

# LONG-TERM SURVIVAL AFTER HEPATIC CRYOSURGERY VERSUS SURGICAL RESECTION FOR METASTATIC COLORECTAL CARCINOMA: A CRITICAL REVIEW OF THE LITERATURE

Véd R. Tandan, MD, MSc; Athanasios Harmantas, MD, MSc; Steven Gallinger, MD, MSc

**OBJECTIVE:** To critically assess the evidence for long-term survival after hepatic resection and hepatic cryosurgery for metastatic colorectal cancer. The purpose of this review is to determine if a randomized controlled trial comparing these two treatment modalities is justified.

**DATA SOURCES:** A review of the medical literature from 1973 to 1995 using the MEDLINE and CANCERLIT databases. References were also retrieved from the bibliographies of identified articles and from experts in the field of hepatobiliary and pancreatic surgery.

**STUDY SELECTION:** One hundred and seventy-eight studies were reviewed. Studies presenting original data on the results of hepatic resection or cryotherapy for colorectal liver metastases were selected. Studies were excluded if they did not present survival data longer than 2 years. Studies pertaining to resection for fewer than 60 patients with colorectal metastases to the liver were excluded.

**DATA EXTRACTION:** Data forms were designed before studies were examined in detail. All studies that met the inclusion and exclusion criteria were reviewed and the identified data extracted and tabulated.

**DATA SYNTHESIS:** No controlled studies were identified, only case series. Four reports on hepatic cryosurgery and 9 on hepatic resection met the study criteria. The cryosurgery studies were methodologically poor; the resection studies were larger and more methodologically sound. The median follow-up for cryosurgery ranged from 12 to 28.8 months, that for resection 21 to 69 months. There is clear evidence that hepatic cryosurgery has a role in the management of selected patients with colorectal metastases to the liver. However, valid conclusions cannot be made about the 5-year survival rate. The results of the studies on hepatic resection in patients with colorectal metastases to the liver have greater validity and consistency, with 5-year survival rates of 20% to 40%.

**CONCLUSIONS:** Although hepatic cryosurgery offers some unequivocal and other potential advantages over surgical resection for colorectal metastases to the liver, the published data do not support its use in patients with resectable disease outside a clinical trial, and do not yet justify a randomized trial. A study that collects prospective data on 2 groups of patients (resectable v. unresectable) who differ only in the anatomic location of their metastases within the liver is needed.

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**OBJECTIF :** Procéder à une évaluation critique des données probantes sur la survie à long terme après une résection hépatique et une cryochirurgie hépatique à cause d'un cancer colorectal avec métastases. Cet examen vise à déterminer si une étude contrôlée randomisée où l'on comparerait ces deux modes de traitement est justifiée.

**SOURCES DE DONNÉES :** Recension des récits médicaux de 1973 à 1995 dans les bases de données MEDLINE et CANCERLIT. On a aussi extrait des références de bibliographies d'articles et l'on en a obtenu d'experts dans le domaine de la chirurgie hépatobiliaire et pancréatique.

**SÉLECTION D'ÉTUDES :** On a examiné 178 études et choisi des études qui présentaient des données origi-

*From the Department of Surgery, University of Toronto, Mount Sinai Hospital, Toronto, Ont.*

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**Correspondence to:** Dr. Steven Gallinger, Mount Sinai Hospital, 600 University Ave., Suite 1225, Toronto ON M5G 1X5

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nales sur les résultats d'une résection hépatique ou d'une cryothérapie pour métastases au foie d'origine colorectale. On a exclu les études qui ne présentaient pas de données sur une survie de plus de deux ans, de même que les études portant sur les résections chez moins de 60 patients atteints de métastases au foie d'origine colorectale.

**EXTRACTION DE DONNÉES :** Les formules de données ont été conçues avant l'analyse détaillée des études. On a examiné toutes les études qui satisfaisaient aux critères d'exclusion et d'inclusion et extrait les données identifiées que l'on a organisées en tableau.

**SYNTHÈSE DES DONNÉES :** On n'a trouvé aucune étude contrôlée, mais des séries de cas seulement. Quatre comptes rendus de cryochirurgie hépatique et neuf rapports de résection hépatique satisfaisaient aux critères de l'étude. La méthodologie des études sur la cryochirurgie était médiocre. Les études sur la résection avaient plus d'envergure et une méthodologie plus solide. La médiane du suivi a varié de 12 à 28,8 mois dans le cas de la cryochirurgie et de 21 à 69 mois dans celui de la résection. Des données probantes indiquent clairement que la cryochirurgie hépatique a un rôle à jouer dans le traitement de certains patients atteints de métastases au foie d'origine colorectale. On ne peut toutefois tirer de conclusions valables au sujet du taux de survie à cinq ans. Les résultats des études sur la résection hépatique chez les patients atteints de métastases au foie d'origine colorectale sont plus valides et uniformes et les taux de survie à cinq ans varient de 20 % à 40 %.

**CONCLUSIONS :** Même si la cryochirurgie hépatique présente des avantages sans équivoque et d'autres avantages possibles par rapport à la résection chirurgicale de métastases au foie d'origine colorectale, les données publiées n'appuient pas son utilisation chez les patients atteints d'une maladie résécable, sauf dans le cadre d'une étude clinique, et ne justifient pas encore une étude randomisée. Il faut procéder à une étude dans le cadre de laquelle on recueillera des données prospectives sur deux groupes de patients (tumeurs résécables c. non résécables) qui ne diffèrent que par l'emplacement anatomique de leurs métastases au foie.

Each year in Canada, approximately 16 000 new cases of colorectal carcinoma are diagnosed and 6000 to 7000 patients die from this disease.<sup>1</sup> In 20% to 25% of these patients, the liver is the only site of metastatic spread; however, only 10% to 20% of patients with metastatic disease confined to the liver are candidates for surgical resection.<sup>2-4</sup> A large number of case series have reported 5-year survival rates ranging from 25% to 45% for hepatic colorectal metastases treated by surgical resection. Many patients who have unresectable disease have metastases that are too close to major vascular structures, bilobar disease or other comorbid conditions that preclude hepatic resection.

Cryosurgery, a treatment in which tumours are frozen and then left in situ to be reabsorbed, was first applied to the liver by Cooper in 1963.<sup>5</sup> Cryosurgery has the advantage of being a focal treatment, thus allowing treatment of lesions affecting multiple sites in the liver. In addition, lesions adjacent to large blood vessels can be frozen without sacrificing the vessels,

since the flowing blood acts as a heat sink and protects the vessels.<sup>6</sup> Advances in surgical technique and the advent of intraoperative ultrasonography have made hepatic cryosurgery a practical and safe procedure.

In this report we critically assess the evidence for both hepatic resection and cryosurgery in the treatment of metastatic colorectal cancer to the liver. The primary end point used for comparison is the 5-year survival rate, with particular emphasis on the margin of error in this estimate.

## METHODS

We carried out a detailed review of the medical literature to identify all articles dealing with hepatic resection and cryosurgery for colorectal metastases. Three separate MEDLINE searches covering the period 1973 to 1995 were carried out independently, 2 by the authors, and 1 by a medical librarian who used several different search strategies. This time frame was chosen for 2 reasons. First, the organization of the MEDLINE database made these dates convenient to use.

More importantly, we felt that articles published before 1973 were unlikely to reflect the more modern results due to changes in surgical technique and perioperative care in patients who undergo hepatic resection. A similar search was done on the CANCERLIT database. References were also retrieved from the bibliographies of identified articles and from experts in the field of hepatobiliary and pancreatic surgery.

Citations were initially classified according to their content as determined by title or abstract, or both. Initially, we included articles that presented original data on the results of resection or cryotherapy for any liver tumours. Review articles that did not present original data were scanned for references but were not included in this review. Articles that did not describe any patients with colorectal metastasis were excluded. Articles were also excluded if they did not present any survival data longer than 2 years after resection for colorectal metastasis. The articles on surgical resection included series of 19 to 859 patients with very heterogeneous criteria for management. Most

of the larger series were more recent updates of previously reported smaller series. As a result, for the resection data only, we excluded series containing fewer than 60 patients with colorectal metastases to the liver. When there were several reports from the same centre, only the most recent report that included data on patients presented in earlier reports was included.

Articles were then classified according to study design. Methodologic criteria had been selected to categorize case-control studies and cohort studies. Unfortunately these criteria were not applicable as no controlled trials could be found in the literature using the approach described. The only reports found were case series or case reports with no controls. Methodologic criteria for articles dealing with clinical course and prognosis were applied to the case series identified (Table I<sup>7</sup>).

## RESULTS

### Cryosurgery

Forty-nine citations were reviewed. Of the 13 citations that presented original data on cryosurgery for the initial management of colorectal metastases to the liver, only 6 presented data with follow-up of longer than 2 years. Two of these citations were available in abstract form only.<sup>8,9</sup> The 4 remaining articles are summarized in Table II.<sup>10-13</sup>

**Table I**

#### Methodologic Criteria for Assessing Clinical Course and Prognosis<sup>7</sup>

Inception cohort assembled
Referral pattern described
Complete follow-up achieved
Objective outcome criteria developed and used
"Blind" outcome assessment
Adjustment for extraneous prognostic factors

Two cryosurgery articles<sup>11,13</sup> met 3 of the 6 methodologic criteria, 1 article<sup>10</sup> met 2 criteria and 1 article<sup>12</sup> met only 1 criterion. Only 1 reference<sup>11</sup> assembled a true inception cohort, defining patients with histologically proven metastases to the liver for treatment. Given the operator dependence of intraoperative ultrasonography, one wonders how many of the survivors reported in the other 3 papers may have had cryotherapy for lesions that were not in fact metastases. This would clearly bias the results toward an improved survival. None of the papers described their referral pattern; however, they are all from known tertiary care centres, and currently this type of therapy is usually performed at a tertiary care centre with experience in hepatic surgery. Complete follow-up was achieved in all but 1 report, and objective outcome criteria for recurrence were defined in all studies. The outcome assessment was not blinded in any of the studies. This could have biased the results in favour of not reporting subtle recurrences; however, the reporting of death (cause of death was not stratified) would not likely be affected. Blinding could have been achieved by having an independent blinded observer interpret the results of the CEA levels, CT and ultrasonography used to detect recurrence. None of the articles made adjustments for important extraneous prognostic factors such as Dukes' staging of primary tumours or the number of patients with significant comorbid disease.

There are clearly some patients in each series who have achieved long-term survival after hepatic cryosurgery for colorectal metastases. The median follow-up varied from 12 to 28.8 months among the 4 papers, with ranges from 3 to 88 months; however, none of the studies stated how many patients were followed up and for how

long. Thus, it is virtually impossible to interpret the survival rates presented in each study.

### Resection

We reviewed 129 articles. Of these, 32 passed the initial exclusion criteria, presenting primary data on hepatic metastases from colorectal cancer treated by hepatic resection with a minimum of 2 years of follow-up. Only 9 presented data on 60 or more patients with colorectal metastasis and were not followed by a more recent update presenting data on the same patients. These articles are outlined and their methodologic criteria described in Table III.<sup>14-22</sup>

It is important to note that the largest series<sup>14</sup> had data on 859 patients from the US Registry of Hepatic Metastases. This registry collected retrospective data on consecutive patients treated between 1948 and 1985 from 24 participating institutions. There was likely considerable overlap between the patients in this series and those reported in 4 other series<sup>17,20-22</sup> since these centres participated in the registry. It is impossible to distinguish which patients in these reports were included in the registry. Even if all 665 patients in these 4 reports had been included in the registry, 194 patients would be described who had not otherwise been considered in this review and should be included.

In contrast to the cryosurgery data, the resection data were more uniform in terms of both results and methodology. The best study<sup>18</sup> met 4 of the methodologic criteria, 6 of the 9 series met 3 of these criteria and 2 studies<sup>17,19</sup> met only 2 criteria. Only 2 of the studies<sup>18,19</sup> met the important criterion of assembly of an inception cohort; these were the only prospective series reported in the literature. The remainder of the series were retrospective,

and complete follow-up was available on all patients. One prospective series<sup>19</sup> had follow-up on 65 of 69 patients. None of the reports described their re-

ferral patterns, but all reports were from tertiary care centres. Unlike cryosurgery, liver resection for colorectal metastases is also performed at non-

tertiary care centres, so this information would be more relevant to the resection data. Objective outcome criteria were used in all studies, but none

**Table II**

**Data on Series of Patients Who Underwent Cryosurgery for Hepatic Metastases From Colorectal Cancer**

Data	Series			
	Ravikumar et al, 1991 <sup>10</sup>	Onik et al, 1991 <sup>11</sup>	Kane, 1993 <sup>12</sup>	Morris, 1995 <sup>13</sup>
Period of study	1985–1990	1985–1989	ND	ND
No. of patients	24	18	51	92
Mean age, yr	67	55	60	60
Inception cohort assembled	No	Yes	No	No
Referral pattern described	No	No	No	No
Complete follow-up	Yes	Yes	No	Yes
Objective outcome criteria	Yes	Yes	Yes	Yes
“Blind” outcome assessment	No	No	No	No
Adjustment for extraneous prognostic factors	No	No	No	Yes
Median (range) follow-up, mo	24 (5–60)	28.8 (11–60)	12 (3–88)	13.4
No. followed up for 5 yr	ND	ND	ND	ND
Dukes’ class	ND	ND	ND	ND
Indications for cryosurgery	No extrahepatic disease, unresectable due to bilaterality, anatomic location or comorbid conditions	No extrahepatic disease, unresectable due to bilaterality, anatomic location or comorbid conditions. Curative intent only	No extrahepatic disease, unresectable due to location, multiplicity, extent of disease or comorbid conditions	No extrahepatic disease, unresectable due to bilaterality, anatomic location or comorbid conditions
Mean (range) no. of lesions frozen	ND	6.08 (1–12)	1.4 (1–3)	3.9
30-d death rate, %	0	0	0	0.5
Median hospital stay, d	ND	ND	7	ND
Lesions confirmed pathologically, %	0	100	ND	ND
Received postop. chemotherapy, %	ND	ND	ND	“Almost all”
5-yr survival, %	ND	ND	Projected 40%	ND
Result	33.5% survival, 29% disease-free survival	33% survival, 22% disease-free survival	64% survival, 29% disease-free survival. Kaplan–Meier projection 40% 5-yr survival	Median survival 25.3 mo

ND = not described

**Table III**

**Data on Series of Patients Who Had Resection for Hepatic Metastases From Colorectal Cancer**

	Series								
	Hughes et al, 1986 <sup>14</sup>	Nordlinger et al, 1987 <sup>15</sup>	Ekberg et al, 1987 <sup>16</sup>	Fortner, 1988 <sup>17</sup>	Scheele et al, 1991 <sup>18</sup>	Steele et al, 1991 <sup>19</sup>	Savage and Malt, 1992 <sup>20</sup>	Rosen et al, 1992 <sup>21</sup>	Gayowski et al, 1994 <sup>22</sup>
Period of study	1948-1985	1970-1985	1971-1984	1971-1985	1960-1988	1984-1988	1962-1988	1960-1987	1981-1991
No. of patients	859	80	68	77	266	69	104	280	204
Mean age, yr	ND	59	62	57	58	61-70?	60	ND	59
Inception cohort assembled	No	No	No	No	Yes	Yes	No	No	No
Referral pattern described	No	No	No	No	No	No	No	No	No
Complete follow-up	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Objective outcome criteria	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
"Blind" outcome assessment	No	No	No	No	No	No	No	No	No
Adjustment for extraneous prognostic factors	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Median follow-up, mo	21	ND	20	ND	52	ND	ND	51	69
5-yr follow-up, %	10	ND	ND	25	13	ND	10	> 80	> 36
Dukes' class, %	B 26, C 37, ? 37	B 24, C 69, ? 7	A 5, B 26, C 69	A 7, B 36, C 50, ? 7	A, B 29, C 68, ? 3	ND	B 33, C 52, ? 12	B 45, C 50, ? 5	A 1, B 26, C 46, ? 27
Extrahepatic disease ruled out	No	Yes	No	Yes	ND	Yes	No	No	No
Solitary lesion, %	59	55	50	ND	56	67	55	66	45
30-d death rate, %	ND	4	5.6	ND	5.6	2.7	ND	2	0
Median (range) hospital stay, d	ND	ND	ND	ND	ND	ND	ND	ND	ND
Lesions confirmed pathologically, %	ND	100	ND	ND	ND	ND	ND	ND	ND
Received postop chemotherapy, %	Some	ND	ND	57	6	ND	ND	Some	ND
5-yr survival (median, mo), %	33	25 (?)	20 (22). Periop deaths excluded	49 (59). Periop deaths excluded	31 (M 40, F 33)	ND (37.1)	18 (25)	25 (33.6)	32 (33)

ND = not described

had blinded assessments. The problems with lack of blinding and possible solutions have already been discussed. In contrast to the cryosurgery reports, 8 of the resection reports adjusted for extraneous prognostic factors such as Dukes' stage of the primary tumour.

Only 1 report stated that lesions were confirmed by pathological examination; however, with retrospective reviews of resected specimens it is reasonable to assume that the lesions were confirmed.

The median length of follow-up ranged from 21 to 69 months, which is significantly longer than that for cryosurgery, and in 6 of the 9 reports a significant number of patients had been followed up beyond 5 years making the 5-year survival data much more precise. The 5-year survival data were fairly consistent, in the range of 20% to 40%, although it should be noted that 2 series<sup>16,17</sup> excluded perioperative deaths in the calculation of the 5-year survival rate. This is clearly incorrect and biases the survival upward.

## DISCUSSION

Despite the many methodologic flaws in the reports on hepatic resection, the results were similar and supported by numerous other smaller series from many countries. In addition, these data span almost 50 years of experience. Although the best evidence would come from a randomized controlled trial of resection versus no therapy or chemotherapy, such a trial will likely never be performed for ethical reasons because the weight of evidence suggests that surgical resection in properly selected patients can provide 5-year survival rates in the range of 20% to 40%, which is far greater than any reported results for nonsurgical therapies. Therefore, it seems that if cryosurgery is to be used to treat patients who have

potentially resectable disease, the results of cryosurgery should be validated against resection, ideally in a randomized controlled trial.

Data on length of hospital stay were not provided in any of the resection articles, and in only 1 of the cryosurgery articles, making comparison impossible, but it has been suggested that patients treated with cryosurgery leave hospital earlier.<sup>23</sup> The perioperative death rate for resection, when reported, was between 2% and 5% in 4 of the 9 resection articles. The lower death rate reported in the cryosurgical series must be considered carefully since only 185 patients were treated in the combined series. The variance around the estimate of death rate is large and the rate could easily have been underestimated due to the small sample size.

It is clear from several of the reports that there is no uniformity in post-resection treatment; some patients received systemic chemotherapy, some hepatic arterial infusion chemotherapy and some no adjuvant therapy. The percentage of patients receiving each of these therapies is unclear in all but 1 report, and none of the articles stratified patients according to this criterion. Therefore, it is impossible to separate the effects of surgery or cryosurgery from chemotherapy. This is clearly a major flaw in all the studies of cryosurgery and resection, and one might assume that "unresectable" patients treated with cryosurgery were even more likely to have been treated with postoperative adjuvant therapy than the resection patients. This last point could clearly make cryosurgery appear better than it actually is, compared with resection.

From the literature, it is difficult to draw valid conclusions on the 5-year survival rate of patients treated with cryosurgery. Some evidence of efficacy is necessary to justify a randomized trial.

It is interesting to note that even in the era of evidence-based medicine some surgeons do not feel that such a trial is necessary and are already treating resectable patients with cryosurgery.<sup>23</sup> In fact, of the "resections" performed in one series,<sup>19</sup> 11% were actually not resections at all, but rather cryosurgery, and the results were combined.

Kaplan–Meier projections of 5-year survival rate in the cryosurgery reports could be severely biased if they were based on only 1 or 2 patients, who may not have had metastatic liver disease at all, because no histologic data were available in these 2 reports. Since none of this information was provided in the cryosurgery reports, most of which were methodologically poor, one must assume either that the authors' conclusions are correct (a very dangerous assumption) or that it is impossible to draw any valid conclusions on the 5-year survival rate of patients treated with cryosurgery for hepatic metastases from colorectal carcinoma.

## CONCLUSIONS

Cryosurgery offers some unequivocal and many potential advantages over surgical resection for colorectal metastases to the liver. The published data do not support the use of cryosurgery in patients with resectable disease outside a clinical trial and in our opinion do not yet justify a randomized trial. We believe the most ethical approach is to collect prospective data on 2 groups of patients who differ only in the anatomic location of their metastases within the liver. All patients who are deemed to have technically resectable disease and are able to tolerate the procedure should undergo resection. Patients whose metastases are of similar size and number who cannot undergo resection because of bilobar disease, proximity to major vascular structures, or comorbid conditions

that preclude resection but not cryosurgery, should be treated with cryosurgery. In this manner it would be possible to collect concurrent prospective data on cases (cryosurgery) and controls (resection) that are as similar as possible within the ethical constraints.

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