Reduction in Recurrence Risk for Involved or Inadequate Margins With Edge Cryotherapy After Liver Resection for Colorectal Metastases

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Hypothesis: The usefulness of additional edge cryotherapy after liver resection for liver metastases from colorectal cancer to improve involved or inadequate (less than 1 cm) margins is uncertain.

Design: Retrospective analysis of prospectively collected data.

Setting: Department of surgery at a university hospital.

Patients: Eighty-six consecutive patients with hepatic metastases from colorectal cancer in whom we applied additional edge cryotherapy to involved or inadequate margins. This group was compared with 134 patients who underwent resection without edge cryotherapy (control group) during the same period.

Intervention: Potentially curative treatment was achieved by adding edge cryotherapy to insufficient resection sites in patients not eligible for further resection.

Main Outcome Measures: Edge recurrence rate in the study group; validation of an additional treatment to improve curative resectability; and comparison of morbidity and local recurrence rates with the control group.

Results: At a median follow-up of 39 months, 47 patients were alive and 39 had died. Local recurrence at the resection site was diagnosed in 9 patients (10%), of which 7 occurred in patients with involved margins and 2 in patients with resection margin less than 1 cm. Thirty-six patients (42%) experienced recurrence in the remnant liver. Extrahepatic recurrence occurred in 38 patients (44%), the lungs being the most common site (22 patients [26%]).

Conclusions: Edge cryotherapy is a potent additional surgical treatment option in patients with liver metastases from colorectal cancer. The percentage of patients who can be treated for cure can be increased, especially if complex liver surgery is demanded.

Arch Surg. 2001;136:1154-1157

Until recently, liver resection was the only potentially curative treatment for patients with liver metastases from colorectal cancer (CRCLM).1-4 Unfortunately, only a small proportion of patients are eligible for curative surgical treatment when the diagnosis of CRCLM is established.5,6 The advent of several imaging-controlled ablative techniques now offers the potential of survival advantage to a small number of patients with unresectable disease.7-12 Several attempts have been undertaken to increase the number of patients in whom curative resection can be performed. Techniques such as neoadjuvant chemotherapy,13 portal vein embolization,14 and contralateral-lobe tumor destruction15 have contributed to extend the percentage of patients eligible for curative complex liver surgery. Cryotherapy is an established treatment tool in destroying tumor tissue.16-18 In patients with either impaired liver function or small-volume remnant liver, cryotherapy is preferred to further liver resection to maintain maximal normal liver tissue and reduce the risk of postoperative liver failure. Dwerryhouse et al18 previously reported on the use of edge cryotherapy, but those results lacked long-term follow-up.

The present study evaluates the efficacy of edge cryotherapy in addition to liver resection, to improve inadequate margin and prevent local recurrence in a considerable number of patients with a median follow-up of more than 3 years. Data from these patients were compared with those from a control group of patients treated by liver resection without edge cryotherapy during the same period.

RESULTS

Data from 86 consecutive patients who underwent curative hepatic resection including edge cryotherapy to an involved or inadequate margin were analyzed and compared with those of the 134 patients who did not undergo edge cryotherapy.
PATIENTS AND METHODS

All hepatic resections performed in patients with colorectal metastases at the Liver Unit of the Department of Surgery, St George Hospital (University of New South Wales, Sydney, Australia) were retrieved from the prospective liver unit database. From May 1, 1992, to February 28, 2000, a total of 220 liver resections were performed for CRCLM. Cryotherapy was applied to either an involved or an inadequate (<1 cm) margin in 86 patients. These 86 patients represent the study population and were followed up every 3 months until August 31, 2000, or death. The study group was compared with the remaining 134 patients who underwent liver resections during that period. Adequacy of intraoperative margin assessment and recurrence pattern were analyzed separately.

All patients underwent preoperative screening to exclude extrahepatic disease and to assess the extent of liver disease. Patients with peritoneal disease, primary site recurrence, or portal lymph node involvement were excluded by means of examination through a small right subcostal incision. Intraoperative ultrasound was performed and the number, size, and relationship of the CRCLM to portal sheath and hepatic veins were assessed. Liver resection was performed with an ultrasonic dissector (Selector; Spembly, Andover, England). The adequacy of the resection margin was assessed by the surgeon, and in case of involvement or proximity (<1 cm) of the tumor to the resection margin edge, cryotherapy was applied to the margin by means of a plate or a cylindrical probe to achieve a 1-cm margin (under ultrasound guidance). Cryotherapy was delivered with a liquid nitrogen–based system (2 types: Cryotech LCS 3000; Spembly; or Cryo 6 System; Erbe, Tübingen, Germany).

There were 35 female (41%) and 51 male (59%) patients with a median age of 58 years (range, 31-83 years). Seven patients had synchronous CRCLM, and the liver resection was performed after the resection of the primary tumor as a 1-stage procedure.

Routine follow-up after liver resection consisted of clinical examination and serum carcinoembryonic antigen (CEA) measurements every 3 months. In CEA nonsecretors, follow-up examination included chest x-ray and abdominal computed tomography at 6-month intervals.

Disease recurrence was confirmed by computed tomography. Edge recurrence was demonstrated by a typical low-density area in the liver remnant adjacent to the clips used during liver transection.

Biological factors analyzed included serum CEA level before hepatic resection, maximum diameter of the largest nodule, number of metastases, unilobar vs bilobar liver involvement, synchronous or metachronous appearance, differentiation, mucin production within the CRCLM, and perioperative requirement of homologous blood transfusions.

Survival and disease-free survival estimates were calculated by the Kaplan-Meier method. Possible prognostic factors were assessed for their impact on survival time by the log-rank test (categorical variables) or Cox regression model (continuous variables) for unifactorial analysis (a significant difference was assumed for P<.05). Statistical analysis was performed with SPSS version 9.0 software (SPSS Inc, Chicago, Ill.).

Perioperative mortality and morbidity in these selected patient groups are illustrated in the Table.

In the study group, there were 2 perioperative deaths (<30 days after resection): 1 from myocardial infarction after extended right lobectomy with synchronous sigmoid colectomy and 1 from septicemia following postoperative pancreatitis after extended right lobectomy. Postoperative morbidity complicated the recovery in 29 patients (34%); the morbidity mainly resulted from subphrenic abscess (8 cases), biloma (5), pleural effusion (3), atelectasis (3), tachycardic arrhythmia (3), and postoperative bleeding requiring relaparotomy (2).

In the group without edge cryotherapy, 1 patient died of septicemia. The overall perioperative morbidity was similar, with 38 patients (28%) experiencing complications (Table).

Surgery performed in the study group included 16 right trisectionectomies, 18 right hemihepatectomies, 12 left lateral sectionectomies, 8 left hemihepatectomies, 2 left trisectionectomies, 7 bisegmentectomies, and 23 segmentectomies.

Preoperative CEA levels were not elevated in 12 patients (nonsecretors), were between 5 and 50 ng/mL in 33 patients, and were greater than 50 ng/mL in 25 patients. Preoperative CEA level was unknown in 16 patients. The median diameter of the largest resected CRCLM was 5 cm (range, 1-18 cm). The median number of resected metastases was 2; 38 patients had a solitary metastasis resected; 20 patients had 2 metastases removed; and 28 patients had more than 2 CRCLM resected. Thirty-one patients were treated for bilobar liver involvement and 55 patients had their CRCLM confined to 1 lobe. Synchronous liver resection after primary bowel resection was performed in 7 patients, and 79 patients had metachronous liver involvement and treatment. Of the resected metastases, 73.3% were moderately differentiated, 8.1% were poorly differentiated, and only 4.7% of the specimens were well differentiated; 13.9% of tumors were not classified. Mucin production was identified in the liver metastases of 12 patients (14%). Perioperative blood transfusions were required in 35 patients (41%), with a median of 3 units given (range, 2-20 units).

There was no significant difference in any of these factors when the group of patients with involved margins was compared with the group with inadequate margins.

Pathological examination of the specimens of the study group demonstrated resection edge involvement by tumor in 48 patients (56%), and a tumor-free margin of less than 1 cm was found in 38 patients (44%). The median tumor-free margin in these patients was 2 mm (range, 1-8 mm).

In the pathological examination of the specimens of patients without additional edge cryotherapy, we found clear margins (>1 cm) in 98 patients (73%), margins less than 1 cm in 27 patients (20%), and involved margins in 9 patients (7%). In 4 of the 9 patients with involved
The primary end point of this analysis was edge recurrence where edge cryotherapy had been used. After a median follow-up of 39 months, 9 patients (10%) experienced tumor recurrence involving the resection edge. Edge recurrence was observed in 7 patients in the involved margin group (14%) and in 2 patients in the group with close margins (5%). Of the 9 patients with edge recurrence, 6 had additional recurrent lesions within the liver remnant. Median time to edge recurrence was 7.5 months (95% confidence interval, 4.96-9.97).

In the control group without edge cryotherapy, 5 patients (5%) experienced edge recurrence of the 97 patients (72%) with adequate follow-up. Four patients were found to have had involved margins, and 1 patient had an inadequate margin (<1 cm) on pathological examination. This shows an edge recurrence rate of 44% (4/9) in the group with an involved resection edge and 4% (1/27) in the group with inadequate margins.

In the study group, a total of 36 patients (42%) had CRCLM recurrence in the liver remnant and 38 patients (44%) had recurrences outside the liver, with the lungs being the most common site (22/38 [58%]).

Overall survival for patients with involved vs inadequate margins was not significantly different. The median survival for patients with involved margins was 33.7 months, and for patients with margins less than 1 cm it was 42.7 months (P=.38, Figure 1). The survival of patients with edge recurrence and/or liver remnant recurrence was not significantly different from survival in those with recurrence elsewhere, or for those with liver and systemic recurrence (median survival for liver recurrence vs systemic recurrence vs liver and systemic recurrence, 39 vs 37 vs 31 months).

Median tumor recurrence–free survival time was 16 months. At last follow-up, a total of 34 patients (40%) were tumor free, 14 patients (16%) had liver recurrence, 22 patients (26%) had liver and systemic recurrence, and 16 patients (19%) had systemic recurrence alone. There was no statistically significant difference in tumor recurrence–free survival time in patients with involved resection margins (14.6 months) compared with that of patients with close margins (16.3 months) (P=.16, Figure 2). Of the 9 patients with edge recurrence, 2 had developed concomitant lung metastases and 2 had developed peritoneal disease.

After a median follow-up of 23 months, liver recurrence–free survival times were not statistically different for

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<th>Perioperative Morbidity and Mortality in Patients With and Without Edge Cryotherapy</th>
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<td><strong>Cause</strong></td>
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<td>Cardiopulmonary</td>
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<td>Arrhythmia</td>
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<td>Pulmonary embolism</td>
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<td>Death from myocardial infarction</td>
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<td>Gastrointestinal</td>
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<td>Biloma</td>
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<td>Intra-abdominal bleeding</td>
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<td>Subphrenic hematoma</td>
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<td>Septicemia</td>
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<td>Death from sepsis</td>
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*Percentage of the 86 patients with morbidity or mortality. †Percentage of the 134 patients with morbidity or mortality.

![Figure 1. Overall survival times (Kaplan-Meier) of patients undergoing liver resection and edge cryotherapy for colorectal metastases depending on involved or inadequate margin (log rank test, P=.38). Symbols represent censored cases.](image1)

![Figure 2. Recurrence-free survival times (Kaplan-Meier) of patients undergoing liver resection and edge cryotherapy for colorectal metastases depending on involved or inadequate margin (log rank test, P=.16). Symbols represent censored cases.](image2)
patients with involved edges (19 months) compared with those of patients with close edges (34 months) \((P=.66)\).

None of the investigated prognostic variables reached significance levels during univariate analyses for overall or recurrence-free survival.

A tumor-free and adequate resection margin of 1 cm was identified by several authors\(^1,2,19-21\) as a significant prognostic factor after resection of colorectal liver metastases. Cady and coworkers\(^22\) found a doubling of recurrence rates in patients with a positive margin and a significantly higher rate of recurrence in patients with less than a 1-cm margin compared with that of patients with a margin greater than 1 cm. As liver resection is still the gold standard in achieving long-term survival for colorectal liver metastases, numerous attempts have been made to increase the percentage of patients becoming eligible for curative resection. Once presurgical attempts to increase curative resectability of CRCLM have failed, palliative treatment options offer only a limited chance of prolonging survival.

Cryotherapy has been proved to destroy tumor tissue effectively, both as an additional treatment to remaining lesions after liver resection and as a sole treatment in patients not eligible for liver resection. Only curative surgical removal or destruction of tumor tissue has been shown to improve survival. In liver surgery, the amount of surrounding normal liver tissue that has to be resected with curative intent is still under discussion.\(^23\) Proximity of a tumor to major vessels and inadequate remaining liver volume have therefore been features leading to unresectability.

The results of using cryotherapy to improve inadequate resection margin as described in this report define a new treatment modality that may make more patients eligible for curative resection of CRCLM. The safety of edge cryotherapy appears adequate; our rate of postoperative complications was similar to that of patients undergoing liver resections without cryotherapy. Intrahepatic recurrence rates of up to 100% have been described in patients with involved resection margin.\(^19\) In patients with tumor-free resection margin of less than 1 cm, a recurrence rate of up to 50% has been reported.\(^19\) In our selected patient group with so-called inadequate liver resections for CRCLM, we were able to achieve a favorable edge recurrence–free survival when we applied cryotherapy to improve clearance. The edge recurrence–free survival was 95% in patients with margins less than 1 cm and 86% in patients with involved margins after a median follow-up of more than 3 years. Intrahepatic recurrence occurred in 42% of our patients after edge cryotherapy, irrespective of involved or close margins. We were able to achieve intrahepatic recurrence–free survival times similar to those reported for patients with a margin greater than 1 cm (median, 32 months for involved margin and 37 months for margin <1 cm).\(^24\) Overall survival was similar in both groups, and we attained a median survival time of 39 months (95% confidence interval, 36.8-41.2) in the whole study group. This is equivalent to results achieved by other groups in patients with so-called clear margins.\(^1\)

Our data suggest that resection of colorectal liver metastases can be potentially curative, even in a high-risk patient group with inadequate resection margins, when additional edge cryotherapy is applied during surgery. This may be useful in extending the proportion of patients with CRCLM in whom potentially curative treatment can be performed.

We are grateful to Spembly, Andover, England, for support and equipment (Cryotech LC system 3000); Erbe, Tubingen, Germany, for equipment (Cryo 6 system); Health Care of Australia, Service of Mayne Nickless Ltd, Sydney, Australia, for supporting our unit.

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REFERENCES