

Neoadjuvant chemotherapy in a patient with metastatic colorectal cancer

Claus-Henning Köhne, MD, PhD

Clinic for Oncology/Hematology, Klinikum Oldenburg, Oldenburg, Germany

For patients with initially unresectable metastatic colorectal cancer who are otherwise medically fit, neoadjuvant chemotherapy offers the possibility of transforming unfavorable metastatic disease to a resectable tumor burden. In concert with surgical excision, which represents the most effective treatment of colorectal liver metastases, such chemotherapy makes it possible to eradicate or significantly reduce malignant tissue outside the resected

A patient with colorectal cancer (CRC) manifesting retroperitoneal adenopathy, well-defined hepatic lesions localized to a single lobe of the liver, and no evidence of extrahepatic dissemination warrants consideration for neoadjuvant chemotherapy and subsequent surgical resection. In concert with surgical excision—which represents the most effective treatment of colorectal liver metastases—neoadjuvant chemotherapy offers the hope of eradicating or significantly reducing malignant tissue outside the resected field. This approach has contributed to improved 5-year survival by transforming previously inoperable patients who demonstrate an objective response to chemotherapy into appropriate surgical candidates.^{1,2} Manifestation of an objective response is an important clinical indicator that is highly correlated with rates of secondary tumor resection. In a recent review,³ this correlation was higher and steeper in selected, potentially curable patients in comparison with unselected subjects from a number of studies, indicating that a larger number of patients could be rendered potentially resectable and supporting administration of the most highly active regimens to appropriate patients for whom potential cure, rather than palliation, is the treatment objective.

Case history

A 43-year-old man presents with dull, upper-quadrant abdominal pain, weight loss, and intermittent passage of bright-red blood via the rectum. Workup reveals adenocarcinoma of the transverse colon; six synchronous, variably sized (4–6 cm) lesions in the right lobe of the liver, including one that appears to be contiguous with the inferior vena cava; and bulky retroperitoneal lymphadenopathy. Neither computed tomography scanning nor positron-emission tomography reveals any evidence of extrahepatic disease. The patient has no comorbidity and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0. Liver and renal function are normal, as is blood pressure.

Transforming inoperable patients into surgical candidates

Several studies specifically describe long-term patient outcomes following neoadjuvant chemo-

Manuscript received February 26, 2007; accepted March 16, 2007.

Correspondence to: Claus-Henning Köhne, MD, PhD, Clinical Director, Clinic for Oncology/Hematology, Klinikum Oldenburg, Dr.-Eden-Str. 10, 26133 Oldenburg, Germany; telephone: 011-49-441-403-2611; fax: 011-49-441-403-2654; e-mail: onkologie@klinikum-oldenburg.de.

therapy for initially unresectable colorectal metastases in the liver. From 1988 to 1996, 872 patients with CRC were assessed for resectability at a single institution; of them, 171 (19.6%) were candidates for prompt curative resection, and 701 were considered nonresectable and received neoadjuvant chemotherapy.² The vast majority of these patients received 5-fluorouracil (5-FU; 700–1,200 mg/m²/day), folinic acid (300 mg/m²/day), and oxaliplatin (Eloxatin; 25 mg/m²/day), administered over 4–5 days at 2- to 3-week intervals. Restaging following treatment identified 95 patients (13.5%) who had achieved a measurable response; these patients subsequently underwent potentially curative resection.

This post-neoadjuvant, downstaged, resected subgroup achieved a 5-year survival rate of 35%. Comparable survival rates for other categories of initial nonresectability were highest (60%) for patients with large lesions and lowest (18%) for patients with extrahepatic disease. Of 87 patients completing 5 years of follow-up, 34 (39%) were alive, and of them, 19 (22%) had no evidence of disease. Overall, neoadjuvant chemotherapy increased the rate of tumor resectability in this group of 872 subjects from 20% to 30% and facilitated 5-year survival among initially nonresectable individuals that was comparable to that among patients with initially resectable lesions.²

A retrospective update to this single-center report was published in 2004, by which time 1,104 patients with initially nonresectable colorectal liver metastases had been treated with 5-FU/LV (leucovorin)-based chemotherapy combined with oxaliplatin (70%), irinotecan (Camptosar; 7%), or both (4%) given as chronomodulated infusion (87%) for 10 cycles. Consistent with the earlier report, 12.5% of

patients were converted to resectable status, with most of them undergoing potentially curative major hepatectomy. Survival was 33% and 23% at 5 and 10 years, respectively, and disease-free survival was 22% and 17%, respectively. Multivariate analysis identified four preoperative factors as being independently associated with decreased survival: a primary rectal lesion, three or more metastases, a maximum tumor size above 10 cm, and a level of the tumor marker CA 19-9 greater than 100 IU/L.⁴

Figure 1 compares survival of 335 patients initially considered resectable with 138 patients initially considered unresectable but who were downstaged following chemotherapy. The longer follow-up showing median survival of 39 months provides evidence that with complete treatment of appropriately selected patients, longer survival, accompanied by low operative risk, can be obtained. The lower survival rate in this group is likely a factor in the more extensive tumor spread

of patients who were initially considered unresectable.

A European investigation evaluating irinotecan, 5-FU/LV, and hepatic arterial infusion (HAI) of pirarubicin in nonresectable liver metastases enrolled 31 patients over a 2-year period.⁵ The regimen was moderately toxic: 48% of cycles were associated with grade 3/4 neutropenia; 22%, with diarrhea (generally grade 1/2); 14%, with mucositis; and 13%, with non-neutropenic fever. Partial tumor responses were observed in 15 of the 31 patients (48%), and liver resection was made possible in 11 responding patients (35%). Most patients received continued therapy following resection without HAI. Median overall survival (OS) was 20.5 months for the entire study population, 13.9 months in patients who were not resected, and had not yet been reached among operated subjects. At the time of the report, 2- and 3-year survival rates for patients who underwent resection were 100% and 65%, respectively.

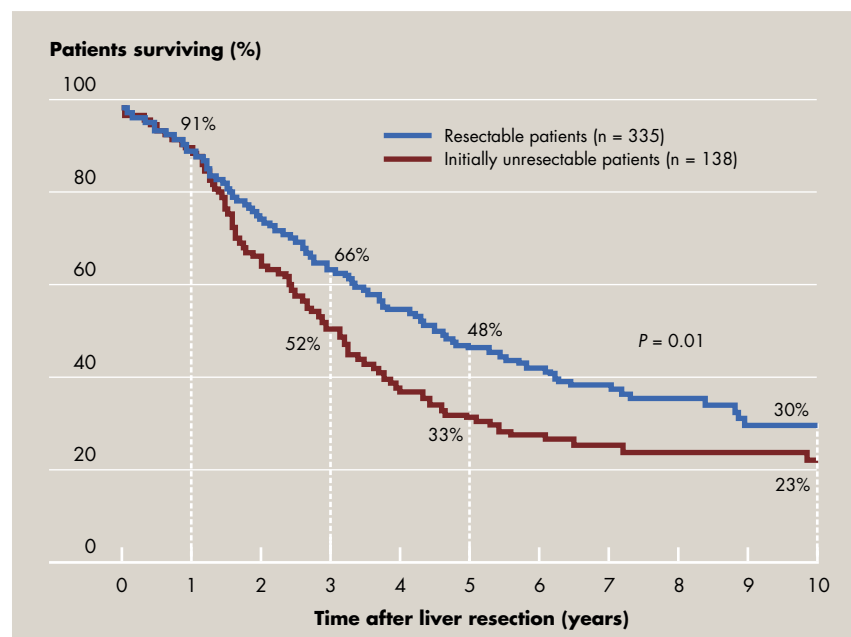


FIGURE 1 Kaplan-Meier plots showing 10-year survival after liver resection among resectable patients and initially unresectable patients who received neoadjuvant chemotherapy. Adapted, with permission, from Adam et al.⁴

Median progression-free survival (PFS) in these subjects was 20.2 months versus just over 4 months in nonoperated patients.⁵

The activity of irinotecan-based neoadjuvant therapy was evaluated in a prospective study enrolling 40 patients with CRC and initially unresectable liver metastases.⁶ The principal goal of this study was to assess the effects of treatment on the overall radical resection rate for hepatic metastases; disease-free and overall survival were secondary outcome measures. Criteria for unresectability were stringent: unfavorable location, insufficient liver reserve, a relatively large number of metastases (six or more in one lobe, or more than three in each of two lobes), and metastases of substantial size (at least one lesion > 5 cm). Chemotherapy consisted of irinotecan (180 mg/m² on day 1), folinic acid (200 mg/m² on days 1 and 2), 5-FU (400 mg/m² on days 1 and 2), and 5-FU (1,200 mg/m² continuous 48-hour infusion on day 1). Treatment was repeated every 2 weeks, with response assessed every 6 cycles. Treatment was well tolerated. Grade 3/4 neutropenia was reported in 14 patients (35%) and grade 3/4 diarrhea, in 5 (12.5%).

All 40 patients were evaluable for response. The overall objective response rate was 47.5% (19 patients), including 2 complete responses. A total of 16 patients (40%) were considered suitable for surgery (8 patients after 6 cycles, 4 after 9 cycles, and 4 after 12 cycles). Laparoscopic evaluation excluded 3 patients because of the presence of additional unresectable disease; the remaining 13 patients (33%) underwent radical resection. Median disease-free survival among those undergoing resection was 14.3 months, compared with 5.2 months in nonoperated subjects. At the time of initial publication, all resected patients were alive at a median follow-up of 19 months.⁶

In the most recent update of the study, encompassing a median follow-up of 30.4 months, median survival for all patients was 30.1 months.⁷ Median survival in non-resected patients was 24 months; OS in resected patients had not been reached. Of resected patients, all were alive and nine were disease free at 1 year; all were alive and six were disease free at 2 years; and nine were alive and six were disease free at last follow-up. These results indicate a possible role for modified FOLFIRI in neoadjuvant treatment of initially unresectable patients and suggest further evaluation of irinotecan-based combinations.⁷

A prospective, multicenter North Central Cancer Trials Group study evaluated 42 patients with unresectable liver metastases who received oxaliplatin, 5-FU, and leucovorin (the FOLFOX4 regimen).⁸ Reasons for unresectability included a large number of lesions (19 patients), an unfavorable location (3 patients), a large tumor size (3 patients), and various combinations of factors (15 patients); reasons were not available for 2 individuals. Most patients (31) had not received prior chemotherapy. All patients completed FOLFOX4 treatment, with a median of 10 courses; 32 of 42 patients had at least one grade 3 or greater adverse event. Responses were designated as complete, partial (at least a 50% decrease in tumor burden), or regression (evidence of definite reduction in assessable disease).

A reduction in tumor burden was documented in 25 patients, with 17 (40%) proceeding to surgical resection. Of 14 patients who had a successful surgical resection, 10 received postoperative FOLFOX4. Median postoperative follow-up was 22 months, during which time 11 recurrences occurred in 15 patients, all of whom were either complete or partial responders. The median time to disease progression for

resected patients was 19 months, and median survival was 26 months. More than two-thirds of resected patients were alive at a median follow-up of 32 months, and median OS for this group has not yet been reached. It is of interest that a liver surgeon who reviewed patients when they entered the study found that 10% who had been deemed unresectable by their treating surgeon were in fact potentially resectable, emphasizing that such evaluations are surgeon dependent.⁸

More recently, the Gruppo Oncologico Nord Ovest evaluated a triplet combination of irinotecan, oxaliplatin, and 5-FU/LV (FOLFOXIRI) versus FOLFIRI in a randomized, phase III trial enrolling 244 patients, including 81 with hepatic metastases only. The primary endpoint of this study was response rate; secondary endpoints included the rate of secondary surgical resection. The response rate for FOLFOXIRI, determined by an external panel, was 60%, compared with 34% for FOLFIRI ($P < 0.00001$). This highly efficacious regimen supported radical secondary metastasectomy in a higher percentage of the entire study cohort (14% vs 6% for FOLFOXIRI vs FOLFIRI, respectively; $P = 0.05$) and in a threefold greater proportion of subjects with hepatic metastases (36% vs 12%; $P = 0.02$). The study is ongoing, with median follow-up currently in excess of 20 months. At a median follow-up of 15.2 months, median survival among the resected patients had not been reached, and significantly improved PFS (9.8 vs 6.9 months; hazard ratio [HR], 0.63; $P = 0.0006$) and median OS (22.6 vs 16.7 months; HR, 0.70; $P = 0.032$) for the entire study group strongly favored the triplet regimen.⁹

Challenging issues

Neoadjuvant therapy poses many unique challenges, and important

questions are as yet unanswered. The role of the newer biologic agents is undefined and currently undergoing study. It is not yet fully understood how antiangiogenic agents such as bevacizumab (Avastin) affect wound healing or hepatic regeneration following major hepatectomy. Crucially, neoadjuvant chemotherapy may pose unanticipated hepatotoxicity issues. A number of vascular changes, as well as steatohepatitis and the “blue-liver” syndrome (vascular alterations and spongiform consistency similar to that seen in early cirrhosis), have been reported with chemotherapy, mostly with oxaliplatin but also with irinotecan; these and other complications may have profound implications for technical aspects of surgery and for overall patient safety. Determination of the relative merits as well as protocols for preoperative and postoperative chemotherapy awaits further data.¹⁰ In addition, patient selection criteria should be standardized to facilitate the design and interpretation of clinical trials.¹¹ Balanced against these considerations is the reality that for the patient with CRC and evidence of disease extension to the liver, neoadjuvant therapy offers the possibility of transforming unfavorable metastatic disease to a resect-

able tumor burden.

An accumulating body of literature, based on long-term outcome analyses evaluating a range of chemotherapy regimens, suggests that our patient in the current scenario may derive a substantial survival advantage from a preoperative strategy of tumor downsizing followed by hepatic resection. This represents yet another level of intervention that was previously inconceivable to those caring for patients with advanced CRC, and it is an avenue that should not go unexplored in otherwise medically fit patients.

References

1. Adam R, Lucidi V, Bismuth H. Hepatic colorectal metastases: methods of improving resectability. *Surg Clin North Am* 2004;84:659–671.
2. Adam R, Avisar E, Ariche A, et al. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal [liver] metastases. *Ann Surg Oncol* 2001;8:347–353.
3. Folprecht G, Grothey A, Alberts S, Raab HR, Kohne CH. Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. *Ann Oncol* 2005;16:1311–1319.
4. Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Ann Surg* 2004;240:644–657.
5. Zelek L, Bugat R, Cherqui D, et al. Multimodal therapy with intravenous biweekly leucovorin, 5-fluorouracil and irinotecan com-

bined with hepatic arterial infusion pirarubicin in non-resectable hepatic metastases from colorectal cancer (a European Association for Research in Oncology trial). *Ann Oncol* 2003;14:1537–1542.

6. Pozzo C, Basso M, Cassano A, et al. Neoadjuvant treatment of unresectable liver disease with irinotecan and 5-fluorouracil plus folinic acid in colorectal cancer patients. *Ann Oncol* 2004;15:933–939.

7. Pozzo C, Basso M, Quirino M, et al. Long-term follow-up of colorectal cancer (CRC) patients treated with neoadjuvant chemotherapy with irinotecan and fluorouracil plus folinic acid (5-FU/FA) for unresectable liver metastases. *J Clin Oncol* 2006;24(18S):3576.

8. Alberts SR, Horvath WL, Sternfeld WC, et al. Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a North Central Cancer Treatment Group phase II study. *J Clin Oncol* 2005;23:9243–9249.

9. Falcone A, Masi G, Brunetti I, et al. The triplet combination of irinotecan, oxaliplatin and 5FU/LV (FOLFOXIRI) vs the doublet of irinotecan and 5FU/LV (FOLFIRI) as first-line treatment of metastatic colorectal cancer (MCRC): results of a randomized phase III trial by the Gruppo Oncologico Nord Ovest (G.O.N.O.). *J Clin Oncol* 2006;24(18S):3513.

10. Bilchik AJ, Poston G, Curley SA, et al. Neoadjuvant chemotherapy for metastatic colon cancer: a cautionary note. *J Clin Oncol* 2005;23:9073–9078.

11. Chong G, Cunningham D. Improving long-term outcomes for patients with liver metastases from colorectal cancer. *J Clin Oncol* 2005;23:9063–9066.

ABOUT THE AUTHOR

Affiliation: Dr. Köhne is Director, Medical Oncologist, Clinic for Oncology/Hematology, Klinikum Oldenburg, Oldenburg, Germany.

Conflicts of interest: None disclosed.