

Neoadjuvant Chemotherapy in the Management of Colorectal Metastases: A Review of the Literature

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Abstract

Introduction: Five-year survival rates of between 20% and 45% are achievable in patients following hepatectomy for liver metastases from colorectal cancer. Sadly, a great majority of patients present with unresectable liver disease with virtually no long-term survival. This paper reviews the development and role of preoperative chemotherapy in trying to downstage unresectable liver disease. **Methods:** The author retrieved most of the citations by performing a PubMed search for studies related to preoperative chemotherapy followed by surgical resection of liver metastases. **Results:** Larger series have reported resectability rates ranging from 10% to 40% for unresectable colorectal liver metastases after treatment with preoperative chemotherapy. Chemotherapy generally consisted of oxaliplatin added to 5-fluorouracil/leucovorin administered in a chronomodulated fashion. A median of about 5 to 10 months of treatment was necessary for adequate tumour reduction. The 5-year survival rates, after surgery, in completely resected patients were between 30% and 60%. The majority of these patients will relapse, of which half of these will remain confined to the liver. Patients who are able to undergo a repeat hepatectomy may achieve long-term survival rates similar to the initial resection. Preliminary data from a recent study suggest that initial treatment with an oxaliplatin-containing regimen may lead to a higher resectability rate compared to an irinotecan-containing combination (18% versus 7%). Selective intra-arterial infusion has not demonstrated a clear advantage over systemic infusion and, if administered preoperatively, it may even compromise the safety of surgery. **Conclusions:** Palliative chemotherapy remains the standard of care for unresectable colorectal liver metastases. However, in carefully selected patients, neoadjuvant chemotherapy may be able to downstage the disease adequately for curative resection.

Ann Acad Med Singapore 2003; 32:205-11

Key words: Chronomodulated, Downstaging, Hepatectomy, Oxaliplatin, Preoperative chemotherapy

Introduction

Colorectal cancer accounts for the most number of deaths after lung cancer, both in the West as well as locally in Singapore. Liver is the most common site of metastasis in colorectal cancer; an estimated 15%¹ of patients will present synchronously, whilst approximately 50% will develop hepatic secondaries at some point during the course of their illness.^{2,3} In as many as a third of these patients, the liver represents the sole site of metastasis.⁴ Without any treatment, the median survival is about 9 months with virtually no long-term survival.^{2,5} Although 5-fluorouracil (5-FU) has been in use for the past 40 years, it is only during the past decade that palliative chemotherapy has been shown to improve the quality of life and survival for patients with metastatic colorectal cancer. It has since been accepted as the standard of care.^{6,7} This is largely due to the advent of biomodulation of 5-FU with leucovorin (LV), which results in superior response rates and prolonged survival compared to 5-FU alone.⁸⁻¹⁰ In addition, the early

use of chemotherapy in asymptomatic patients appears to be advantageous.⁶ Despite these gains, median survival remains modest at 12 months and long-term survival remains elusive.

Liver metastases from most other primary cancers reflect a state of systemic dissemination and, as such, are not candidates for curative resection. In contrast, surgical resection of liver metastases from colorectal cancer is potentially curative and is, indeed, the only modality of cure for selected patients. This situation is possible due to 2 unique differences. The portal venous drainage system favours metastases to the liver without systemic dissemination. This can be seen in about one-third of cases where the liver is the only site of spread. Metastatic efficiency¹¹ has been suggested as a possible biological basis for the development of oligometastases in the liver, often after a relatively great preponderance of time following the primary surgery. Unknown host/tumour factor(s) lead to the destruction of the majority of the microscopic

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deposits within the lymphovascular channels, thus allowing few or none to progress to clinical disease. Unfortunately, only 10% to 20% of patients presenting with liver metastases are amenable to curative resection.¹²⁻¹⁴

Against a background of such modest results with chemotherapy and such discouraging resectability rates for liver metastases, the outlook has been generally gloomy. The recent emergence of novel chemotherapeutic options and the exciting concept of chronotherapy have led to the development of highly effective, but significantly less, toxic regimens. This, coupled with growing expertise in liver surgery, may herald a new era by offering new hope to patients with colorectal metastatic liver cancer. Historically, chemotherapy has been administered both pre- and postoperatively in an attempt to improve the surgical outcome. Adjuvant chemotherapy aims to destroy residual microscopic metastases while neoadjuvant chemotherapy aims to render what is initially unresectable to become potentially resectable. The purpose of this article is to review the development and role of neoadjuvant chemotherapy in patients with unresectable colorectal liver metastases.

Surgery for Liver Metastases

Several retrospective studies have tried to study the natural history of potentially resectable liver metastases that did not undergo resection. The 5-year survival rates were dismal, approximating zero percent.^{2,5,15} Results from several series have confirmed that 5-year survival rates of between 20% and 45% are achievable with hepatectomy.¹⁶⁻²⁰ Increasingly, a second and even a third resection is being performed for recurrences occurring within the liver after surgery. A 3-year survival rate of 33% has been reported in patients after secondary liver resection.²¹

Unfortunately, the majority of patients have unresectable disease. Reasons for unresectability have, in the past, included tumour size, tumour number, bilaterality, and an inability to achieve adequate resection margin (>1 cm).^{12,22} At present the only absolute contraindication to liver resection is the presence of extrahepatic disease.²⁰ A multitude of prognostic factors for survival after resection have been identified. They included the presence of extrahepatic disease, microscopic resection margin, extent of liver involvement, number of metastases, size of metastases, synchronicity with the primary tumour, original staging of the primary tumour, time interval between the primary tumour and metastases and the preoperative carcinoembryonic antigen (CEA) level.^{18-20,23-27} However, the 2 variables most consistently associated with poor outcome and tumour recurrence are the presence of extrahepatic disease and histologically positive resection margin. Although these clinical prognostic parameters are helpful in improving patient selection for surgery, they

should not be used as the sole basis to preclude individual patients from surgery. A good outcome is still possible even in the presence of unfavourable prognostic factors.

Improving expertise in liver surgery has brought down the mortality rate to close to zero.^{20,28,29} The current challenges in liver surgery are to increase resectability, improve sparing of normal liver tissue and enhance survival by multimodality approaches. Two-staged hepatectomy and portal vein embolisation are surgical techniques that have been employed to overcome the problem of postoperative liver failure due to inadequate functional reserve of the liver remnant. Local tumour ablative techniques can be used in conjunction with resection when the number, or the location, of metastases is not amenable to resection. Preoperative chemotherapy is a medical strategy that tries to meet all these challenges.

Systemic Chemotherapy of Unresectable Liver Metastases

The development of neoadjuvant chemotherapy cannot take place without the progress made in palliative chemotherapy for unresectable colorectal metastases. Until recently, the only agent with significant activity in colorectal cancer was 5-FU. Treatment for unresectable colorectal cancer generally consisted of 5-FU and LV (5-FU/LV), which produced response rates of about 20%.⁸⁻¹⁰ The introduction of 2 new drugs, oxaliplatin (LOHP) and irinotecan (CPT-11), has brought into conception new and highly active regimens. Two pivotal randomised studies have evaluated the effectiveness of CPT-11 added to 5-FU/LV as first-line therapy for metastatic colorectal cancer.^{30,31} Both studies reported an improvement in response rates (39% to 49%), delay in time to progression (7 months) and an improvement in overall survival (15 to 17 months). LOHP, in combination with 5-FU/LV, was also studied as initial therapy for metastatic colorectal cancer in randomised trials.^{32,33} Once again, superior response rates (50%) and progression-free survival (9 months) were seen in the LOHP-containing arms, but they failed to translate into any significant overall survival difference. Further phase III trials are currently underway comparing CPT-11 regimens versus LOHP regimens. Phase II evaluations of CPT-11 added to LOHP and 5-FU/LV (FOLFOXIRI) have already commenced.

Normal proliferative tissue and 5-FU metabolising enzyme dihydropyrimidine dehydrogenase (DPD) display a diurnal variation in their activity. The activity of the former is at its lowest and that of the latter is at its highest between 00:00 hour and 04:00 hours. Coinciding the time of peak infusion rate of 5-FU with the time of greatest tissue tolerability permits escalated doses to be given without increasing systemic toxicity. More importantly, 1 of the 2 peaks of tumour mitosis is thought to occur between

midnight and 2 in the morning.³⁴ Two consecutive multi-centre randomised studies compared chronomodulated versus flat infusion of LOHP added to 5-FU/LV in previously untreated metastatic colorectal cancer.^{35,36} Chronotherapy yielded a higher response rate (51%) and longer progression-free survival (6 months). Moreover, the median dose intensity of 5-FU was 22% higher with chronotherapy than with constant-rate infusion.

Neoadjuvant Chemotherapy of Unresectable Liver Metastases

The concept of preoperative tumour debulking is not new. Neoadjuvant chemotherapy has been employed preoperatively in a number of different primary tumours in an attempt to downstage bulky disease. However, disease burden and chemosensitivity are likely to limit the degree of success in many cases. One example where neoadjuvant chemotherapy has shown effectiveness is in the preoperative reduction of locally advanced breast cancer. In the past, progress of neoadjuvant chemotherapy for liver metastases from colorectal cancer has been largely hampered by a lack of highly active treatment. With the availability of potent combination regimens and modern dose schedules, renewed hope and promising possibilities for unresectable liver metastases now exist.

There are several reasons to develop and advance this strategy for colorectal liver metastases. First and foremost, the resectability rate for liver metastases is very disappointing (10% to 20%). Initially, unresectable liver metastases may be converted to resectable disease, thus allowing more patients a chance at potentially curative surgery. Debulking may minimise the incidence of histologically positive margin, which is a strong and consistent poor prognostic factor of survival. Survival of patients with positive resection margins hardly differs from the natural history of unresected metastases. Downstaging also allows greater sparing of normal liver tissue. This is not only important because surgical mortality is related to the extent of liver resection, but more so because secondary resections are being increasingly performed. About 40% of recurrences after surgery again seemed confined to the liver and repeat liver resections^{21,37-39} can achieve a 3-year survival of 30%. Upfront chemotherapy represents a distinct opportunity to test for chemoresponsiveness. A good response may provide an argument for continuation of treatment postoperatively. At the same time, systemic neoadjuvant chemotherapy has the theoretical advantage of potentially being able to eradicate the presence of any systemic micrometastases.

Several small series have evaluated the role of systemic neoadjuvant chemotherapy. Here, the author reviews results from the 3 largest series. To date, most of the neoadjuvant

experiences reported are those using the LOHP/5-FU/LV combination. Bismuth et al¹² evaluated 330 patients with unresectable disease who received systemic chemotherapy containing chronomodulated LOHP/5-FU/LV. In 16% of the patients, the disease was converted to resectable tumour and the 5-year survival rate after resection was 40%. Hepatic recurrence occurred in 64% of the patients who underwent resection. Repeat surgery was feasible in about half of the recurrences. In a retrospective analysis by Giacchetti et al,⁴⁰ 151 patients with colorectal liver metastases, which were initially deemed unresectable, received infusional chemotherapy with the 3 drugs. A majority of the patients (83%) received their treatment in a chronomodulated fashion. Therapy resulted in a major reduction in tumour size (>50%) in 59% of the patients and an overall median survival of 24 months with 28% of patients alive at 5 years. A median of 5.5 months of chemotherapy was necessary to achieve optimal preoperative tumour reduction. Half of the patients underwent surgery with the intent to cure, but only 38% had all their disease completely resected. The estimated 5-year survival rate in the resected group was 58%. In this study, multivariate analyses indicated that the number of metastases (≤ 4) and the interval between chemotherapy and surgery (>6 months) predicted for complete resection of metastases; and the number of metastases (>4), initial CEA level (>10 ng/mL) and the ability to perform surgery predicted for survival. There was no surgical mortality associated with this series. Most of the patients (72%) with complete resection of metastases relapsed within a median of 12 months, of which 48% were in the liver. About half of the patients with liver-again recurrences underwent further chemotherapy followed by repeat hepatectomies. Adam et al²² reported their experience with neoadjuvant chemotherapy in a prospective, non-randomised study of 701 patients with unresectable colorectal liver metastases followed up for a median of 5 years. The great majority of patients were treated with chronomodulated chemotherapy with LOHP/5-FU/LV. This group of investigators achieved a resection rate of 13.5% after a mean of 10 months of treatment. The overall 5-year survival was 35% from the time of surgery. In this series, unresectable lesions were classified into 4 categories: large size, ill location, multinodularity and extrahepatic disease. Respective 5-year survival rates were 60%, 49%, 34% and 18%. Several caveats must be borne in mind when attempting to interpret these data. Interpretation is confounded by a lack of clear and rigorous definition of “unresectability”. Selection bias is an inherent methodological problem in non-randomised studies. The success of resection is also, in part, determined by available surgical expertise. Multi-centre studies often report lower survival data compared with single institution studies, thus underscoring the importance of experience in

high volume centres. Furthermore, different surgical techniques were used to enable the resection. It would probably be impossible and ethically unacceptable to design a randomised study comparing surgery versus no surgery after tumour reduction following systemic chemotherapy. Despite these setbacks, research activity evaluating the benefits of neoadjuvant chemotherapy continues steadily. Preliminary results from a small study by a group of investigators from the Mayo Clinic⁴¹ reiterated the high response rates and improvement in resectability seen in patients with unresectable liver metastases treated with LOHP combination therapy.

Addressing a different aspect of chemotherapy, a recent phase III study tried to establish the most optimal sequence of treatment by comparing FOLFOX (LOHP/5-FU/LV combination), then FOLFIRI (CPT-11/5-FU/LV) with FOLFIRI and then FOLFOX.⁴² Two hundred and twenty-six patients were randomised to receive either FOLFOX or FOLFIRI first, and with crossover upon progression. After first-line FOLFOX therapy, 18% of patients were resectable, in contrast to 7% after first-line FOLFIRI. This result appears to suggest that therapy with first-line FOLFOX increases resectability over FOLFIRI. This difference is not explained by the comparable response rates (56% to 57%) and the progression-free survival (8.4 months to 8.9 months) seen in both arms after first-line therapy. As this report has only been presented in an abstract form, it is not known at this stage if there is an imbalance for resectable patients in the first-line FOLFOX arm. More recently, another group of investigators are testing neoadjuvant chemotherapy in the setting of resectable, instead of unresectable, metastatic cancer.⁴³ Patients either received FOLFOX preoperatively, followed by FOLFIRI postoperatively, or all the chemotherapy postoperatively. For patients treated with FOLFOX prior to surgery, the response rate was 80%, with 13% showing complete response. The follow-up is still short and the survival results are immature.

Regional Chemotherapy of Unresectable Liver Metastases

Liver metastases derive their blood supply predominantly from the hepatic artery whereas normal hepatocytes derive theirs preferentially from the portal vein. This difference can be exploited to improve delivery of cytotoxics to the tumour by selective infusion of chemotherapy into the hepatic artery. Selective delivery of drug optimises tumour drug concentration, but at the same time avoids excessive systemic exposure and toxicity. Floxuridine (FUDR) is the drug of choice for regional chemotherapy because of its high extraction ratio during the first hepatic pass (94% to 99%) and its high solubility.

Hepatic artery infusion (HAI) chemotherapy has been most extensively investigated in untreated patients with liver-only metastases. Several randomised studies⁴⁴⁻⁵¹ and meta-analyses^{52,53} comparing hepatic intra-arterial FUDR with systemic fluorinated chemotherapy have failed to show any clear survival difference despite a definite improvement in response rates (34% to 62%). The failure to demonstrate a clear survival advantage may be due to a number of methodological limitations associated with these studies.

The German Co-operative Group on Liver Metastases recently reported their results of a large randomised trial⁵⁴ in which patients were assigned to 1 of the 3 arms of treatment: systemic 5-FU/LV, HAI 5-FU/LV or HAI FUDR. Not surprisingly, HAI chemotherapy produced a higher response rate compared to systemic therapy (>40% versus 20%). Although time to progression and median survival were not significantly different among the 3 arms, patients who were treated with HAI 5-FU/LV appeared to do most favourably whilst those who received HAI FUDR did the worst. More interestingly, the HAI FUDR arm also experienced the highest rate of extrahepatic progression of disease compared with regional or systemic 5-FU/LV (40% versus <20%). These findings have several implications. The effectiveness of intra-arterial 5-FU/LV, accompanied by all its related technical complexities and locoregional toxicity, does not appear significantly better than the simpler intravenous administration of 5-FU/LV. Although regional FUDR results in high local response rates, it may not provide adequate systemic control.

The concept of preoperative HAI therapy is appealing because of the high tumour response rate associated with intra-arterial delivery of drugs. Only a very scarce number of studies have looked at this approach and they are mainly small retrospective series. Clavien et al⁵⁵ reported a resection rate of 26% and a 3-year survival of 50% in 23 patients with unresectable liver metastases treated with HAI FUDR preoperatively. In contrast, only 5% of patients underwent resection after HAI therapy in another series.⁵⁶ Elias et al⁵⁷ noted some of the major hurdles encountered in surgery when adopting this approach. HAI therapy impairs hepatic function and induces parenchymal and hemodynamic changes in the liver, thus rendering hepatectomy technically difficult and fraught with increased postoperative complications.

Future Directions

An increasing understanding of the genetic and molecular pathways in the pathogenesis of cancer has led to the generation of novel therapeutic approaches and compounds that target the disruptions in these pathways. A multitude of options are currently being developed and they include

anti-sense therapy, gene therapy, farnesyl transferase inhibitors, tyrosine kinase inhibitors, anti-epidermal growth factor receptor monoclonal antibodies, anti-vascular endothelial growth factor receptor monoclonal antibodies, cyclo-oxygenase-2 inhibitors, matrix metalloprotein inhibitors and immunotherapy. Some of these have shown synergy with cytotoxics and may result in improved tumour regression when used in combination with conventional chemotherapy.

Cost Effectiveness

Results from the de Gramont phase III trial suggest that treatment with LOHP in combination with 5-FU/LV will achieve a mean increase of 2.75 months in progression-free survival compared with 5-FU/LV alone.³² Based on the clinical data from this study, Nicholls et al⁵⁸ performed a cost effectiveness analysis to assess whether the benefits of combining LOHP with 5-FU/LV can be achieved at an acceptable additional cost from the United Kingdom (UK) National Health Service's perspective. The results of the analysis indicate that the costs to achieve an additional progression-free month are around £2,133, which works out to an average incremental cost of £25,600 to achieve an additional progression-free year. The same group of investigators also conducted a cost effectiveness comparison between LOHP added to 5-FU/LV and CPT-11 added to 5-FU/LV.⁵⁹ They reported a "comparable" incremental cost-effectiveness ratio in terms of progression-free survival (£26,665 versus £30,171). But in terms of response rates, the costs incurred per year to achieve an additional responding patient are £31,065 for LOHP in combination versus £46,343 for CPT-11 in combination. Poston et al⁶⁰ studied the costs of neoadjuvant chemotherapy and surgery for patients with colorectal metastases. The decision model used in this study assumed a resectability rate of 11.4% for patients treated with LOHP added to 5-FU/LV and 4.1% for 5-FU/LV alone, based on data from the de Gramont study.³² The incremental cost per life-year gained was about £11,985.

Based on the balance of clinical and cost effectiveness, the UK National Institute for Clinical Excellence Technology Appraisal Guidance No. 33 recommends that the use of LOHP, in combination with 5-FU/LV, should be considered first-line in advanced colorectal cancer patients with liver-only metastases that may become resectable. Neither CPT-11 nor LOHP in combination with 5-FU/LV are recommended in routine first-line therapy for advanced colorectal cancer.

Conclusions

For a majority of patients with unresectable colorectal cancer systemic chemotherapy remains the standard of practice. Modern combinations containing CPT-11 or

LOHP are the most highly active regimens available, producing response rates of about 50%. Higher dose intensities can be achieved with chronotherapy without increasing systemic toxicity. However, chronomodulated-dosing schedules are fairly complicated to deliver and may prove impractical for the general oncology community. Nevertheless, these advances in combination chemotherapy raise the hope that treatment can now better debulk tumours preoperatively, so that more patients will become amenable to complete resection. Administering chemotherapy preoperatively may achieve up to a 38% complete resection rate in patients initially considered to have unresectable disease. A 5-year survival rate of 58% after surgery was reported in this group of patients. Evidence from 1 study suggests that the most effective neoadjuvant regimen is LOHP in combination with 5-FU/LV. It should be remembered that additional cost would be incurred through the use of innovative treatment to gain additional clinical benefits. Although recent evidence suggests that a survival benefit may be associated with adjuvant HAI chemotherapy after resection of liver metastases,^{61,62} the benefit in unresected disease remains unclear and highly debatable. Since it will never be possible to design a phase III study for neoadjuvant chemotherapy in unresectable colorectal liver metastases, efforts should be put into conducting good quality large prospective phase II studies with detailed description of disease parameters, surgical treatment and long-term outcomes.

Acknowledgements

The author expresses his utmost appreciation to Dr Koo Wen Hsin from the Department of Medical Oncology, National Cancer Centre, Singapore, for his invaluable input and discussions on these issues, without which this article would not have been possible in its current form.

REFERENCES

1. Fong Y, Kemeny N, Paty P, Blumgart L H, Cohen A M. Treatment of colorectal cancer: hepatic metastasis. *Semin Surg Oncol* 1996; 12: 219-52.
2. Scheele J, Stangl R, Altendorf-Hofmann A. Hepatic metastases from colorectal carcinoma: impact of surgical resection on the natural history. *Br J Surg* 1990; 77:1241-6.
3. Steele G Jr, Ravikumar T S. Resection of hepatic metastases from colorectal cancer. Biologic perspective. *Ann Surg* 1989; 210:127-38.
4. Cromheecke M, de Jong K P, Hoekstra H J. Current treatment for colorectal cancer metastatic to the liver. *Eur J Surg Oncol* 1999; 25: 451-63.
5. Stangl R, Altendorf-Hofmann A, Charnley R M, Scheele J. Factors influencing the natural history of colorectal liver metastases. *Lancet* 1994; 343:1405-10.
6. Expectancy or primary chemotherapy in patients with advanced asymptomatic colorectal cancer: a randomized trial. Nordic Gastrointestinal Tumor Adjuvant Therapy Group. *J Clin Oncol* 1992; 10:904-11.

7. Scheithauer W, Rosen H, Kornek G V, Sebesta C, Depisch D. Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. *BMJ* 1993; 306:752-5.
8. Poon M A, O'Connell M J, Wieand H S, Krook J E, Gerstner J B, Tschetter L K, et al. Biochemical modulation of fluorouracil with leucovorin: confirmatory evidence of improved therapeutic efficacy in advanced colorectal cancer. *J Clin Oncol* 1991; 9:1967-72.
9. Borner M M, Castiglione M, Bacchi M, Weber W, Herrmann R, Fey M F, et al. The impact of adding low-dose leucovorin to monthly 5-fluorouracil in advanced colorectal carcinoma: results of a phase III trial. Swiss Group for Clinical Cancer Research (SAKK). *Ann Oncol* 1998; 9:535-41.
10. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. Advanced Colorectal Cancer Meta-Analysis Project. *J Clin Oncol* 1992; 10:896-903.
11. Sugarbaker P H. Metastatic inefficiency: the scientific basis for resection of liver metastases from colorectal cancer. *J Surg Oncol Suppl* 1993; 3:158-60.
12. Bismuth H, Adam R, Levi F, Farabos C, Waechter F, Castaing D, et al. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. *Ann Surg* 1996; 224:509-20; discussion 520-2.
13. Adson M A. Resection of liver metastases—when is it worthwhile? *World J Surg* 1987; 11:511-20.
14. Doci R, Gennari L, Bignami P, Montalto F, Morabito A, Bozzetti F. One hundred patients with hepatic metastases from colorectal cancer treated by resection: analysis of prognostic determinants. *Br J Surg* 1991; 78:797-801.
15. Cady B, Monson D O, Swinton N W. Survival of patients after colonic resection for carcinoma with simultaneous liver metastases. *Surg Gynecol Obstet* 1970; 131:697-700.
16. Fortner J G, Silva J S, Golbey R B, Cox E B, Maclean B J. Multivariate analysis of a personal series of 247 consecutive patients with liver metastases from colorectal cancer. I. Treatment by hepatic resection. *Ann Surg* 1984; 199:306-16.
17. Adson M A, van Heerden J A, Adson M H, Wagner J S, Ilstrup D M. Resection of hepatic metastases from colorectal cancer. *Arch Surg* 1984; 119:647-51.
18. Hughes K S, Rosenstein R B, Songhorabodi S, Adson M A, Ilstrup D M, Fortner J G, et al. Resection of the liver for colorectal carcinoma metastases. A multi-institutional study of long-term survivors. *Dis Colon Rectum* 1988; 31:1-4.
19. Scheele J, Stang R, Altendorf-Hofmann A, Paul M. Resection of colorectal liver metastases. *World J Surg* 1995; 19:59-71.
20. Fong Y, Cohen A M, Fortner J G, Enker W E, Turnbull A D, Coit D G, et al. Liver resection for colorectal metastases. *J Clin Oncol* 1997; 15:938-46.
21. Nordlinger B, Vaillant J C, Guiguet M, Balladur P, Paris F, Bachellier P, et al. Survival benefit of repeat liver resections for recurrent colorectal metastases: 143 cases. Association Francaise de Chirurgie. *J Clin Oncol* 1994; 12:1491-6.
22. Adam R, Avisar E, Ariche A, Giachetti S, Azoulay D, Castaing D, et al. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal. *Ann Surg Oncol* 2001; 8:347-53.
23. Nordlinger B, Guiguet M, Vaillant J C, Balladur P, Boudjema K, Bachellier P, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. *Cancer* 1996; 77:1254-62.
24. Jaeck D, Bachellier P, Guiguet M, Boudjema K, Vaillant J C, Balladur P, et al. Long-term survival following resection of colorectal hepatic metastases. Association Francaise de Chirurgie. *Br J Surg* 1997; 84: 977-80.
25. Jamison R L, Donohue J H, Nagorney D M, Rosen C B, Harmsen W S, Ilstrup D M. Hepatic resection for metastatic colorectal cancer results in cure for some patients. *Arch Surg* 1997; 132:505-10; discussion 511.
26. Elias D, Cavalcanti A, Sabourin J C, Lassau N, Pignon J P, Ducreux M, et al. Resection of liver metastases from colorectal cancer: the real impact of the surgical margin. *Eur J Surg Oncol* 1998; 24:174-9.
27. Fong Y, Fortner J, Sun R L, Brennan M F, Blumgart L H. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999; 230:309-18; discussion 318-21.
28. Taylor M, Forster J, Langer B, Taylor B R, Greig P D, Mahut C. A study of prognostic factors for hepatic resection for colorectal metastases. *Am J Surg* 1997; 173:467-71.
29. Rees M, Plant G, Bygrave S. Late results justify resection for multiple hepatic metastases from colorectal cancer. *Br J Surg* 1997; 84:1136-40.
30. Saltz L B, Cox J V, Blanke C, Rosen L S, Fehrenbacher L, Moore M J, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med* 2000; 343:905-14.
31. Douillard J Y, Cunningham D, Roth A D, Navarro M, James R D, Karasek P, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000; 355:1041-7.
32. de Gramont A, Figuer A, Seymour M, Homerin M, Hmissi A, Cassidy J, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000; 18:2938-47.
33. Giacchetti S, Perpoint B, Zidani R, Le Bail N, Faggiuolo R, Focan C, et al. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2000; 18:136-47.
34. Garcia-Sainz M, Halberg F. Mitotic rhythms in human cancer, reevaluated by electronic computer programs. Evidence for chronopathology. *J Natl Cancer Inst* 1966; 37:279-92.
35. Levi F A, Zidani R, Vannetzel J M, Perpoint B, Focan C, Faggiuolo R, et al. Chronomodulated versus fixed-infusion-rate delivery of ambulatory chemotherapy with oxaliplatin, fluorouracil, and folinic acid (leucovorin) in patients with colorectal cancer metastases: a randomized multi-institutional trial. *J Natl Cancer Inst* 1994; 86:1608-17.
36. Levi F, Zidani R, Misset J L. Randomised multicentre trial of chronotherapy with oxaliplatin, fluorouracil, and folinic acid in metastatic colorectal cancer. International Organization for Cancer Chronotherapy. *Lancet* 1997; 350:681-6.
37. Adam R, Bismuth H, Castaing D, Waechter F, Navarro F, Abascal A, et al. Repeat hepatectomy for colorectal liver metastases. *Ann Surg* 1997; 225:51-60; discussion 60-2.
38. Petrowsky H, Gonen M, Jarnagin W, Lorenz M, DeMatteo R, Heinrich S, et al. Second liver resections are safe and effective treatment for recurrent hepatic metastases from colorectal cancer: a bi-institutional analysis. *Ann Surg* 2002; 235:863-71.
39. Fong Y, Blumgart L H, Cohen A, Fortner J, Brennan M F. Repeat hepatic resections for metastatic colorectal cancer. *Ann Surg* 1994; 220:657-62.
40. Giacchetti S, Itzhaki M, Gruia G, Adam R, Zidani R, Kunstlinger F, et al. Long-term survival of patients with unresectable colorectal cancer liver metastases following infusional chemotherapy with 5-fluorouracil, leucovorin, oxaliplatin and surgery. *Ann Oncol* 1999; 10:663-9.
41. Alberts S R, Horvath W L, Donohue J H, Sternfeld W, Goldberg R M, Mahoney M R, et al. Oxaliplatin, 5-Fluorouracil, and Leucovorin for Patients with Liver Only Metastases From Colorectal Cancer: A North Central Cancer Treatment Group Phase II Study. Proceedings of the American Society of Clinical Oncology 2001; 20:abst 511.
42. Tournigand C, Louvet C, Quinaux E, Andre T, Lledo G, Flesch M, et al. FOLFIRI Followed by FOLFOX Versus FOLFOX Followed by FOLFIRI in Metastatic Colorectal Cancer: Final Results of a Phase III Study. Proceedings of the American Society of Clinical Oncology 2001;

- 20:abst 494.
43. Artru P, Taieb J, Tournigand C, Louvet C, Haffraoui S, Paye F, et al. FOLFOX 7/FOLFIRI (MIROX) regimen as neoadjuvant chemotherapy for patients with resectable metastatic colorectal cancer: preliminary results. *Proceedings of the American Society of Clinical Oncology* 2002; 21:abst 672.
 44. Grage T B, Vassilopoulos P P, Shingleton W W, Jubert A V, Elias E G, Aust J B, et al. Results of a prospective randomized study of hepatic artery infusion with 5-fluorouracil versus intravenous 5-fluorouracil in patients with hepatic metastases from colorectal cancer: A Central Oncology Group study. *Surgery* 1979; 86:550-5.
 45. Chang A E, Schneider P D, Sugarbaker P H, Simpson C, Culnane M, Steinberg S M. A prospective randomized trial of regional versus systemic continuous 5-fluorodeoxyuridine chemotherapy in the treatment of colorectal liver metastases. *Ann Surg* 1987; 206:685-93.
 46. Kemeny N, Daly J, Reichman B, Geller N, Botet J, Oderman P. Intrahepatic or systemic infusion of fluorodeoxyuridine in patients with liver metastases from colorectal carcinoma. A randomized trial. *Ann Intern Med* 1987; 107:459-65.
 47. Hohn D C, Stagg R J, Friedman M A, Hannigan J F Jr, Rayner A, Ignoffo R J, et al. A randomized trial of continuous intravenous versus hepatic intraarterial floxuridine in patients with colorectal cancer metastatic to the liver: the Northern California Oncology Group trial. *J Clin Oncol* 1989; 7:1646-54.
 48. Martin J K Jr, O'Connell M J, Wieand H S, Fitzgibbons R J Jr, Mailliard J A, Rubin J, et al. Intra-arterial floxuridine vs systemic fluorouracil for hepatic metastases from colorectal cancer. A randomized trial. *Arch Surg* 1990; 125:1022-7.
 49. Rougier P, Laplanche A, Huguier M, Hay J M, Ollivier J M, Escat J, et al. Hepatic arterial infusion of floxuridine in patients with liver metastases from colorectal carcinoma: long-term results of a prospective randomized trial. *J Clin Oncol* 1992; 10:1112-8.
 50. Allen-Merish T G, Glover C, Fordy C, Mathur P, Quinn H. Randomized trial of regional plus systemic fluorinated pyrimidine compared with systemic fluorinated pyrimidine in treatment of colorectal liver metastases. *Eur J Surg Oncol* 2000; 26:468-73.
 51. Allen-Merish T G, Earlam S, Fordy C, Abrams K, Houghton J. Quality of life and survival with continuous hepatic-artery floxuridine infusion for colorectal liver metastases. *Lancet* 1994; 344:1255-60.
 52. Reappraisal of hepatic arterial infusion in the treatment of nonresectable liver metastases from colorectal cancer. Meta-Analysis Group in Cancer. *J Natl Cancer Inst* 1996; 88:252-8.
 53. Harmantas A, Rotstein L E, Langer B. Regional versus systemic chemotherapy in the treatment of colorectal carcinoma metastatic to the liver. Is there a survival difference? Meta-analysis of the published literature. *Cancer* 1996; 78:1639-45.
 54. Lorenz M, Muller H H. Randomized, multicenter trial of fluorouracil plus leucovorin administered either via hepatic arterial or intravenous infusion versus fluorodeoxyuridine administered via hepatic arterial infusion in patients with nonresectable liver metastases from colorectal carcinoma. *J Clin Oncol* 2000; 18:243-54.
 55. Clavien P A, Selzner N, Morse M, Selzner M, Paulson E. Downstaging of hepatocellular carcinoma and liver metastases from colorectal cancer by selective intra-arterial chemotherapy. *Surgery* 2002; 131:433-42.
 56. Meric F, Patt Y Z, Curley S A, Chase J, Roh M S, Vauthey J N, et al. Surgery after downstaging of unresectable hepatic tumors with intra-arterial chemotherapy. *Ann Surg Oncol* 2000; 7:490-5.
 57. Elias D, Lasser P, Rougier P, Ducreux M, Bognel C, Roche A. [Major hepatectomy after intra-arterial chemotherapy for initially unresectable liver tumors. Frequency, technical problems, results and indications]. *Ann Chir* 1996; 50:130-8.
 58. Nicholls C, Cassidy J, Freemantle N, Harrison M, Carita P. Cost-effectiveness of oxaliplatin in combination with 5-FU/LV compared with 5-FU/LV alone. *J Med Econ* 2001; 4:127-35.
 59. Nicholls C, Cassidy J, Freemantle N, Harrison M, Carita P. Cost-effectiveness of combination chemotherapy (oxaliplatin or irinotecan in combination with 5-FU/LV) compared to 5-FU/LV alone. *J Med Econ* 2001; 4:115-25.
 60. Poston G, Benjamin I S, Diamond T, Finch-Jones M, Parks R W, Primrose J N, et al. Costs of neoadjuvant chemotherapy and surgery in patients with liver metastases from advanced colorectal cancer. *J Med Econ* 2001; 4:167-77.
 61. Kemeny N, Huang Y, Cohen A M, Shi W, Conti J A, Brennan M F, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med* 1999; 341:2039-48.
 62. Kemeny M M, Adak S, Gray B, Macdonald J S, Smith T, Lipsitz S, et al. Combined-modality treatment for resectable metastatic colorectal carcinoma to the liver: surgical resection of hepatic metastases in combination with continuous infusion of chemotherapy—an intergroup study. *J Clin Oncol* 2002; 20:1499-505.