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Is There a Survival Benefit to Neoadjuvant Versus Adjuvant Chemotherapy, Combined with Surgery for Resectable Colorectal Liver Metastases?

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Abstract
Background The benefits of adding chemotherapy to surgery in patients with hepatic colorectal metastases at moderate and high risk for recurrence and the optimal sequence of administration are undetermined.
Methods We followed the overall-survival and event-free survival rates after operation in patients with resectable colorectal metastases confined to the liver. The adjuvant patients first underwent surgery and then treatment, whereas the neoadjuvant patients underwent treatment, surgery, and re-treatment. Assignment was by oncologist and patient preferences. Chemotherapy was oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) based.
Results Fifty-six of 105 patients who underwent liver resections for colorectal metastases (2002–2005) are included. The two groups were comparable for demographics, characteristics of disease (including recurrence risk), treatment protocols, and follow-up. The respective 1-, 2-, and 3-year overall survival rates were 91%, 91%, and 84%, and the event-free survival rates were 63%, 49%, and 49% for the 19 adjuvant patients, and 95%, 91%, and 70%, and 94%, 50%, and 50% for the 37 neoadjuvant patients.
Conclusions The midterm overall survival and disease-free survival rates in this group of patients with resectable colorectal metastases to the liver, who were treated with combination of resection and chemotherapy, were similar, regardless of the sequence of treatment.

Introduction

The liver is the most common and often the only site of distant metastases from colorectal cancer (CRC) [1] Hepatic resection is the only effective therapy for patients with CRC metastatic to the liver, and it is associated with 5-year survival rates ranging from 25% to 40% [2–5]. Between 60% and 85% of patients will, however, develop recurrent metastases after hepatic resection, indicating that they had harbored unrecognized intrahepatic or extrahepatic tumor foci at the time of liver resection [6]. These data indicate that better patient selection is needed to avoid unnecessary operations, and that there may be a role for systemic supplementary chemotherapeutic treatment in eliminating microscopic tumor foci and thereby reducing the risk of recurrence.

To date, systemic therapy has been administered mainly as adjuvant treatment, and results have been contradictory [7–9]. There have been recent improvements in the field of palliative chemotherapy of CRC with the use of new drugs, such as irinotecan, oxaliplatin, and the biological agent bevacizumab. Furthermore, it has become possible to downsize primarily unresectable tumors with systemic chemotherapy, thereby enabling secondary curative

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metastatic resection [10–12]. A neoadjuvant therapeutic approach in primarily resectable liver metastases using systemic combination regimens, especially in patients at high risk for recurrence, has been proposed by several authors [13–15]. Potential advantages of neoadjuvant over adjuvant treatment include the ability to assess response to treatment, to limit the extent of liver resection and reduce R1 resection rates, and to assess tumor biology in the therapeutic "window" during the administration of the chemotherapy, thereby improving patient selection. The disadvantages include the potential induction of chemotherapy-associated steatohepatitis and veno-occlusive changes, especially with the use of oxaliplatin, and a possible increase in perioperative morbidity and mortality.

Positron emission tomography with the glucose analog 18-fluoro-2-deoxy-D-glucose (FDG-PET) is another new and important tool in improving patient selection and long-term results after liver resection of CRC metastases. With FDG-PET performed after standard imaging, approximately 25% of patients are discovered to have new intrahepatic or extrahepatic tumors [16, 17]. Screening with FDG-PET before hepatic resection for CRC has been shown to significantly improve the survival rates of resected patients, probably by refining patient selection [18].

We report the results of a retrospective analysis of liver resection in patients with primarily resectable CRC metastases to the liver. They were all at moderate and high risk for recurrence, and all were staged with FDG-PET and received either adjuvant or neoadjuvant chemotherapy.

Patients and methods

Patients

All patients with resectable CRC liver metastases according to computerized tomographic (CT) scan also underwent FDG-PET scanning. Only those with no evidence of extrahepatic disease according to FDG-PET were included in this study. Risk of recurrence was classified according to the Memorial Sloan-Kettering Cancer Center (MSKCC) clinical score [19], with risk scores between 0 and 5. The risk factors were as follows: the number of metastases >1, carcino-embryonic antigen (CEA) level >200 ng/ml, metastases to regional lymph nodes in the primary tumor, disease-free interval <12 months, and size of largest metastasis >5 cm. Patients at moderate and high risk were defined as having ≥2 risk factors, and only moderate-risk and high-risk patients were included in this study.

There have been several modifications to the MSKCC clinical risk score by other groups of investigators [20–22] who have stressed the additional value in long-term survival of tumor grade, extrahepatic disease, positive resection margins, and perioperative morbidity. When we began our study, the MSKCC risk score was the most accepted one because it was based on a database of more than 1,000 patients who had undergone liver resection. As such, this was the clinical score we chose to use in this study.

Referral

It was our policy to offer our CRC patients with liver metastases neoadjuvant treatment with either an oxaliplatin-based or an irinotecan-based protocol, to re-stage them, and to assign them for surgery accordingly. These were the patients included in group 2 of the current study. Group 1 consisted of our patients who declined this recommendation and of others who were referred by oncologists from other hospitals for liver resection in our institution: they underwent immediate liver resection, followed by oxaliplatin-based or irinotecan-based adjuvant chemotherapy.

Staging

Before they received neoadjuvant chemotherapy, all group 2 patients underwent a triphasic contrast-enhanced CT scan, and most (62.5%) of them also underwent a FDG-PET/CT. The patients in both study groups underwent FDG-PET/CT and abdominal contrast-enhanced CT before liver surgery. The time interval between the last course of chemotherapy and the FDG-PET/CT scan was at least 4 weeks, and surgical exploration took place within one month after the FDG-PET/CT. Because we used an integrated PET/CT technique, precise anatomical localization could be achieved and confirmed with the standard triphasic abdominal CT findings.

Exclusion criteria

Fifty-six of the 105 patients who underwent liver resection for CRC metastases within the study period were suitable for inclusion. Exclusion criteria included incomplete staging (patients who did not undergo FDG-PET/CT), MSKCC clinical risk score <2, extrahepatic disease according to preoperative staging, extrahepatic disease or non-resectable liver metastases on operative exploration, history of a previous liver resection, and/or follow-up interval <12 months.

Chemotherapy

Patients were assigned to one of the two treatment regimens as part of other international multi-center studies. The applied protocols were either oxaliplatin-based

(FOLFOX 4 or 7) [23] or CPT-11 based (FOLFORI 3) [24].

Hepatectomy

All patients underwent surgical exploration and intraoperative ultrasound (IOUS). Resections of all metastatic sites were performed by either anatomic or non-anatomic resections, with a preference for maximal parenchymal preservation by non-anatomic R0 resections. Parenchymal dissection was accomplished with a Cavitron ultrasonic surgical aspirator (CUSA Selector, Integra Neurosciences, England), allowing precise non-anatomic but yet R0 resection for all of the lesions.

Complete clinical response (CCR)

Complete clinical response to neoadjuvant chemotherapy was defined as complete resolution of all metastatic sites according to the CT and PET-CT findings. Careful palpation and IOUS were performed in search of remaining tumor or scarring in these patients. When there was no evidence of either, the tumor sites were resected according to the findings on the original imaging (i.e., on the scans performed before there had been any response to neoadjuvant treatment).

Follow-up

Follow-up consisted of regular clinical visits, periodical CT scans, and lab tests for measuring tumor marker levels. Patients who had equivocal findings or an unexplained rise in their markers underwent FDG-PET/CT. Follow-up was completed in 98% of the patients. Primary endpoints were death, recurrence, or being alive with no evidence of disease. Outcome measures were event-free survival and overall survival rates. We also looked into the patterns of recurrence. Because this was an intention-to-treat analysis, it is important to emphasize that time to recurrence and survival calculations were considered from the point of diagnosis of the liver metastases and patient assignment to one of the two treatment strategies. Therefore for group 2 (neoadjuvant), "event-free" survival is actually being progression free (under chemotherapy, before surgery) and being disease-free after resection.

Results

Patients characteristics

Between March 2002 and January 2005, 105 patients underwent liver resection for metastatic CRC in our institution, and 56 of them were enrolled in our study. Group 1 included 19 patients who underwent immediate liver resection and postoperative adjuvant chemotherapy, and group 2 included 37 patients who received neoadjuvant chemotherapy before liver resection.

Table 1 Study patient profiles

	Group 1 ($n = 19$)	Group 2 ($n = 37$)	P Value
Sex ratio (F/M)	0.6	0.76	0.7
Age, years	66	63	0.5
Site			
Colon	14	25	0.9
Rectum	5	12	–
Metastases to lymph nodes (colonic specimen)	75%	71%	0.9
No. of liver tumors (range)	1.47 (1–3)	2.43 (1–5)	0.01
Mean largest tumor diameter, cm	3.4	3.8	0.2
Mean MSKCC risk score	2.32	2.69	0.19

MSKCC Memorial Sloan-Kettering Cancer Center

The patient profiles are outlined in Table 1. Most patient-related variables were similar between the two groups. The exceptions were that group 2 patients had a significantly larger number of liver lesions (2.43 versus 1.47; $P = 0.01$) and a slightly higher mean MSKCC score (2.69 versus 2.32; $P = 0.19$).

Procedures

Ten patients (10/19, 53%) in group 1 and 21 patients (21/37, 57%) in group 2 underwent a combination of nonanatomic or segmental liver resections, with the remaining patients undergoing a formal hepatic lobectomy or extended resections. Complete resection of the tumors was achieved in 54 of 56 patients. Two patients who underwent non-anatomic resections had microscopic involvement of the surgical margins (one in each study group). The perioperative mortality rate was similar in the two groups (one in group 1 and two in group 2). The postoperative morbidity rate was significantly higher in the neoadjuvant group (overall complications rate, 21% for group 1 versus 38% for group 2). Table 2 lists the major postoperative complications. The average hospital stay was 9.1 days for group 1 and 11 days for group 2.

Chemotherapy

Most patients (83%) were treated with irinotecan-based chemotherapy (FOLFIRI). Ten patients in group 2 (27%) who were enrolled in another study received oxaliplatin-based neoadjuvant chemotherapy (FOLFOX). Twelve

Table 2 Perioperative morbidity and mortality

	Group 1 ($n = 19$)	Group 2 ($n = 37$)
Mortality	1	2
Abdominal collection	1	5
Related to colon surgery	1	0
Dehiscence	1	2
Minor bile leak	0	2
Pulmonary embolus	0	1
Pneumonia	0	2
Hospital stay, days	9.1	11

patients (two in group 1 and ten in group 2) also received bevacizumab. Response to chemotherapy could be assessed in all group 2 patients by means of CT, FDG-PET/CT, and tumor marker levels. Among these patients, there were 14 cases (38%) with complete response (resolution of all CT and FDG-PET/CT lesions, and normalization of CEA levels), 17 cases (46%) with partial response, 1 case (3%) with stable disease, and 5 (13%) cases with progression of disease.

Survival and disease-free survival

The median length of follow-up was 30.1 months for the patients in group 1 and 29.2 months for the patients in group 2. Complete follow-up was achieved in all but one patient. At the time of the last follow-up, 10 patients in group 1 (52%) and 20 patients in group 2 (54%) were without evidence of disease. In group 1, the 1-, 2-, and 3-year overall survival rates were 91%, 91%, and 84%, and the event-free survival rates were 63%, 49%, and 49%, respectively (Figs. 1 and 2). In group 2, the 1-, 2-, and 3-year overall survival rates were 95%, 91%. and 70%, and the event-free survival rates were 94%, 50%, and 50%, respectively (Figs. 1 and 2).

CCR

Fourteen patients of the neoadjuvant group achieved CCR. These patients underwent resection of all metastatic sites according to the original CT and PET-CT findings recorded before the administration of chemotherapy. We found that the patients who achieved CCR had better event-free survival ($p = 0.03$) and better overall survival than the rest of the patients in the neoadjuvant group, although the difference did not reach a level of significance ($P = 0.08$). 1-, 2-, and 3-year overall survival of 100%, 90%, and 90% versus. 91%, 85%, and 55%, and 1-, 2-, and 3-year event-free survival of 91%, 82%, and 82% versus 87%, 31%, and 31%, respectively.

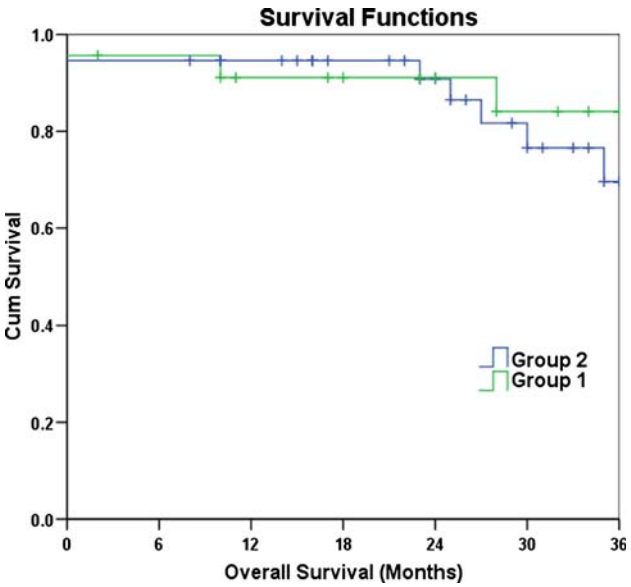

Fig. 1 Overall survival

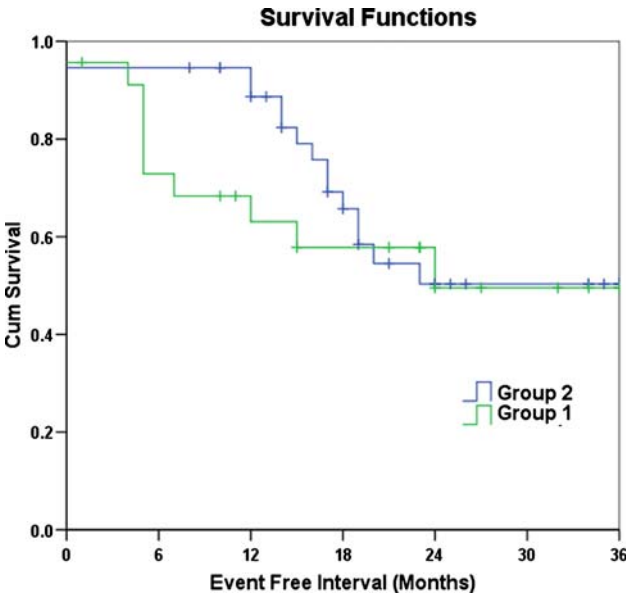

Fig. 2 Event-free survival

Patterns of recurrence

There were 11 cases of cancer recurrence in group 1 and 19 in group 2. The sites of recurrence are listed in Table 3. There were 20 cases of liver recurrence in the two study groups, only one of which was due to local recurrence in the resection bed of a previous metastasis. All other cases were new metastatic lesions that were anatomically separate from the previously resected metastases. Extrahepatic recurrence occurred after a mean interval of 11.3 months in group 1 ($n = 6$) and after 11.5 months in group 2 ($n = 11$).

Table 3 Patterns of recurrence

	Group 1 ($n = 19$)	Group 2 ($n = 37$)
Patients with recurrence	11	19
Hepatic recurrence	8	12
Mean time to recurrence (months)	14.4	14.8
Extrahepatic recurrence	6	11
Mean time to recurrence (months)	11.3	11.5
Site of recurrence		
Lung	3	6
Peritoneal	1	0
Ovaries	1	1
Brain	0	1
Para-aortic		
Lymph node	0	1
Colon		
Anastomosis	0	2
Abdominal wall	1	0

The lung was the most frequent extrahepatic site of metastases (Table 3). Seven patients had both hepatic and extrahepatic recurrences (three in group 1 and four in group 2). The hepatic and extrahepatic metastases appeared simultaneously in four patients, the lung metastases preceded the liver metastases in two patients, and the liver metastases preceded peritoneal spread in two patients.

Discussion

At the present time, the standard treatment of patients with primarily resectable liver metastases from CRC is curative attempt by surgical resection alone. The majority (70%–85%) of these patients, however, experience recurrence within 5 years after curative resection [6]. New chemotherapeutic agents, including irinotecan, oxaliplatin, and the biologic agent bevacizumab, have yielded improved response rates in the treatment of advanced metastatic CRC. The use of these agents had previously been shown to be an effective approach for administering neoadjuvant treatment for initially non-resectable liver metastases [10–12]. Such treatment led to a downsizing of lesions and facilitated surgical resection in a significant proportion of the patients. Several small series have reported the use of neoadjuvant treatment for resectable liver metastases. Tanaka et al. [13] reported the results of 48 patients with multiple (>5) metastases who were treated with neoadjuvant 5-flourouracil (5-FU), leucovorin, and either irinotecan or oxaliplatin. In that retrospective analysis, the patients had improved survival compared to patients who did not receive neoadjuvant treatment. Allen et al. [14] showed that response to neoadjuvant chemotherapy was an important prognostic factor in patients with synchronous colorectal liver metastases that were primarily resectable. In their study, however, administration of neoadjuvant treatment did not result in improved survival.

A neoadjuvant treatment approach has several theoretical advantages over adjuvant treatment, including the ability to downsize non-resectable disease, reduce the extent of liver resections, and assess response to chemotherapy (thereby allowing alteration of chemotherapeutic agents in poor responders). It may also improve patient selection by opening a biological window during the administration of the chemotherapy in which progression under treatment and/or appearance of new metastases spares these patients major futile operations. Following this rationale, our policy was to administer neoadjuvant therapy to patients with moderate and high oncological risk ($\geq$2 risk factors) according to the MSKCC clinical risk score proposed by Fong et al. [18]. Patients in group 1 received the treatment postoperatively, either because they were referred for surgery from another hospital that does not use neoadjuvant treatment or because of patient preference. This special setting allowed us to compare the two approaches. As mentioned earlier, the two groups were comparable in terms of oncological status, and the overall survival curves of the two groups were parallel (Fig. 1). The neoadjuvant group had an event-free survival benefit in the first year which, however, disappeared in the second and third years (Fig. 2). These observations suggest that neoadjuvant treatment does not have either a long-term overall survival benefit or an event-free survival benefit over adjuvant treatment in patients with resectable tumors who are at high risk of recurrence.

The results of this series compare favorably with the results of the original MSKCC series reported by Fong et al. [18], where 3-year survival rates ranged from 60% (clinical score 2) to 27% (clinical score 5) in patients who did not receive adjuvant or neoadjuvant chemotherapy with irinotecan or oxaliplatin, Our results support an important benefit for a treatment protocol that combines chemotherapy with surgery.

The potential disadvantages of neoadjuvant treatment include the possibility of developing liver steatosis [20], which may limit the extent of major resection and may have a negative impact on perioperative morbidity and mortality. There was a significantly higher morbidity rate in our neoadjuvant group, mainly attributable to infectious complications (abdominal collections, pneumonia), but there was no increased rate of wound complications. The postoperative hospital stay was slightly shorter in the adjuvant group (9.1 versus 11 days). Our impression was that operative safety was minimally impaired among the neoadjuvant group of patients: larger series are needed to

accurately assess the actual surgical impact of the neoadjuvant treatment, mainly when it precedes major and extended liver resections.

Fourteen of the group 2 patients achieved CCR, with resolution of all lesions demonstrated on CT and PET-CT and normalization of CEA levels. When feasible, we routinely resect all metastatic sites of lesions that vanished after chemotherapy, guided either by IOUS, in which a remnant scar can usually be identified at the metastasis site, or by the imaging that had been performed before administration of chemotherapy. We found that the small number of group 2 patients who achieved CCR had better 3-year overall and event-free survival than the group 2 patients who did not achieve CCR.

Another important issue especially relevant to patients undergoing liver resection for colorectal metastases is preoperative staging. With few exceptions, surgery is not performed when there is extensive extrahepatic disease or if the hepatic disease is not amenable to complete resection. The standard preoperative staging included abdominal and chest CT. However, FDG-PET was recently shown to be more sensitive than CT in the detection of deposits of colorectal liver metastases [18]. Fernandez et al. [17] reported that staging patients with colorectal liver metastases with FDG-PET resulted in a 5-year survival rate of 58.6%, which is substantially better than the rates for historical series. In our series, most group 2 patients were screened with FDG-PET/CT before beginning neoadjuvant therapy, and all the patients in both groups underwent FDG-PET/CT before operation. All patients with extrahepatic disease or with nonresectable liver disease were excluded from the study. Therefore, we recognize that the survival benefit in the patients in our series compared to the historical series may be partially attributable to the improved staging and not solely to the contribution of chemotherapy.

Conclusions

When compared to historical controls, the addition of oxaliplatin-based or irinotecan-based chemotherapy to surgery may add a survival benefit to patients with colorectal liver metastases. Administration of chemotherapy as neoadjuvant treatment, however, did increase morbidity associated with the operative procedure, mainly from infectious complications. Moreover, although we could show much better overall survival and event-free survival rates than those for historical controls when chemotherapy was combined with surgery, we failed to demonstrate any similar advantage of the neoadjuvant approach over the adjuvant approach. Based on the present data, we recommend administration of chemotherapy in either an adjuvant or neoadjuvant setting to patients with moderate to high risk for recurrence. Larger prospective randomized studies are needed to evaluate the justification of neoadjuvant chemotherapy prior to liver resections for colorectal metastases

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