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Effect of Hepatic Artery Chemotherapy on Survival of Patients with Hepatic Metastases from Colorectal Carcinoma Treated with Cryotherapy

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Abstract. Thirty-eight patients with unresectable multiple liver metastases from colorectal carcinoma were treated with either hepatic artery chemotherapy (HAC) and cryotherapy ($n = 27$) or cryotherapy alone ($n = 11$). Follow-up survival data were summarized using Cox regression. Allowing for the effect of the pathology of the primary tumor and the preoperative carcinoembryonic antigen (CEA) level, those patients who did not receive HAC after cytoreduction were three times as likely to die as those given HAC (RR 3.3, 95%; CI 1.2–9.3). The estimated median survival of patients treated with cryotherapy alone was 245 days, whereas for those given more than 3 months of HAC plus cytoreduction therapy it was 570 days. It is recommended that all patients who receive cryotherapy for multiple liver metastases from colorectal rectal carcinoma be given subsequent hepatic artery chemotherapy.

Liver metastases occur in up to 75% of patients with colorectal carcinoma. Although the best prospect of cure is achieved by hepatic resection [1, 2], only 5% of patients with liver metastases are suitable for surgical treatment. The reported average survival among patients with untreated hepatic metastases is generally around 6 months [3, 4]. However, there is good evidence that hepatic artery chemotherapy (HAC) can increase survival in those patients who are unsuitable for surgery [5–8].

Hepatic cryotherapy is another modality of treatment that has received considerable attention as a treatment for inoperable metastatic disease [9, 10]. As a result, considerable advances have been made in the localization of metastases, probe placement, control of the freezing process by intraoperative ultrasonography, and refinement of the liquid nitrogen cryoprobes [9, 11–15]. There are already encouraging tumor markers and radiologic and survival data supporting the use of hepatic cryotherapy for metastases from colonic carcinoma [15–17]. However, there have been no reports of the effect of combining HAC with cryotherapy.

This paper reports a retrospective cohort study that allowed comparison of survival following cryotherapy alone and cryotherapy in combination with HAC when used for treatment of unresectable liver metastases from colorectal carcinoma.

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Subjects and Methods

Subjects

Potential subjects were those patients who were considered unsuitable for surgical resection of liver metastases from colorectal carcinoma and who instead received hepatic cryotherapy with or without subsequent intraarterial chemotherapy. Extrahepatic disease was excluded by chest radiography, CT scan of the abdomen and pelvis, and bone scans. Patients who survived less than 4 months were not included in the study. All patients were followed to the end of the study period, and all gave informed consent. The research protocol was approved by the South Sydney Area Health Service Ethics Committee.

Cryotherapy

The liver was examined directly with an ultrasound probe, initially using a Siemens SL1 scanner and later an ALOKA 650. Both machines used linear array probes. The cryotherapy equipment used was a Cryotec LCS 2000 [18]. Detailed descriptions of the procedure and perioperative care are found elsewhere [14, 19]. Briefly, intraoperative ultrasonography was used to control the freezing process so the iceball extended 1 cm on each aspect of a lesion.

Hepatic Artery Chemotherapy

All patients had a Silastic catheter system inserted at operation after cholecystectomy, ligation of the right gastric artery and all superior duodenal vessels, and mobilization of the gastroduodenal artery. The reservoir was located in a subcutaneous chest wall pocket, and the catheter fed into the abdomen and tied into the gastroduodenal artery. Methylene blue was injected into the reservoir, and immediate bilobar coloration of the liver was used to confirm perfusion. The system was then heparinized (500 units/ml).

The cytotoxic regimen, 1 g 5-fluorouracil (5FU) loaded in a Baxter disposable latex bladder "pump," was given daily for 4 days

on an outpatient basis. Patients were given 50 mg folinic acid by bolus intraarterial injection until November 1992 when we changed to daily oral 15 mg tds for the 4 days because of a high rate of catheter blockage [20]. The systems were flushed twice weekly and the cytotoxic treatments repeated monthly.

Treatment Groups

All 38 eligible subjects were included in the study. Of them, 11 received less than 3 months' HAC and comprise the "no-HAC" group. Five had their catheter system fail within 3 months, and two additional subjects had their HAC stopped because of evidence of cardiac toxicity. Four subjects did not receive any HAC because of their referring physicians' preference ($n = 3$) or evidence of duodenal perfusion ($n = 1$). The 27 subjects who had at least 3 months' chemotherapy were included in the "HAC" group.

Data Analysis

The association of patients' age and sex, their preoperative carcinoembryonic antigen (CEA) levels, the histology of the primary tumor, its Dukes' staging, the number of hepatic metastases, and the diameter of the largest hepatic metastasis with the treatment group was tested using a logistic regression.

The relation of treatment group with survival time was summarized using Cox regression [21]. All seven patient descriptors, above, were considered potential confounders of the relation of treatment group and survival and were included in the initial Cox regression model of time in treatment. To determine if there was a relation between the time the HAC remained functional and survival in the "no-HAC" group, an interaction term was inserted in the regression. This term was the product of group (0 = HAC, 1 = no-HAC), and the time the HAC remained functional (in months). Observations were censored if subjects were still alive at the end of the study period (April 1993).

Data included in the Cox regression analyses were assessed for conformity to the proportional hazards assumption using the p(PH) statistic [22], and models were tested for colinearity and influential observations [23]. The final model was developed by a backward elimination of nonconfounders so as to retain the estimated regression coefficients of the predictor variables of interest while increasing the precision of the estimate [23]. The effect of filling missing values with group means was checked by repeating analyses with observations with missing values excluded.

Analyses were performed on an Epson 3/33 PC using the Statistical Package for Interactive Data Analysis (Spida, Statistical Laboratory, Macquarie University).

Results

When all seven patient descriptors were considered together in a logistic regression with the outcome study group, there was no significant difference between the 11 "no-HAC" and 27 "HAC" patients (Table 1). Six "no-HAC" patients died during the first year of follow-up and three survived, giving a 1-year survival rate of 33%. Two observations were censored during the first year. One "no-HAC" patient died, and another observation was censored during the second year of follow-up. As one "no-HAC" patient survived more than 2 years, the 2-year survival for the group was 12.5%. Seven "HAC" patients died during the first year of follow-up and 14 survived, giving a 1-year survival rate of 67%. Three "HAC" patients survived more than 2 years after surgery, and four patients died during the second year of follow-up. As 13 observations were censored during the first 2 years of follow-up, the 2-year survival rate for the "HAC" group was 21%.

Table 1. Variables for subjects.

Variables	No HAC ($n = 11$)	HAC ($n = 27$)
Continuous variables		
Age (years)	53.7 ± 14.7[a]	60.4 ± 10.0
Hepatic metastases	4.8 ± 4.3	4.9 ± 4.6
Largest hepatic metastasis (diameter, cm)	4.7 ± 1.8	4.4 ± 1.9
Preoperative CEA (ng/ml)	414 ± 798	228 ± 366
Ordinal variables		
Sex (males)	9[b] (82%)	22 (81%)
Dukes' classification of primary		
A or B	4 (36%)	12 (44%)
C or D	7 (64%)	15 (56%)
Pathology of primary		
Well to moderately differentiated	8 (89%)	16 (59%)
Moderately to poorly differentiated	1 (11%)	11 (41%)

[a]Mean ± SD.
[b]Number of subjects.

Table 2. Final Cox regression model of cryotherapy with and without HAC and survival.

Variable	p value	RR	95% CI RR
Treatment group (HAC = 0, No HAC = 1)	0.025	3.3	1.2–9.3
Pathology of primary (poorly diff. = 0, well diff. = 1)	0.052	2.9	1.0–8.7
Preop CEA (300 ng/ml units)	0.006	1.13	1.03–1.25

The two groups' median survival times were estimated using the Kaplan-Meier function: no-HAC, 331 days; HAC, 582 days ($p < 0.065$ logrank). The final Cox regression model of survival time is displayed in Table 2. (Note: preoperative CEA level is coded in 300 ng/ml units, the interquartile range.) Allowing for the effect of the histology of the primary tumor and preoperative CEA level, subjects given 3 months or less of HAC were three times as likely to die as those given more than 3 months of HAC after cytoreduction through cryotherapy (RR 3.3, 95% CI 1.2–9.3). Reading from the survival curves plotted from the final Cox regression model (Fig. 1), the estimated median survival time for those given more than 3 months' HAC was 570 days, whereas for those given 3 months or less of HAC after cryotherapy it was 245 days.

Discussion

This study is the first to use HAC in addition to cryotherapy for hepatic metastases from colorectal carcinoma and the first to demonstrate that the use of HAC in this situation is associated with increased survival. This finding is consistent with the results of several randomized, controlled trials that have found that HAC alone achieves significantly higher response rates than systemic

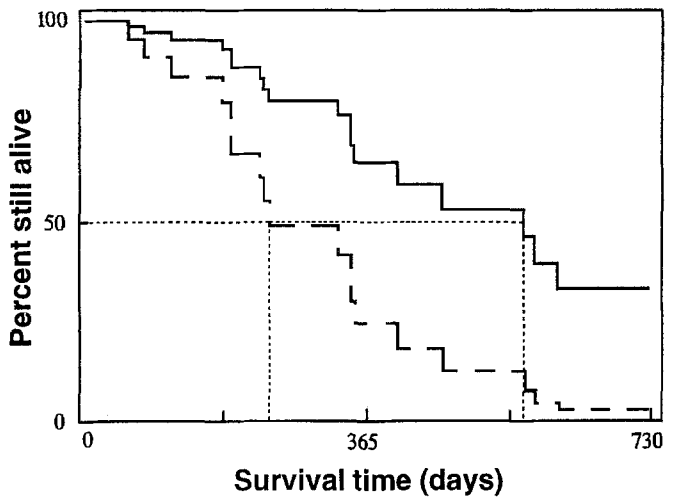

Fig. 1. Estimated survival of patients treated with HAC and cryotherapy (unbroken line) or cryotherapy alone (broken line) calculated using final Cox regression model (Table 2).

chemotherapy [24] and, in two studies, improves survival at least in patients with small volume disease [5, 25].

As the present study was not a randomized trial, the observed results may have been caused by the hepatic artery catheter being more likely to fail in those subjects who were more likely to die. However, if this were the case, the sooner the catheter failed the more likely the patients would be to die. When this possibility was investigated by inserting an interaction term into the regression analysis, there was no measurable association between the time the catheter functioned and survival in the "no-HAC" group. It suggests that there was no association between catheter failure and survival other than through the premature curtailment of HAC.

The median estimated survival for cryotherapy and HAC with 5FU, 570 days, compares favorably with that achieved by hepatic artery infusion of FUDR [24]. Moreover, it should be noted that our survival times are from the date of insertion of the hepatic artery catheter rather than the date of the primary tumor diagnosis or date of resection. Cryotherapy also offers the prospect of cure to a small proportion of patients with unresectable disease who are free of extrahepatic disease and who have a limited number of hepatic lesions [16, 17]. Our data strongly support the use of HAC following cytoreduction by hepatic cryotherapy.

Résumé

Trente-huit patients ayant des métastases hépatiques multiples non reséquables d'origine colorectale ont été traités soit par chimiothérapie par voie artérielle (CVA) associée à la cryothérapie (n = 27) soit par cryothérapie seule (n = 11). Les survies ont été analysées selon la méthode d'analyse du Modèle de Cox. En tenant compte de l'effet de la pathologie de la tumeur primitive et du niveau préopératoire de l'ACE, les patients n'ayant pas eu de CVA après un acte cytoréductif avaient trois fois plus de chances de décéder que ceux qui en ont eu (RR 3.3, 95% IC 12 à 9.3). L'estimation de la survie médiane des patients traités par la cytoréduction seule a été de 245 jours, alors que celle des patients traités par les deux avec une CVA d'au moins trois mois, a été de 570 jours. On recommande que tous les patients ayant des métastases multiples du foie à partir des cancers colorectaux aient une CVA par la suite.

Resumen

En el presente estudio, 38 pacientes con metástasis hepáticas múltiples y no resecables de carcinoma colo-rectal fueron tratados con quimioterapia administrada en la arteria hepática (HAC) y crioterapia (n = 27) o crioterapia sola (n = 11). Los datos del seguimiento fueron resumidos según el método de regresión de Cox. Teniendo en cuenta el efecto de la patología del tumor primario y el nivel preoperatorio de antígeno carcino-embrionario, se halló que aquellos pacientes que no recibieron HAC luego de la citorreducción tuvieron una probabilidad de muerte 3 veces mayor que los que recibieron HAC (RR 3.3, 95% CI 1.2 a 9.3). La sobrevida media estimada de los pacientes tratados con crioterapia sola fue de 245 días, en tanto que aquellos que recibieron HAC por tres meses y terapia de citorreducción fue de 570 días. Se recomienda que todos los pacientes que reciben crioterapia para metástasis hepáticas múltiples de carcinoma colo-rectal reciban luego quimioterapia por vía de la arteria hepática.

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Invited Commentary

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The survival rates of patients with unresectable liver metastases from colorectal cancer has changed little over the past decades. Attempts by clinicians rendered helpless when faced with such patients have given rise to a retinue of options: technologic, pharmacologic, biologic, radiopharmaceutical, and immunologic. Cryosurgery is one such development, aided by the technologic advances in our ability to (1) deliver subzero temperatures to the depths of tissues using closed liquid nitrogen systems; and (2) monitor such cryodestruction precisely with intraoperative ultrasound transducers. Preclinical investigation and clinical studies during the last 10 years have demonstrated that the cryosurgical approach to treat liver tumors is: (1) performed with relative safety, with no or low mortality and minimal morbidity; (2) reasonably effective for the control of treated lesions, as demonstrated by pathologic, radiologic, and tumor marker correlates; and (3) potentially a modality that can prolong overall and disease-free survival in patients with hepatocellular carcinoma or liver metastases from select primary sites such as colorectal cancer and functional neuroendocrine tumors.

Professor Morris and his coworkers are among the leaders in this field. In this issue of *World Journal of Surgery,* they summarize one of the first reports on using hepatic artery chemotherapy to improve on the regional control of colorectal liver metastases achievable by cryosurgery alone. The study is based on a sound rationale: Cryosurgery destroys all "gross disease" within the liver, and hepatic artery infusion chemotherapy is most effective in a "minimal residual disease" setting. There are some reservations about the overall design and analysis of the trial. (The authors state that it is a "prospective research protocol" but present a "retrospective cohort study"; patients surviving less than 4 months were not included in the study analysis; the data were analyzed as though it was a two-arm design but in fact was a single-arm study, with the group that had trouble receiving adequate hepatic infusion chemotherapy being assigned to the cryosurgery-only arm.) Nevertheless, this paper makes a significant contribution by demonstrating that cryosurgery and regional chemotherapy may be an effective modality for a cohort of patients with unresectable disease. We and other investigators are conducting phase I/II trials that are variations of this theme; the data are likely to support the conclusions drawn in this paper.

There are bound to be controversies with regard to future directions in the application of cryosurgery for treatment of tumors of the liver. The existing body of knowledge lends itself to the following possibilities.

1. Although single institutional phase II data have emerged, reproducibility of the studies in a multiinstitutional setting is needed. It should include protocols for cryosurgery alone (perhaps for one to three lesions) and cryosurgery plus regional (or systemic) chemotherapy for more than three lesions. Quality assurance across the board and cost-effectiveness must be ascertained.
2. Specific response rates for individual tumor types (e.g., hepatoma, colorectal, neuroendocrine, sarcoma) could also be gleaned from such studies.
3. Phase III trials should compare the efficacy of cryosurgery with that of other modalities. Although this testing is contentious for resectable tumors, a trial comparing cryosurgery plus regional infusion chemotherapy with the standard of care (? systemic chemotherapy utilizing 5FU and leucovorin) is justifiable.