sigmoidectomy + anterior rectal resection / 2	Liver / 19	33	63

Postoperative treatment

Postoperatively, 2 to 8 cycles of chemotherapy were given to complete the oncological treatment. Two patients did not get complementary chemotherapy due to prolonged malnutrition. Two patients received 2 to 8 cycles of FOLFOX regimen, one had 12 cycles of FOLFOX-4/ bevacizumab and bevacizumab alone for 10 months, two had 2 cycles of OCFL-BC, one had a therapy with capecitabine alone and one received capecitabine alone followed by 2 cycles of FOLFOX.

Additional pelvic radiotherapy was given to two patients with rectal primary tumors. The first patient received five times 25 Gy (5x5 Gy) and the second one received 50 Gy (25x2 Gy).

Colorectal surgery

With a median time interval of two months (range 1 – 5 months) after liver surgery, all patients underwent surgical resection of the primary tumor. Two patients underwent left hemicolectomy, one had enlarged right hemicolectomy associated with metastasectomies of the liver, closure of ileostomy and draining of an abdominal abscess, two had low anterior resection, one had low anterior resection with sigmoidectomy, one had sigmoidectomy, and one had proctectomy. The last patient underwent an emergency right hemicolectomy since he presented subileus caused by an occluding colonic tumor.

Postoperatively, five patients presented complications. One presented a subileus, while another patient developed a partial hepatic failure. A third patient presented a bacteriemia with gram negative germs, which needed a treatment with antibiotics and developed an acute coronary syndrome. A patient benefited from metastasectomies at the same time as the colorectal surgery and developed perihepatic fluid collections, which had to be drained under CT-Scan control twice.

The fifth patient developed a fibrino-biliary peritonitis caused by a small bowel perforation. He underwent emergency laparotomy with a segmental ileum resection of 10 cm. There was no intraoperative or postoperative death. Median hospital stay was 11 days (range 6 – 33 days).

Length of hospital stay

Median overall hospital stay in this study was 38 days (range 14 - 63 days), with a median of 15 days (range 8 – 53 days) for liver resection and a median of 11 days (range 6 – 33 days) for colorectal tumor excision. Length of hospital stay was mostly influenced by postoperative complications.

Recurrence

Recurrence of tumor was encountered in seven patients after a median time interval of 7 months (range 0 – 17 months) after colorectal surgery. Six patients had recurrence in the liver, while the seventh one had new polyps in the caecum and ascending colon. The patient with polyp recurrences was treated with polyp excision. Since he presented several recurrences, a research for DNA mutations was made and showed mutations of the DNA mismatch repair genes (hMLH-1, hMSH-2, hMSH-6, hPMS-2). Hence, he was found to have microsatellite instability.

For the six patients with hepatic recurrence, different treatment regimens were used. All patients got chemotherapy, five of them with curative intent. Two patients were additionally treated with RFA combined with hepatic resection. One patient had stereotaxical radiotherapy followed by RFA and one had liver resection only. One patient died with disease progression and another was transferred in a palliative approach by progressive disease under treatment. Three patients with hepatic relapse were in May 2011 alive without evidence of new liver metastases.

Survival

The last follow-up of patients was made in May 2011. The patient's oncologists were consulted if no recent document was found in the CHUV database. Two patients died, both at 9 months after colorectal surgery, one from upper and lower gastrointestinal bleeding, the other from denutrition in a context of global drop in general health. Overall survival for those two patients was respectively 17 and 15 months. Median follow-up was 25 months (range 15 – 37 months). At this time, seven from nine patients are still alive after a median period of 27 months (range 17 – 37 months). The median disease-free survival was 9 months (range 0 – 17 months). Two patients did not show recurrence yet.

Discussion

In this study, we evaluated our first results of the reversed treatment of synchronous colorectal liver metastases, starting by chemotherapy, undergoing liver resection then and processing colorectal surgery at last. Several arguments support this reversed treatment sequence.

First, new chemotherapeutics combinations, including agents such as cetuximab (Erbitux®, anti-EGFR monoclonal antibody) and bevacizumab (Avastin®, anti-Angiogenesis monoclonal antibody), show a response rate up to 70%.[10, 11] This encourages to start with medication targeting both liver metastases and primary colorectal tumor as a first step in the treatment sequence. Theoretically, delayed surgery could lead to disease progression of so far resectable liver metastases, thus turning them into non-resectable lesions with bad prognosis. In this study, this problem was not encountered, and all patients underwent liver resection. This finding is in accordance to the current evidence in the literature that covered by systemic treatment, surgery can be safely delayed.[12]

New chemotherapy agents have more specific targets and are therefore generally better tolerated.[10] In this study, several patients encountered drug-related complications, sometimes requiring to postpone the treatment, but chemotherapy was globally well tolerated and all subjects could benefit from a complete treatment. Only one patient had to interrupt the treatment because of an anaphylactic reaction. After a switch in the regimen, he could complete chemotherapeutic treatment without further severe complication.

Response to chemotherapy is a prognostic factor for survival. Patients with disease progression under chemotherapy show higher recurrence rates and lower survival rates than those with controlled or regressive disease.[13,14,15] Identifying patients with responsive disease and those with progressive disease under chemotherapy is then crucial. Thereby, the latter patients group with its poor

prognosis can avoid undergoing unnecessary major surgery, but benefit from a palliative approach.

Patients with initially unresectable liver metastases can benefit from a downstaging of the metastases, and will become eligible for a curative approach. Symptoms associated to the primary tumor can also be diminished trough systemic treatment since downsizing of the primary tumor will relieve luminal obstruction and compression syndromes. E.g., one patient in our series presented occlusion of the sigmoid colon which had to be stented. During neoadjuvant chemotherapy, luminal obstruction completely disappeared, and he spontaneously expulsed the stent.

Resection of liver metastasis prior to colorectal surgery avoids delayed hepatic tumor excision in case of complications after colorectal surgery, as it would happen in the standard treatment sequence. Neoadjuvant chemotherapy was somewhat controversial due to the potential drug-induced liver injury. Chemotherapy-associated parenchymal damage include: vascular modifications (sinusoidal dilatation and sinusoidal obstruction syndrome) and chemotherapy-associated steatohepatitis (CASH).[16] In our study, histological examination of the resected liver specimens revealed two patients with sinusoidal dilatation but no sinusoidal obstruction syndrome, and six patients with minor CASH. None of them developed clinically relevant liver dysfunction.

In case of rectal primary tumor, the reversed strategy allows to perform preoperative radiotherapy of the rectum before excision of the primary tumor. Thereby, it avoids postponing radiotherapy if complications of rectum surgery are encountered. Preoperative rectal radiotherapy has shown better results than postoperative radiotherapy. In fact, preoperative radiotherapy is associated with reduced toxicity, less local relapse, and improvement of disease-free survival.[17,18,19] In this study, two patients had preoperative radiotherapy of the rectum that was well tolerated.

In this preliminary experience, seven out of nine patients could undergo the whole treatment. Those seven patients are still alive after a median period of 27 months. Two of them did not show recurrence of disease yet. Among the four

patients with liver recurrence who benefited from a treatment of the relapse, three are alive with no evidence of further liver metastases. The median disease-free survival was 9 months. This shows that even with an aggressive treatment, synchronous CRLM still remain a complex disease which needs a multidisciplinary approach. Thanks to the new advances in surgical techniques, oncological treatments and radiofrequency, we are able nowadays to offer to some patients with stage IV colorectal cancer a curative approach. Nevertheless, in a greater part of them, all treatments remain palliative.

Conclusion

Due to the small number of patients included in this study, no definitive conclusion can be made on this basis. However, it seems that this reversed strategy is a valuable alternative to classic treatment for stage IV colorectal cancer with liver synchronous metastases in well selected patients. Results are encouraging but to better evaluate this new treatment modality, larger multicentric studies are needed.

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