ORIGINAL CONTRIBUTION

Long-term Results of the "Liver First" Approach in Patients With Locally Advanced Rectal Cancer and Synchronous Liver Metastases

Ninos Ayez, M.D.[1] • Jacobus W. A. Burger, M.D., Ph.D.[1] • Anne E. van der Pool, M.D., Ph.D.[1]
Alexander M. M. Eggermont, M.D., Ph.D.[2] • Dirk J. Grunhagen, M.D., Ph.D.[1]
Johannes H. W. de Wilt, M.D., Ph.D.[3] • Cornelis Verhoef, M.D., Ph.D.[1]

1 Division of Surgical Oncology, Erasmus MC, Daniel den Hoed Cancer Centre, Rotterdam, The Netherlands
2 Institut de Cancérologie Gustav Roussy, Villejuif, France
3 Division of Surgical Oncology, Radboud University Medical Centre, Nijmegen, The Netherlands

BACKGROUND: There are no reports available on the long-term outcome of patients with the "liver first" approach.

OBJECTIVES: The aim of this study was to present the long-term results of the "liver first" approach in our center.

DESIGN: This study is a retrospective analysis.

SETTING: This study was conducted at a tertiary referral center.

PATIENTS: Patients from May 2003 to March 2009 were included.

INTERVENTIONS: Patients with locally advanced rectal cancer and synchronous liver metastases were first treated for their liver metastases. If the treatment was successful, patients underwent neoadjuvant chemoradiotherapy and surgery for the rectal cancer. If metastases could not be resected, resection of the rectal primary was not routinely performed.

MAIN OUTCOME MEASURES: The primary outcome measured was long-term results of the "liver first" approach.

RESULTS: Of the 42 patients included (median age, 61 years), all but one (98%) started with neoadjuvant chemotherapy. In total, 31 (74%) patients completed the "liver first" approach. In 11 patients, curative therapy was not possible because of unresectable metastases; in 10 of these patients (91%), the primary tumor was not resected.

LIMITATIONS: This study was limited because it was a retrospective analysis without a control group.

CONCLUSIONS: By applying the "liver first" approach, the majority of this group of patients (74%) could undergo curative treatment of both metastatic and primary disease in combination with optimal neoadjuvant therapy. This strategy may avoid unnecessary rectal surgery in patients with incurable metastatic disease. In this selected patient group, long-term survival may be achieved with a 5-year survival rate of 67%.

KEY WORDS: Locally advanced rectal cancer; Liver metastases; Liver first approach.

Liver resection is the standard for curative therapy of colorectal liver metastases. Treatment of patients with advanced rectal cancer and synchronous liver metastases differs from patients with colon cancer and synchronous liver metastases, because rectal cancer often requires long-course neoadjuvant radiotherapy to reduce local recurrence rates.[1,2] Long-course chemoradiotherapy usually takes about 5 weeks to complete; 6 to 10 weeks after the last day of radiotherapy, patients undergo rectal surgery. If no complications occur, synchronous liver metastases will traditionally be treated as early as 3 months after rectal surgery. However, complications following rectal surgery are common and often delay adequate therapy. In a prospective randomized controlled trial Sauer et al[3] demonstrated that up to 50% of patients do not receive optimal treatment after rectal surgery because of postoperative complications.

Financial Disclosures: None reported.

Correspondence: Cornelis Verhoef, M.D., Ph.D., Department of Surgical Oncology, Erasmus MC (Daniel den Hoed), Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands. E-mail: c.verhoef@erasmusmc.nl

Dis Colon Rectum 2013; 56: 281–287
DOI: 10.1097/DCR.0b013e318279b743

One way to overcome this problem is to start with neoadjuvant radiotherapy (with or without chemotherapy) followed by the combination of rectal and liver surgery. Although this approach has the advantage of a single operation, combining (extended) pelvic surgery with liver surgery might increase morbidity and mortality.[4–6] As a consequence, the advantage of the 1-stage approach in patients with synchronous liver metastases is far from proven in patients with rectal cancer.[7]

Mentha et al[8] have described the "liver first" approach in patients with colon and rectal cancer who have advanced synchronous liver metastases. However, we carry out the "liver first" approach in patients with locally advanced rectal cancer and synchronous liver metastases. This "liver first" approach facilitates optimal treatment of the liver metastases and adequate neoadjuvant treatment for the primary tumor. Initial results from our center have been published[6]; this study reports on a larger group of patients with a long-term follow-up.

PATIENTS AND METHODS

All consecutive patients at our center from May 2003 until March 2009 with locally advanced rectal cancer and synchronous liver metastases were treated with this protocol. All included patients had a potential minimal follow-up of 2 years.

The treatment protocol has been described previously, and those patients (n = 23) are also included in this study.[6] In summary, patients were primarily treated with systemic neoadjuvant chemotherapy. If there was no progressive disease, a laparotomy was performed with the intention to perform a resection of the liver metastases. After successful resection of liver metastases, patients were treated with neoadjuvant radiotherapy (with or without chemotherapy) for the primary rectal tumor. Four weeks after the end of neoadjuvant radiotherapy, a CT scan of the thorax and abdomen and pelvic MRI were performed. If there were no unresectable metastases, rectal resection was performed 8 to 10 weeks after the last radiotherapy dose. Resectability of metastases was defined as the presence of technically removable metastases (preserving at least 2 segments of the liver parenchyma), and the possibility of an oncological radical procedure. If this was not technically possible, metastases were defined as unresectable. None of the patients received adjuvant chemotherapy.

Neoadjuvant Chemotherapy and Response

The response to neoadjuvant chemotherapy was assessed after 2 or 3 cycles by CT scan and CEA levels. When further courses were administered, a CT scan was performed after the final course. In the neoadjuvant setting, we prefer a limited number of chemotherapy cycles (≤6) to prevent increased morbidity and mortality after liver surgery.[9,10] When the multidisciplinary tumor board deemed the liver metastases resectable based on response and extent of the disease, patients were scheduled for liver surgery. Liver surgery was performed at least 3 weeks after the last course of systemic neoadjuvant chemotherapy. Bevacizumab was excluded from the last course of chemotherapy to ensure an interval of at least 6 weeks between administration of bevacizumab and surgery.

Liver Resection

Liver resection was performed through a right subcostal incision. The abdomen was thoroughly inspected and palpated to detect extrahepatic metastasis or second primary tumors. The liver was mobilized, inspected, palpated, and examined by intraoperative ultrasonography when indicated. The hepatoduodenal ligament was palpated and, in the case of palpable nodes, a radical lymph node dissection of the ligament was performed. Segmental resections were based on the segmental anatomy as described by Couinaud.[11] All hepatectomies were performed with a curative intent (ie, with a tumor-free hepatic resection margin status). In our clinic, the first CT scan is a roadmap for further surgery. This means that, in case of a clinically complete response on the CT scan, all known metastases were resected routinely.

The pathology findings were defined as follows: complete response (CR) was defined as the absence of vital tumor tissue, partial response (PR) was defined as the presence of vital tumor cells and necrosis, and stable disease (SD) was defined as vital tumor cells and no necrosis.

Chemoradiation and Rectal Surgery

If liver resection was successful, patients received neoadjuvant radiotherapy (with or without chemotherapy) for their locally advanced rectal cancer. In our center, locally advanced rectal cancer is defined as a histologically proven adenocarcinoma with one of the following characteristics: tumor >5 cm at colonoscopy and MRI (clinically large T3); clinically fixed tumor or with ingrowth in adjacent organ on MRI (T4); N+ tumor (lymph node >8 mm and/or >4 nodes >5 mm on CT scan or MRI). Regardless of size criteria, any lymph node depicted on MRI with an irregular border or mixed signal intensity was considered a positive node. T4 tumors, but also advanced T3 tumors with a close relation to the circumferential margin, were considered locally advanced rectal cancer.

Patients were treated with a long-course radiotherapy, ie, 45 to 50 Gy (in fractions of 1.8–2 Gy) with or without chemotherapy (capecitabine 825 mg/m^2 twice a day on radiotherapy days). Radiotherapy was followed by surgery with a delay of 6 to 10 weeks. Intraoperative radiotherapy was applied if the distance to the circumferential resection margin was <2 mm.[12] No laparoscopic resections were performed.

Follow-up

Follow-up was performed at the outpatient clinic and consisted of endoscopic surveillance after 1 year, and abdominal CT or ultrasonography and serum CEA every 3 months during the first year, every 6 months during the second year, and once a year thereafter. Progression-free survival (PFS) was calculated from the start of neoadjuvant chemotherapy until local recurrence, new metastases, or the date of last follow-up without progression. Overall survival (OS) was calculated from the start of treatment until death or the date of the last follow-up.

Statistics

Descriptive statistics are expressed as median (range). Survival analysis was performed by the Kaplan-Meier method. The SPSS statistical package (version 17.0, IBM SPSS Statistics, IBM Corporation, Armonk, NY) was used for statistical analysis and a p value of ≤ 0.05 was considered statistically significant.

RESULTS

Patients between May 2003 and March 2009, 42 consecutive patients with locally advanced rectal cancer and synchronous liver metastases were treated and included in this analysis. Table 1 presents the patient characteristics.

TABLE 1. Data on the 42 patients and their tumor characteristics

	Value (%)/median (range)
Male	33 (79)
Age (in years)	61 (42–78)
Clinical risk score	
Low (0–2)	22 (52)
0	0 (0)
1	4 (10)
2	18 (43)
High (3–5)	20 (48)
3	14 (33)
4	5 (12)
5	1 (2)
Liver metastases (preoperative)	
Diameter, cm	2.7 (1–13)
Number of metastases	4 (1–12)
Bilobar	22 (52)
Extrahepatic	4 (10)
CEA, μg/L	41 (1–5315)
Primary tumor (pathology)	
CR	8 (25)
T1	1 (3)
T2	3 (9)
T3	18 (56)
T4	2 (65)
N+	11 (34)
N1	4 (13)
N2	7 (22)

N+ = positive lymph nodes.

Neoadjuvant Chemotherapy

A flow diagram of the treatment of all 42 patients is given in Figure 1.

One patient underwent liver metastasis resection without neoadjuvant chemotherapy. Forty-one patients were treated with a median of 5 (2–26) cycles of neoadjuvant chemotherapy. Thirty-six patients received a FOLFOX/CAPOX regimen, of whom 18 patients received concomitant bevacizumab. Four patients received leucovorin and 5-fluorouracil plus irinotecan, all with bevacizumab. One patient received capecitabine and bevacizumab. The majority of patients were treated with the intention of the "liver first" approach (37/42 patients, 88%). Five patients were primarily treated with palliative systemic chemotherapy. These 5 patients received >10 cycles of chemotherapy and were then referred to our hospital.

Liver Metastases

None of the patients were considered irresectable. Based on the CT scan after chemotherapy, the metastases disappeared in 2 patients, 31 patients had a PR, and 8 patients had SD. Laparotomy was performed after a median interval of 6 (0–15) weeks after the last chemotherapy course. Forty-one patients underwent a laparotomy for partial liver resection with curative intent (Fig. 1). At laparotomy, 1 patient was diagnosed with unexpected extensive disease of the liver on intraoperative ultrasound and did not undergo liver resection. Four patients underwent an intended 2-stage liver resection, and 36 patients underwent a 1-stage curative liver resection for liver metastases (Table 2).

Median hospital stay was 7 (3–19) days. Minor postoperative complications were observed in 10 patients (5 patients Dindo I, 5 patients Dindo II).[13]

Histopathological evaluation demonstrated a CR in 3 patients, a PR in 37 patients, and SD in 1 patient. Of the 4 patients scheduled for a 2-stage liver resection, the pathologist reported a PR in all 4 patients after the first resection. Owing to metastatic progression, only 1 of the 4 patients completed the second-stage resection, after which histopathology showed a PR.

On histological examination, 6/38 (16%) patients had an R1 resection of the rectal liver metastases (ie, the presence of microscopic tumor invasion in the resection margin) of whom 3 also had intraoperative radiofrequency ablation.

Rectal Cancer

After successful resection of the metastases (n = 37), patients received neoadjuvant radiotherapy for the rectal cancer (Fig. 1). Thirty-five patients received a long course of radiation therapy (total dose of 50 Gy or a biologically equivalent dose); 30 of these patients received radiation therapy in combination with chemotherapy (capecitabine) followed by an interval of 8 (5–13) weeks before resection

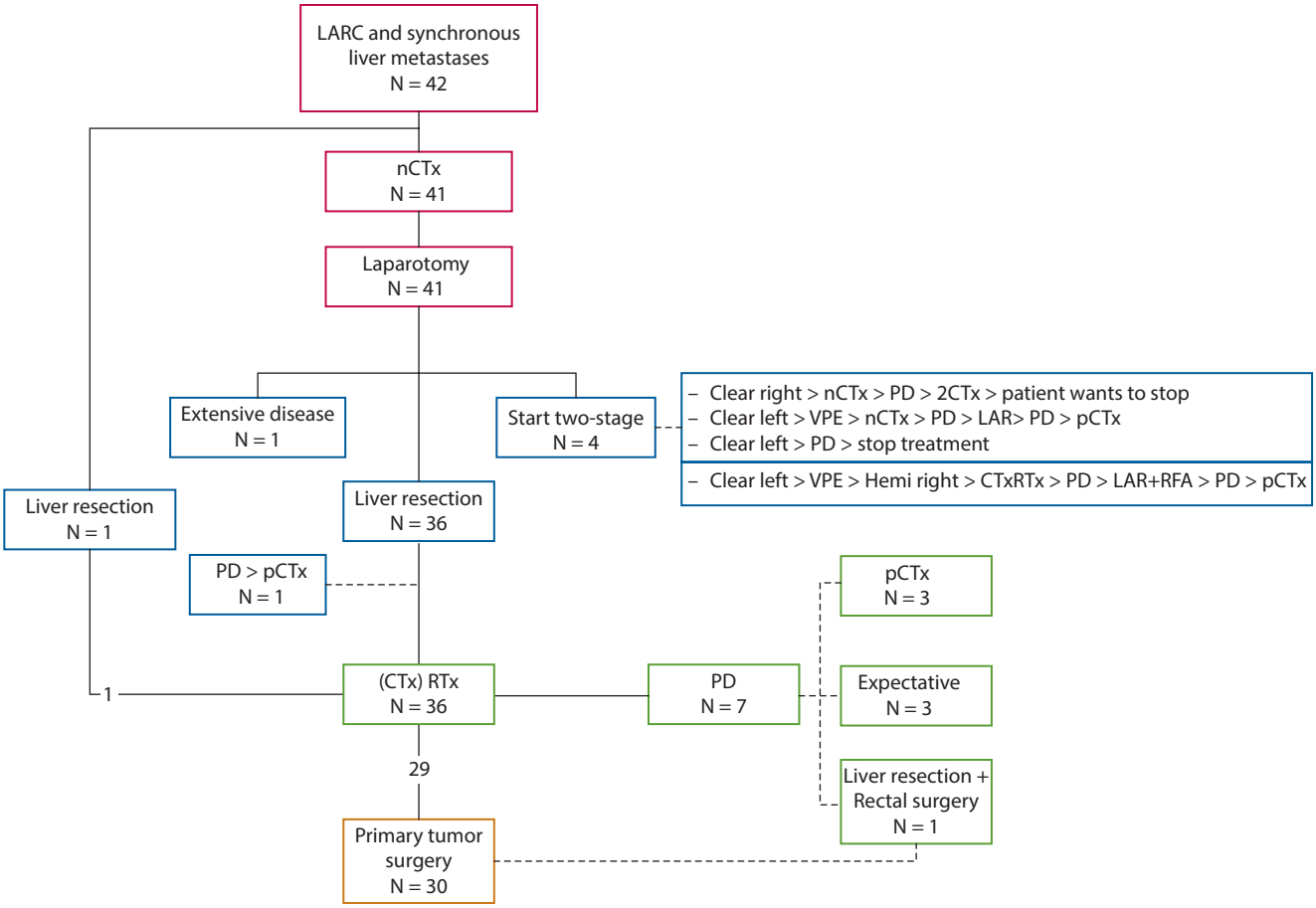

FIGURE 1. Flow diagram of the 42 study patients. CTx = chemotherapy; CTxRTx = chemoradiation therapy; pCTx = palliative chemotherapy; nCTx = neoadjuvant chemotherapy; 2CTx = second-line chemotherapy; FU = follow-up; LARC = locally advanced rectum carcinoma; LAR = low anterior resection; RFA = radiofrequency ablation; PD = progressive disease; POD = postoperative death; VPE = vena porta embolization.

TABLE 2. Surgical procedures in patients with liver metastases

Type of surgery	*No. of patients*
Liver surgery	
Two-stage resections	4
Extra-anatomic resection	13
Extra-anatomic resection + RFA	5
Left hemihepatectomy + RFA	3
Left hemihepatectomy + extra-anatomic	1
Left hemihepatectomy + extra-anatomic + RFA	1
Right hemihepatectomy	7
Right hemihepatectomy + extra-anatomic	6
Right hemihepatectomy + RFA	1
No resection	1
Primary tumor surgery	
Subtotal colectomy	1
LAR	20
APR	10
TEM	1
No operation	10

RFA = radiofrequency ablation; LAR = low anterior resection; APR = abdominoperineal resection; TEM = transanal endoscopic microsurgery.

of the rectal cancer. Two patients received a short course of radiation (5 × 5 Gy); one with an interval of 3 days and one with an interval of 10 weeks before resection.

Eleven (26%) patients developed unresectable metastatic disease before rectal surgery, and 31 (74%) patients completed the "liver first" protocol, ie, complete resection of the metastases and the primary tumor. Tables 2 presents the characteristics of the liver and rectal surgery performed. Median hospital stay after rectal surgery was 8 (4–14) days. Postoperative complications were observed in 7 patients: 2 Dindo I, 4 Dindo II, and 1 Dindo IIIa.[13] Pathological examination of the rectum revealed microscopically positive margins in 2 patients; these patients were treated with intraoperative radiotherapy because frozen sections were performed during surgery. Eight patients (25% of resected patients) had a CR. The 3 patients who had a histological CR of liver metastases also had a histological CR of the primary tumor. Two patients with a PR of liver metastases, described as mostly necrosis and minimal vital tumor cells, had a CR of the primary tumor. Of the 15 patients who had a mixed response of

the liver metastases (necrosis and vital tumor cells), 3 had a CR of the rectal cancer.

In 10 of the 11 patients (91%) in whom new or progressive unresectable metastases were diagnosed, resection of the primary tumor was not performed. Five patients had progressive disease before the start of radiotherapy, and radiotherapy was subsequently cancelled. Six patients were progressive after neoadjuvant chemoradiotherapy.

In one of these 11 patients, rectal resection was performed during follow-up because of severe symptoms caused by the primary tumor. Three further patients developed symptoms of pain and fullness that could be managed with pain medication. Five patients received a diverting ileostomy or colostomy to prevent obstruction caused by the rectal tumor; 2 before neoadjuvant chemotherapy, 2 concomitant with the liver resection, and 1 patient after chemoradiotherapy. The overall survival of these 11 patients was 18 (95% CI: 13–23) months.

Follow-up

All patients had a minimal follow-up of 2 years unless death occurred earlier.

Median length of follow-up was 30.5 (10–91) months. The PFS for the total group was 14 months (95% CI: 9–19), with a 1-, 3-, and 5-year PFS of 62%, 36%, and 32%. Median OS for the total group was 49 (95% CI: 34–64) months, with a 1-, 3-, and 5-year survival rate of 98%, 60% and 43% (Fig. 2).

Median follow-up of the 31 patients who completed the "liver first" protocol was 39 (16–91) months. Median time to progression was 19 (95% CI: 7–31) months, with a 1-, 3-, and 5-year PFS of 74%, 45%, and 40%. The median OS in this group was 69 (95% CI: 30–108) months, with a 1-, 3-, and 5-year OS rate of 100%, 79%, and 67% (Fig. 2).

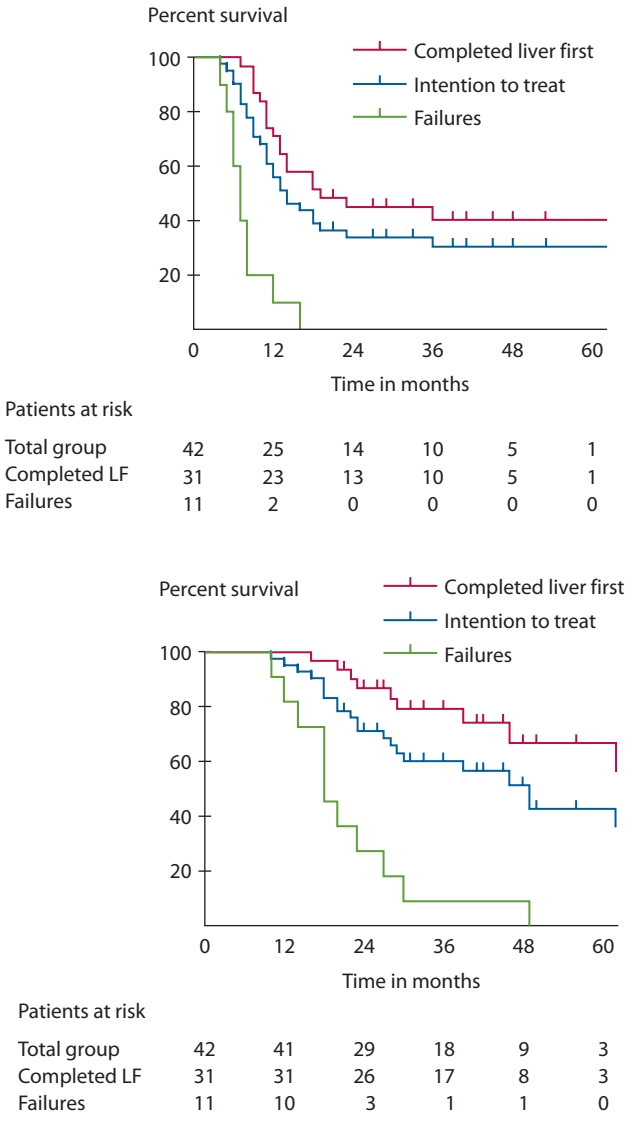

FIGURE 2. Data on progression-free survival and overall survival. LF = liver first.

DISCUSSION

This study reports on the largest series of patients to date with locally advanced rectal cancer and synchronous liver metastases who underwent the "liver first" approach. The results show that, in this selected group of patients, the majority (74%) could undergo optimal neoadjuvant treatment of both liver metastases and rectal cancer, followed by curative resection of both liver metastases and rectal cancer. Of the 11 patients with unresectable metastatic disease, 10 (91%) did not need rectal surgery.

The first report on the "liver first" approach was described by Mentha et al[14] demonstrating the safety of this procedure. Brouquet et al[15] described the "liver first" approach and demonstrated that it is associated with similar outcomes as the classical approach. de Jong et al described their 5-year experience with the "liver first" approach and found that it was feasible in approximately four-fifths of their patients.[16] All of these studies have described the "liver first" approach in patients with colon and rectal cancer who have advanced synchronous liver metastases.

A strength of the present study is that all patients had a locally advanced rectal primary tumore with synchronous liver metastases. The common denominator of the locally advanced rectal primary tumor makes this series unique. Another difference between the present study and the current literature is that patients were only included if they had a potential follow-up ≥2 years.

Some consider resection of the primary tumor to be indicated when the primary tumor is symptomatic.[17] However, resection does not provide immediate palliative benefit in case of an asymptomatic primary, and is associated with a high mortality (6%–10%) and morbidity (20%–25%) in patients with metastatic disease.[17–20] Recent

reviews by Venderbosch et al[21] and Verhoef et al[22] suggest a survival benefit in patients who underwent resection of the primary tumor; however, randomized studies are still lacking. In a review, Poulsides et al[23] demonstrated that, in patients with unresectable metastatic disease, resection of the primary tumor is not warranted, because almost 14 asymptomatic patients need to undergo prophylactic resection of their primary tumor to save 1 patient from a subsequent operation for obstruction or perforation. In our series of 11 patients with locally advanced rectal cancer and a high metastatic tumor burden, none of these patients underwent a prophylactic resection of the primary tumor. In 1 patient, secondary resection was necessary at a later stage because of symptoms caused by the primary rectal tumor. Five patients with unresected rectal cancer received a diverting ileostomy or colostomy to prevent obstruction caused by the rectal tumor, even though the primary tumor was still resectable. Two patients received a diverting stoma before neoadjuvant chemotherapy, 2 concomitant with the liver resection and 1 patient after chemoradiotherapy. One may argue that several or all of the stomas could have been avoided had a rectum first approach been chosen. In these specific cases, the disadvantages of a rectal resection (with the associated morbidity and mortality) have to be balanced against those of stoma construction.

Despite these strengths, a limitation of our study is that it is a retrospective analysis of selected patients in a single institute. The referral selection bias and the absence of a control group are limitations that need to be considered. A concern regarding the "liver first" approach is nonresponse to chemotherapy or progression after initial response in patients who present with resectable disease. Another possible concern regarding the "liver first" approach is that the primary tumor may progress beyond resection. This did not occur in our series, nor has it been described in the mentioned series.[8,14–16] Even in the patients with progressive extra hepatic metastases, the primary tumor did not progress into adjacent structures. In contrast, in the case of an excellent response to chemotherapy, vanishing metastases may be a concern because the risk of regrowth is high.[24] Regular imaging after 2 or 3 cycles of chemotherapy is warranted to minimize the risk on vanishing metastases and/or progression beyond resection of the primary tumor.

In the present series, we found 16% R1 resections after neoadjuvant chemotherapy, which might be a concern. In the era of parenchyma-saving surgery, 16% R1 resections is within the range reported in the literature. In several large series, the reported R1 was 8% to 24%.[15,25–28] Two independent studies demonstrated that, in the era of modern chemotherapy, patients with an R1 resection and chemotherapy perform equally to patients with an R0 resection.[27,29]

Three patients who had a histological CR of liver metastases also had a histological CR of the primary tumor after additional neoadjuvant chemoradiotherapy. Two patients, in whom the liver metastases were described as mostly necrotic with minimal focal vital cells remaining (PR), also had a CR of the primary tumor. It seems that in patients with a CR or a near CR (near total necrosis) of the liver, these patients are likely to have a CR of the rectal primary tumor as well, albeit after neoadjuvant chemoradiotherapy. In such cases, resection of the primary tumor may be limited to local excision (transanal excision or transanal endoscopic microsurgery) or even watchful waiting. However, prospective studies are needed to justify such a strategy.

CONCLUSION

In this group of patients, the "liver first" strategy resulted in curative resection of both liver metastases and locally advanced rectal cancer in 74% of selected patients. Moreover, all patients received optimal treatment for both liver metastases and rectal cancer. In patients in whom progressive disease precluded curative rectal surgery, palliative rectal surgery was not necessary in 10 of 11 patients. Thereby, unnecessary morbidity, mortality, and delay of palliative chemotherapy could be avoided.

REFERENCES

1. Gérard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. *J Clin Oncol.* 2006;24:4620–4625.
2. Bosset JF, Collette L, Calais G, et al; EORTC Radiotherapy Group Trial 22921. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med.* 2006;355:1114–1123.
3. Sauer R, Becker H, Hohenberger W, et al; German Rectal Cancer Study Group. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med.* 2004;351:1731–1740.
4. Vermaas M, Ferenschild FT, Hofer SO, Verhoef C, Eggermont AM, de Wilt JH. Primary and secondary reconstruction after surgery of the irradiated pelvis using a gracilis muscle flap transposition. *Eur J Surg Oncol.* 2005;31:1000–1005.
5. Vermaas M, Ferenschild FT, Verhoef C, et al. Total pelvic exenteration for primary locally advanced and locally recurrent rectal cancer. *Eur J Surg Oncol.* 2007;33:452–458.
6. Verhoef C, van der Pool AE, Nuyttens JJ, Planting AS, Eggermont AM, de Wilt JH. The "liver-first approach" for patients with locally advanced rectal cancer and synchronous liver metastases. *Dis Colon Rectum.* 2009;52:23–30.
7. Adam R. Colorectal cancer with synchronous liver metastases. *Br J Surg.* 2007;94:129–131.
8. Mentha G, Roth AD, Terraz S, et al. 'Liver first' approach in the treatment of colorectal cancer with synchronous liver metastases. *Dig Surg.* 2008;25:430–435.
9. Karoui M, Penna C, Amin-Hashem M, et al. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. *Ann Surg.* 2006;243:1–7.

10. Allen PJ, Kemeny N, Jarnagin W, DeMatteo R, Blumgart L, Fong Y. Importance of response to neoadjuvant chemotherapy in patients undergoing resection of synchronous colorectal liver metastases. *J Gastrointest Surg.* 2003;7:109–117.
11. Couinaud C. Liver anatomy: portal (and suprahepatic) or biliary segmentation. *Dig Surg.* 1999;16:459–467.
12. Ferenschild FT, Vermaas M, Nuyttens JJ, et al. Value of intraoperative radiotherapy in locally advanced rectal cancer. *Dis Colon Rectum.* 2006;49:1257–1265.
13. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* 2004;240:205–213.
14. Mentha G, Majno PE, Andres A, Rubbia-Brandt L, Morel P, Roth AD. Neoadjuvant chemotherapy and resection of advanced synchronous liver metastases before treatment of the colorectal primary. *Br J Surg.* 2006;93:872–878.
15. Brouquet A, Mortenson MM, Vauthey JN, et al. Surgical strategies for synchronous colorectal liver metastases in 156 consecutive patients: classic, combined or reverse strategy? *J Am Coll Surg.* 2010;210:934–941.
16. de Jong MC, van Dam RM, Maas M, et al. The liver-first approach for synchronous colorectal liver metastasis: a 5-year single-centre experience. *HPB (Oxford).* 2011;13:745–752.
17. Stillwell AP, Buettner PG, Ho YH. Meta-analysis of survival of patients with stage IV colorectal cancer managed with surgical resection versus chemotherapy alone. *World J Surg.* 2010;34:797–807.
18. Mäkelä J, Haukipuro K, Laitinen S, Kairaluoma MI. Palliative operations for colorectal cancer. *Dis Colon Rectum.* 1990;33:846–850.
19. Law WL, Chan WF, Lee YM, Chu KW. Non-curative surgery for colorectal cancer: critical appraisal of outcomes. *Int J Colorectal Dis.* 2004;19:197–202.
20. Rosen SA, Buell JF, Yoshida A, et al. Initial presentation with stage IV colorectal cancer: how aggressive should we be? *Arch Surg.* 2000;135:530-534.
21. Venderbosch S, de Wilt JH, Teerenstra S, et al. Prognostic value of resection of primary tumor in patients with stage IV colorectal cancer: retrospective analysis of two randomized studies and a review of the literature. *Ann Surg Oncol.* 2011;18:3252–3260.
22. Verhoef C, de Wilt JH, Burger JW, Verheul HM, Koopman M. Surgery of the primary in stage IV colorectal cancer with unresectable metastases. *Eur J Cancer.* 2011;47(suppl 3):S61–S66.
23. Poultsides GA, Paty PB. Reassessing the need for primary tumor surgery in unresectable metastatic colorectal cancer: overview and perspective. *Ther Adv Med Oncol.* 2011;3:35–42.
24. Benoist S, Brouquet A, Penna C, et al. Complete response of colorectal liver metastases after chemotherapy: does it mean cure? *J Clin Oncol.* 2006;24:3939–3945.
25. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg.* 1999;230:309–318.
26. Pawlik TM, Scoggins CR, Zorzi D, et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. *Ann Surg.* 2005;241:715–722.
27. de Haas RJ, Wicherts DA, Flores E, Azoulay D, Castaing D, Adam R. R1 resection by necessity for colorectal liver metastases: is it still a contraindication to surgery? *Ann Surg.* 2008;248:626–637.
28. Tanaka K, Nojiri K, Kumamoto T, Takeda K, Endo I. R1 resection for aggressive or advanced colorectal liver metastases is justified in combination with effective prehepatectomy chemotherapy. *Eur J Surg Oncol.* 2011;37:336–343.
29. Ayez N, Lalmahomed ZS, Eggermont AM, et al. Outcome of microscopic incomplete resection (R1) of colorectal liver metastases in the era of neoadjuvant chemotherapy. *Ann Surg Oncol.* 2012;19:1618–1627.