ORIGINAL ARTICLE

A Comparison of Percutaneous Cryosurgery and Percutaneous Radiofrequency for Unresectable Hepatic Malignancies

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Hypothesis: The complication and success rates in patients treated with either percutaneous cryosurgery (PCS) or percutaneous radiofrequency (PRF) for unresectable hepatic malignancies are similar.

Design: Retrospective study.

Setting: University hospital.

Patients and Methods: Sixty-four patients were treated with either PCS (n=31) or PRF (n=33). Patient treatment was based on the random availability of the probes. Tumors were evaluated by a blinded comparison of pretreatment and posttreatment helical computed tomographic scans. All living patients had at least a 6-month follow-up.

Main Outcome Measures: Complication rate, initial treatment success (complete devascularization of the tumor), and local recurrence (tumor revascularization within or at its periphery).

Results: The distribution of tumor types was similar in the 2 groups ($P=.76$). One patient with cirrhosis died of variceal hemorrhage on day 30 after PCS (mortality, 3.2%), while no mortality was observed after PRF ($P=.48$). Complications occurred in 9 (29%) of the patients following PCS and in 8 (24%) of the patients following PRF ($P=.66$). Initial treatment success was comparable in the 2 treatment groups (30 [83%] of 36 tumors following PCS vs 34 [83%] of 41 tumors following PRF). However, local recurrences occurred more frequently after PCS than after PRF (16 [53%] of 30 vs 6 [18%] of 34; $P=.003$). The higher rate of local recurrence was identified for metastases (10 [71%] of 14 after PCS vs 3 [19%] of 16 after PRF; $P=.004$), while the difference was not significant for hepatocellular carcinoma (6 [38%] of 16 after PCS vs 3 [17%] of 18 after PRF; $P=.25$). Multivariate analysis demonstrated that the use of PCS ($P=.003$) and more than 1 treatment ($P=.05$) were independent risk factors for local tumor recurrence.

Conclusion: While similar initial treatment success and complication rates are observed following either PCS or PRF, local recurrences occur more frequently following PCS, particularly for metastases.

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HEPATIC RESECTION is the treatment of choice for hepatic malignancy; however, this may be achieved in fewer than 30% of those with primary[1,2] and in 10% to 20% of those with secondary hepatic malignancies.[1,3,4] Hepatic resection may be contraindicated because of multifocal bilateral disease, tumor proximity to major vascular or biliary structures, technical inaccessibility of the tumor because of previous hepatectomy, or inadequate functional hepatic reserve related to coexistent cirrhosis. For these groups of patients, other techniques of therapy have been explored. In situ techniques for the destruction of tumors, such as cryosurgery and radiofrequency, are accepted as alternative therapies for those with unresectable hepatic malignancies.

Cryosurgery is based on the cyclic application of extremely low temperatures (−196°C) to the tumor through a probe, which is positioned in the tumor, cooled with either circulating liquid nitrogen or argon. Tumor cell destruction occurs by ice crystal formation during the repeated freezing and thawing process, resulting in cellular dehydration, protein denaturation, and microcirculatory failure.[5,6] Radiofrequency is based on thermal coagulation by achieving tissue temperatures exceeding 50°C through a probe, similar to cryosurgery, positioned in the tumor. By delivering a high-frequency (460-500 kHz) alternating current, which is turned into heat through ionic agitation, radiofrequency re-

See Invited Critique at end of article

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sults in tissue hyperthermia and leads to intracellular protein denaturation and cellular destruction.[7]

Cryosurgical treatment of hepatic malignancies may be used when conventional surgical resection is restricted by anatomical limitations[5,8,9] or as an adjunct to resection,[9-12] and is effective and safe in the treatment of hepatic malignancies.[5,9,13] Similarly, radiofrequency has been used for unresectable hepatic malignancies.[14-16] Improvements in the engineering of cryosurgical tools, such as the development of smaller probes, and the experience gained in open cryosurgical treatment have been followed by the introduction of minimally invasive percutaneous approaches to cryosurgery.[17,18] Given the small probes for radiofrequency at its birth, this minimally invasive approach has been demonstrated to be feasible.[19,20] With these technological refinements and the experience gained in ultrasonography, percutaneous cryosurgery (PCS) and percutaneous radiofrequency (PRF) have been made possible.

Although either cryosurgery or radiofrequency may be used as local destructive treatments, no consensus exists for the preferential use of either therapy.[8,21] This report compares the safety, efficacy, and outcomes in patients with unresectable primary and secondary hepatic malignancies treated with either PCS or PRF.

METHODS

From September 1, 1994, to July 31, 2000, 64 patients with unresectable hepatic tumors treated at our institution by PCS (n=31) or PRF (n=33) were evaluated. During this same period, 524 patients with resectable tumors underwent liver resection for either hepatocellular carcinoma (HCC) (n=146) or metastatic disease (n=378). Percutaneous treatment of a hepatic malignancy was considered when patients met the following criteria:

1. Documented primary or secondary hepatic malignancy. Diagnosis was made by either biopsy of the lesion or the combination of increasing levels of tumor markers and the appearance of a lesion on either an ultrasonographic or a computed tomographic (CT) scan.
2. Unresectability of the tumor.
3. Ultrasonographic evidence of the tumor(s) to be treated.
4. Tumors to be treated were mainly 50 mm in diameter or smaller, and there were 3 or fewer tumors.

Patients were deemed to have unresectable disease and were classified by the presence of the following: (1) severe cirrhosis, precluding resection; (2) tumor bilobarity or ill location, precluding a complete macroscopic tumor resection; (3) multiple previous hepatectomies (≥2), precluding tumor accessibility or resulting in an anticipated inadequate hepatic volume; or (4) extrahepatic disease.

All patients underwent baseline ultrasonography to characterize the tumor, to determine the existence of other lesions, and to determine the feasibility of a percutaneous approach. The percutaneous approach was considered in all lesions visible on echography, provided they were neither in contact with a main bile duct nor located in a superficial position given the risk of injury to the biliary tree and neighboring visceral structures. All patients underwent an abdominal CT scan to characterize the lesion(s) and to determine the presence of extrahepatic disease. To complete an extrahepatic evaluation, all patients underwent thoracic CT. Serum laboratory tests, consisting of a complete blood cell count, a platelet count, a coagulation profile, renal and electrolyte panels, a hepatic panel (determination of total bilirubin, alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, and albumin levels), and a test for tumor markers (α-fetoprotein for primary and carcinoembryonic antigen and CA 19-9 for secondary hepatic tumors), were performed in all patients. In the case of HCC, all patients were examined regarding the degree of hepatic dysfunction using the Child-Paul-Brousse classification.[22]

Patients were treated with either modality based on the random availability of the probes, without any preconceived difference between the 2 treatments. At the beginning of the study period, cryosurgery was performed with one system (LCS 2000 apparatus; Spembly Medical, Hampshire, England, and Candela Corporation, Wayland, NY), while later patients were treated with a different system (CRYO-HIT System; Galil Medical Ltd, Yokneam, Israel). Use of either system is similar, but one (LCS 2000 apparatus) delivers liquid nitrogen as the coolant, whereas the other (CRYO-HIT System) uses argon for the cooling process. A 3-mm probe is inserted into the center of the tumor under ultrasonographic guidance and 2 freeze-thaw cycles are performed, each reaching a temperature of −196°C at the tip of the probe. Multiple probes are used simultaneously for lesions larger than 3 cm. The time of freezing is dependent on the achievement of an "ice ball," visible as a hypoechoic region by transabdominal ultrasonography. Furthermore, ultrasonography is used to ensure that all disease and a 1-cm margin are encompassed within the ice ball. The cryoprobe is removed when the tip temperature reaches 0°C to minimize bleeding.

Radiofrequency was performed with one system (RITA System; RITA Medical Systems, Inc, Mountain View, Calif). Similar to the placement techniques used for cryosurgery probe placement, the probe for the radiofrequency apparatus is inserted and positioned under ultrasonographic guidance. For this study, we used a radiofrequency system with a 50-W generator and a 14-gauge probe, which contains 7 individual electrode arms that are deployed in situ after optimal probe positioning. After deployment of the multiple array, 50 W of alternating current is delivered to achieve electrode arm temperatures higher than 90°C for a minimum of 8 minutes. Multiple overlapping treatments are applied for lesions larger than 3 cm. Following treatment, the probe tract is cauterized as the probe is withdrawn. The hyperechoic area of treated tissue is monitored with ultrasonography.

Although important advancements have been made in radiofrequency ablation systems, the 50-W system used was one of the preferred systems at the time of the study.

Blood cell counts, liver function tests, and coagulation profiles were performed at 1 and 2 days following treatment. Postoperative follow-up was performed at 1 month and every 3 months thereafter by physical examination, liver function tests, a test for tumor markers, hepatic ultrasonography, and a CT scan. To determine the efficiency of treatment, a helical CT scan with intravenous contrast for arterial and venous phases was obtained at 1 month and every 3 months thereafter. Helical CT was performed before intravenous injection and 25 (in case of HCC) and 65 seconds after injection of contrast, 2 mL/kg, with iodine, 30 g/L, at a rate of 3 to 4 mL/s. In patients who underwent chemoembolization with Lipiodol Ultra-Fluide (Guerbet, Aulnay-sous-Bois, France) in whom the examination of the vascularization of the tumor was difficult on CT scanning, a magnetic resonance imaging scan was obtained. The magnetic resonance imaging scans were performed with T1- and T2-weighted images and T1-weighted images at 20 and 60 seconds, respectively, after the intravenous injection of gadolinium. All imaging studies were evaluated by 2 expert radiologists (F.K. and another) in hepatic imaging, blinded with the type of technique used to treat each patient.

The efficiency of treatment was evaluated by comparison of pretreatment and posttreatment helical CT scans at each postoperative visit. The initial success of tumor treatment was de-

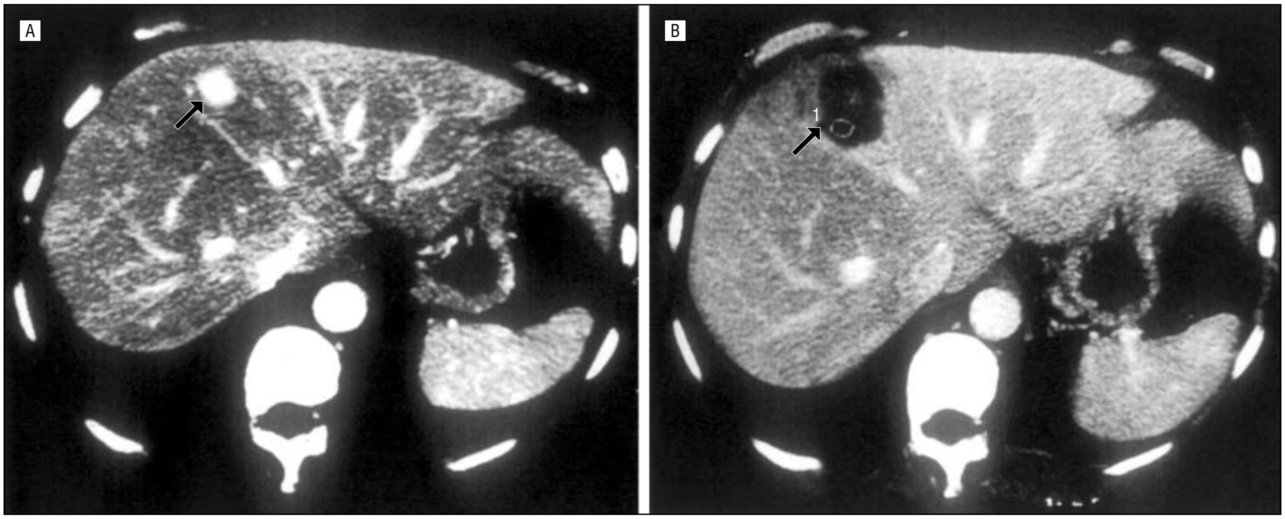

Figure 1. Computed tomographic scan demonstrating successful treatment of a hepatocellular carcinoma. A, Before treatment, the uptake of contrast within the tumor (arrow) indicates active tumor vascularization. B, Following treatment by percutaneous cryosurgery, there is absence of uptake of contrast within the tumor (arrow), indicating successful tumor devascularization.

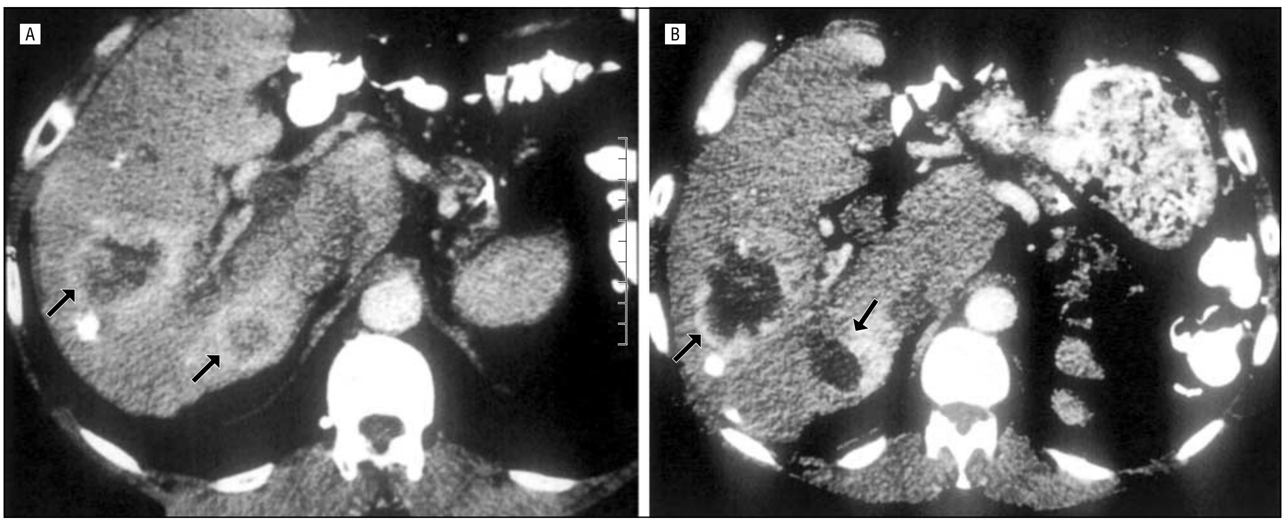

Figure 2. Computed tomographic scan demonstrating persistent tumor following treatment. A, Before treatment for 2 metastatic tumors from a neuroendocrine primary tumor, the uptake of contrast within and surrounding the tumors (arrows) indicates active tumor vascularization. The size of the larger tumor was 7 cm; the smaller, 5 cm. B, Following treatment by percutaneous cryosurgery, the persistence of contrast within and at the periphery of the tumors (arrows) indicates active tumor and unsuccessful treatment.

fined as complete devascularization of the treated tumor on the first postoperative CT scan (**Figure 1**), whereas continued vascularization indicated a persistent tumor (**Figure 2**). Local recurrence was defined as the recurrence of tumor vascularization, as determined by either a helical CT scan with intravenous injection or magnetic resonance imaging. Revascularization at or near the periphery of the treated tumor or revascularization within the tumor was used as evidence of tumor recurrence on postoperative imaging. The initial success of the treatment was determined for each tumor and for each patient treated. For patient analysis, initial success and local recurrence(s) were defined by the cumulative evaluation of all tumors treated in each patient.

Univariate analysis of differences between groups was performed using the χ^2 test or the Fisher exact test for observations with less than 5 categorical variables and the *t* test for numeric variables. Statistical analyses were performed with a statistical analysis program package (StatView 4.5 software; Abacus Concepts, Inc, Berkeley, Calif). Relationships between local recurrences and variables considered as a risk for local recurrence were tested by univariate analyses as indicated. Multivariate analysis was performed using logistic regression analysis and included variables of value in the univariate analysis and variables of interest. Patient survival rates and the cumulative percentage of local recurrence are presented as Kaplan-Meier estimates. $P<.05$ was considered statistically significant. Data are given as mean ± SD unless otherwise indicated.

RESULTS

PATIENT CHARACTERISTICS

A total of 64 patients were treated by either PCS (n = 31) or PRF (n = 33) during the study period. The ages of those treated with PCS and PRF were 60.1 ± 9.6 and 63.5 ± 9.9 years, respectively. Twenty men and 11 women were treated with PCS, and 27 men and 6 women were treated with PRF. Hepatocellular carcinoma was the tumor type in 18 (58%) of those treated with PCS and in 18 (55%) of those treated with PRF. Liver metastases (METS) included patients with colorectal, neuroendocrine, bile duct, or sarcoma cancer primary tumors. Liver metastasis was the cancer diagnosis in 13 (42%) of those treated with PCS and in 15 (45%) of those treated with PRF. In the case of HCC, the Child-Paul-Brousse class of those undergoing PCS was A in 7 (39%), B in 6 (33%), and C in 3 (17%); of those undergoing PRF, the class was A in 6 (33%), B in 7 (39%), and C in 3 (17%). Two patients in each treatment group had noncirrhotic HCC. The 2 groups did not differ in age, sex, tumor type, or Child-Paul-Brousse class. Patients were classified as candidates for PCS or PRF based on the presence of severe cirrhosis, technical limitations (ill-located or bilobar tumor or multiple previous hepatectomies), extrahepatic metastases, or other limitations related to patient operative risk or patient preference. Severe cirrhosis existed in 13 (42%) of the patients undergoing PCS compared with 16 (48%) of those undergoing PRF. Technical limitations existed in 10 (32%) and in 12 (36%) of those undergoing PCS and PRF, respectively. Five patients from each treatment group had extrahepatic metastases (PCS, 5 [16%] of 31; and PRF, 5 [15%] of 33). Other limitations related to patient operative risk or patient preference existed in 3 (10%) of those undergoing PCS compared with 0 of those undergoing PRF. The typical indication within the HCC subgroups was that of cirrhosis (PCS, 13 [72%] of 18 patients; and PRF, 16 [89%] of 18 patients), while a technical limitation was common within the METS subgroups (PCS, 8 [62%] of 13 patients; and PRF, 12 [80%] of 15 patients). Patients did not differ in cause of unresectability.

Systemic chemotherapy was given to all patients with metastatic disease before PCS (13 [100%] of 13 patients) and to most patients before PRF (14 [93%] of 15 patients). Treatment of the hepatic tumor(s) by chemoembolization was performed in 13 (72%) of the 18 patients with HCC before PCS and in 11 (61%) before PRF. Overall, the patients who underwent previous hepatic resection included 20 (65%) before PCS and 18 (55%) before PRF. The treatment groups did not differ in prior treatment by systemic chemotherapy, chemoembolization, or hepatic resection.

TUMOR CHARACTERISTICS

Percutaneous cryotherapy was used to treat 42 tumors in 31 patients during 48 procedures, whereas PRF was performed on 43 tumors in 33 patients during 46 procedures. Five patients underwent both forms of treatments; however, the initial treatment defined the treatment group in which the patient was included. Patients undergoing PCS had 1.39±0.64 tumors treated, whereas those undergoing PRF had 1.32±0.83 tumors treated. No patient had more than a total of 4 tumors treated. The size of the tumors treated by PCS was 22.2±10.5 mm compared with 28.0±16.7 mm for the tumors treated by PRF. The largest tumor treated per patient was 25.5±10.2 mm in the PCS group and 30.0±17.9 mm in the PRF group. The number of tumors treated per patient, the mean size of the tumor treated, and the largest size of tumor treated per patient were not different overall or between the subgroups of patients with HCC and METS.

TREATMENT-RELATED COMPLICATIONS

One patient with cirrhosis developed fatal variceal hemorrhage on postoperative day 30 following PCS (mortality, 3.2%), whereas there was no 30-day mortality following PRF (P=.48). Complications occurred in 9 patients (29%) following PCS vs 8 patients (24%) following PRF (P=.66). Variceal hemorrhage occurred in 2 patients, 1 following PCS and 1 following PRF. Following PCS, 1 patient developed hemodynamic instability on postoperative day 2 because of intrahepatic bleeding. This patient underwent a subsequent operation, during which a ruptured subcapsular hematoma was found. Although 1 patient following PRF developed a large hepatic hematoma, this was not associated with either hemodynamic instability or a required subsequent operation. One hemopneumothorax was identified within each group; each was treated with a thoracostomy drainage tube. One patient from each group had documented septicemia that was successfully treated with antibiotics. Five patients following PCS and 6 following PRF developed fever and were treated with antibiotics. Following PRF, 2 patients with cirrhosis developed worsened ascites, which were successfully managed with medical therapy, and 1 patient developed worsened jaundice. Furthermore, 1 patient following PRF developed a skin burn at the site of puncture, whereas no skin complications were identified following PCS. The hospital stay of those undergoing PCS was 3.6±5.3 days, which was not significantly different (P=.39) from the stay of 4.5±2.7 days following PRF.

TREATMENT OUTCOME

Tumors

All living patients included in the study had at least a 6-month follow-up. Follow-up ranged in all patients from 2 to 60 months following PCS and from 2 to 36 months following PRF. Overall, the patient follow-up periods of 21.2±13.8 and 16.3±8.7 months in the PCS and PRF groups, respectively, were not significantly different (P=.06). For this article, 26 patients who underwent PCS (36 tumors) and 31 who underwent PRF (41 tumors) had evaluable radiographic imaging studies available for review. Each tumor treated was evaluated in a blinded fashion for initial treatment success and local recurrence (**Table 1**).

Treatment Success. Initial success of treatment following 1 treatment was achieved in 69% of the tumors following PCS and in 76% of the tumors following PRF (Table 1), which was not statistically significant overall or between the subgroups of patients with HCC and METS. For those in whom devascularization of the tumor was not achieved, retreatment was undertaken in 8 (73%) of 11 patients who underwent PCS and in 6 (60%) of 10 patients who underwent PRF (data not shown). Successful retreatment, indicated by devascularization of the treated tumor on the first CT scan, was achieved in 5 of 8 and in 3 of 6 patients following PCS and PRF, respectively (data not shown). Initial success of tumor treatment following a single or repeated treatments was achieved in 83% of the

Table 1. Treatment Outcome: Tumors*

Variable	PCS	PRF	*P* Value
Initial success of treatment			
After 1 treatment	25/36 (69)	31/41 (76)	.54
HCC group	13/20 (65)	16/21 (76)	.43
METS group	12/16 (75)	15/20 (75)	.99
After ≥1 treatment	30/36 (83)	34/41 (83)	.36
HCC group	16/20 (80)	18/21 (86)	.70
METS group	14/16 (88)	16/20 (80)	.67
Local recurrence†	16/30 (53)	6/34 (18)	.003
HCC group	6/16 (38)	3/18 (17)	.25
METS group	10/14 (71)	3/16 (19)	.004

*Data are given as number/total for that group (percentage). PCS indicates percutaneous cryosurgery; PRF, percutaneous radio frequency; HCC, hepatocellular carcinoma; and METS, liver metastases.
†Determined in those with initial success of treatment following 1 or more treatments.

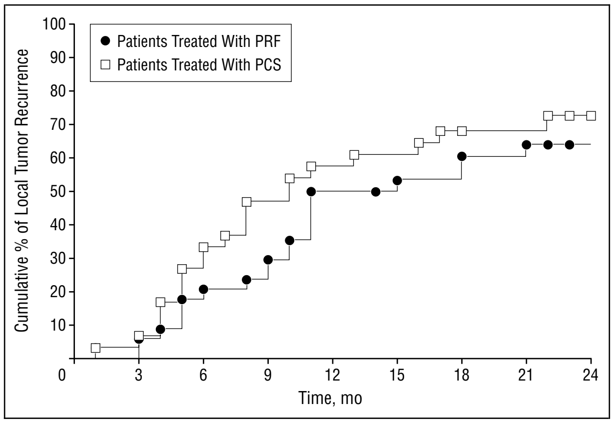

Figure 3. Cumulative percentage of local tumor recurrence in those treated by percutaneous cryosurgery (PCS) or percutaneous radiofrequency (PRF) for unresectable hepatic malignancies.

tumors following PCS and PRF (Table 1), and was not different overall or between the subgroups of patients with HCC and METS. These successfully treated tumors were also observed for tumor recurrence.

Local Recurrence. Local recurrence was determined for those tumors in which initial treatment success following 1 or more treatments was achieved. Recurrence occurred at or near the periphery of the treated tumor in 53% of the tumors following PCS and in 18% of the tumors following PRF (Table 1). When the subgroups of patients with HCC and METS were analyzed, there were significantly more tumor recurrences following PCS than following PRF in the METS subgroup; however, this difference was not identified in the HCC subgroup (Table 1). Of the 16 local recurrences following PCS, 8 tumors (3 HCCs and 5 METS) recurred within 6 months and 8 (3 HCCs and 5 METS) recurred between 6 and 12 months. This compared as follows with the 6 recurrences following PRF: 4 tumors (2 HCCs and 2 METS) recurred within 6 months and 2 (1 HCC and 1 METS) recurred between 6 and 12 months. No local recurrences were observed after 12 months following either treatment. The cumulative percentage of local tumor recurrence according to Kaplan-Meier analysis is shown in **Figure 3**.

Table 2. Treatment Outcome: Patients*

Variable	PCS	PRF	*P* Value
Initial success of treatment			
After 1 treatment	15/26 (58)	22/31 (71)	.30
HCC group	8/15 (53)	12/17 (71)	.31
METS group	7/11 (64)	10/14 (71)	.99
After ≥1 treatment	20/26 (77)	25/31 (81)	.73
HCC group	11/15 (73)	14/17 (82)	.68
METS group	9/11 (82)	11/14 (79)	.99
Local recurrence†	12/20 (60)	4/25 (16)	.002
HCC group	5/11 (45)	2/14 (14)	.18
METS group	7/9 (78)	2/11 (18)	.02

*Data are given as number/total for that group (percentage). PCS indicates percutaneous cryosurgery; PRF, percutaneous radio frequency; HCC, hepatocellular carcinoma; and METS, liver metastases.
†Determined in those with initial success of treatment following 1 or more treatments.

Given the use of different cryosurgical equipment in our study, we analyzed the outcome of treatment related to the cryosurgical machine type. Neither the initial treatment success nor the local recurrence rates were significantly different ($P=.75$) between those treated with either machine (the LCS 2000 apparatus vs the CRYO-HIT System).

Patients

Treatment Success. Similar findings were identified when the cumulative results of each patient were examined (**Table 2**). The initial success following 1 treatment was 58% following PCS and 71% following PRF. In those in whom initial success was not achieved, retreatment was undertaken in 8 (73%) of 11 patients in the PCS group and in 5 (56%) of 9 patients in the PRF group (data not shown). Successful retreatment was achieved in 5 of 8 and in 3 of 5 patients following PCS and PRF, respectively (data not shown). The initial success following 1 or more treatments was 77% following PCS and 81% following PRF (Table 2), and was not different overall or between the subgroups of patients with HCC and METS.

Local Recurrence. As in the tumor analysis, local recurrence was determined in those tumors in which initial treatment success following 1 or more treatments was achieved. Tumors have locally recurred in 60% of the patients following PCS and in 16% of the patients following PRF (Table 2). Within the METS subgroup, tumors recurred in 78% of the patients following PCS and in 18% of the patients following PRF, whereas within the HCC subgroup, recurrence was identified in 45% of the patients following PCS and in 14% of the patients following PRF (Table 2).

UNIVARIATE ANALYSIS: RISK FACTORS FOR LOCAL RECURRENCE

Univariate analysis of risk factors was limited to those tumors in which initial success following 1 or more treatments was achieved and those living patients who had at least 1 year of follow-up. One tumor was excluded from

Table 3. Univariate Analysis of Risk Factors: Local Recurrence

Variable*	% Local Recurrence†	*P* Value
Type of treatment		
PCS	55.2	.002‡
PRF	17.7	
Type of tumor		
HCC	27.3	.18‡
METS	43.3	
Treatment of all hepatic tumors		
Complete	34.6	.91‡
Incomplete	36.4	
Presence of extrahepatic metastases		
No	34.8	.97‡
Yes	35.3	
No. of treated tumors		
1	30.6	.40‡
>1	40.7	
No. of treatments		
1	28.9	.04§
2	42.9	
3	66.7	
4	100.0	

*PCS indicates percutaneous cryosurgery; PRF, percutaneous radio frequency; HCC, hepatocellular carcinoma; and METS, liver metastases.
†n = 63 tumors.
‡χ^2 Test.
§Mantel-Haenszel χ^2 test.

this analysis given the lack of adequate follow-up. Univariate analysis by either the χ^2 test or the *t* test demonstrated that the use of PCS compared with PRF and increasing number of treatments significantly influenced local tumor recurrence (**Table 3**). Although tumors with an METS origin tended to recur more frequently than those with an HCC origin, this was not statistically significant. The size of treated tumors without local recurrence was 25.4±16.0 mm; with local recurrence, 23.5±14.5 mm (*P*=.65, *t* test).

MULTIVARIATE ANALYSIS: RISK FACTORS AND PROBABILITY OF LOCAL RECURRENCE

Factors significantly influencing local tumor recurrence (use of PCS and use of >1 treatment) in addition to variables of interest (METS tumor origin) were used in the multivariate analysis by logistic regression analysis (n=63 tumors). Multivariate analysis demonstrated that those factors independently influencing local recurrence included the use of PCS (risk ratio, 6.89; 95% confidence interval, 1.96-24.16; *P*=.003) and the use of more than 1 treatment (risk ratio, 2.81; 95% confidence interval, 1.02-7.78; *P*=.05). The risk ratio for METS tumor origin was 2.45 (95% confidence interval, 0.73-8.19; *P*=.15). The probability of local recurrence according to the presence of the identified risk factors is shown in **Table 4**.

HEPATIC AND EXTRAHEPATIC TUMOR RECURRENCE

Of all the patients treated in the protocol, 26 (84%) of 31 following PCS and 24 (73%) of 33 following PRF developed a recurrence. In the PCS group, hepatic-only recurrence has occurred in 11 (35%), extrahepatic-only recurrence in 6 (19%), and hepatic and extrahepatic recurrence in 9 (29%). Of the 31 patients in this group, 15 (48%) have died. In the PRF group, hepatic-only recurrence has occurred in 8 (24%), extrahepatic-only recurrence in 6 (18%), and hepatic and extrahepatic recurrence in 9 (27%). Of the 33 patients in this group, 17 (52%) have died.

Table 4. Probability of Local Recurrence: Multivariate Analysis*

Cryotherapy	Metastases	No. of Treatments	Probability of Local Recurrence
+	+	4	0.97
+	+	3	0.92
+	+	2	0.80
+	+	1	0.59
−	+	4	0.82
−	+	3	0.62
−	+	2	0.37
−	+	1	0.17
+	−	4	0.93
+	−	3	0.82
+	−	2	0.62
+	−	1	0.37
−	−	4	0.65
−	−	3	0.40
−	−	2	0.19
−	−	1	0.08

*Logistic regression analysis was performed. + indicates present; −, absent.

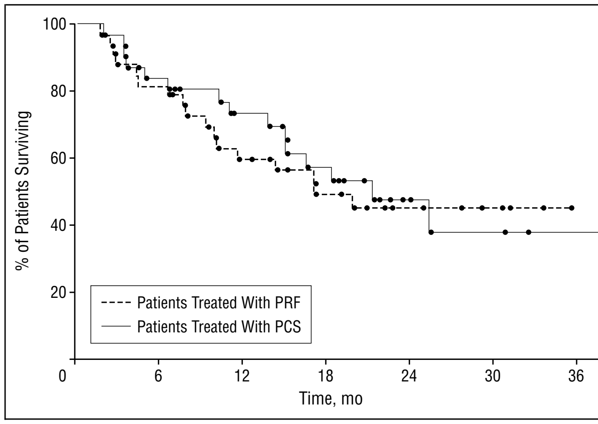

Figure 4. Kaplan-Meier estimates of patient survival following percutaneous cryosurgery (PCS) or percutaneous radiofrequency (PRF).

PATIENT SURVIVAL

Kaplan-Meier estimates of patient survival demonstrate that overall survival rates following PCS at 6 months and 1 year are 84% and 73%, respectively. This is compared with overall survival rates following PRF at 6 months and 1 year of 82% and 60%, respectively (*P*=.76) (**Figure 4**). Survival rates at 6 months and 1 year for those with HCC were 78% and 66% following PCS and 78% and 61% following PRF, respectively (*P*=.83). Survival rates at 6 months and 1 year for those with METS were 92% and

84% following PCS and 87% and 58% following PRF, respectively ($P = .51$).

COMMENT

Despite the advent of more efficient chemotherapeutic protocols and the progress in surgical techniques, such as portal vein embolization[23] and 2-stage hepatectomy,[24] many patients with hepatic malignancies have unresectable disease. In situ destruction methods, such as cryosurgery and radiofrequency, are relatively safe and are used to treat patients with unresectable hepatic malignancies.[25-29]

However, no consensus exists for the preferential use of either cryosurgery or radiofrequency. Two previous nonrandomized studies have been performed to compare the efficiencies of either treatment. The first report to appear was that of Pearson and colleagues,[21] who compared cryosurgery and radiofrequency using an open laparotomy approach. In this series, 40.7% of the patients, including 1 postoperative death, had complications following cryosurgery compared with 3.3% following radiofrequency ($P < .001$). Local recurrences were identified in 13.6% of the patients following cryosurgery and in 2.2% following radiofrequency ($P < .01$). As a result, this group prefers radiofrequency to cryosurgery for treating primary and metastatic hepatic tumors.[30] In contrast, Bilchik and colleagues[8] used cryosurgery and radiofrequency, either alone or as complementary treatments to each other, using various approaches, including laparotomy, laparoscopy, or percutaneous approaches. They found significantly higher rates of blood loss, thrombocytopenia, and pleural effusion following cryosurgery, but similar rates of other complications. The mortality rates following either treatment were similar (3.0% for cryosurgery and 2.5% for radiofrequency). The overall local recurrence rate was 15% following cryosurgery alone compared with 10% following radiofrequency alone (difference was not significant). However, they identified that local recurrence following radiofrequency was higher than following cryosurgery for lesions larger than 3 cm (17% for cryosurgery vs 38% for radiofrequency). Therefore, they recommend a diversified approach, combining cryosurgery for lesions larger than 3 cm and radiofrequency for 3-cm or smaller lesions.

In the present study, we examined the results of PCS and PRF. The percutaneous procedure has proved to be safe using either treatment. We identified 1 patient with cirrhosis who died of variceal hemorrhage at 30 days after treatment, apparently unrelated to PCS (mortality, 3.2%). In contrast to previous studies,[8,21] the complication rate of the present study following either treatment was similar: 29% following PCS and 24% following PRF.

The 2 methods proved to be equally efficient for initial treatment success. However, local recurrences were higher following PCS. Overall, the local recurrence following PCS was 60% of patients and 53% of tumors compared with 16% of patients and 18% of tumors following PRF. These results could be ascribed to the longer follow-up obtained following PCS vs PRF (21.2 vs 16.3 months). However, the difference in the duration of follow-up was not significant, and all of the local recurrences were observed within 1 year following local treatment. Considering the local recurrence rates reported in previous studies specifically dedicated to cryosurgery (2.3%-44.0%)[5,9,10,13] or to radiofrequency (1.8%-18.0%),[14-16,30] a higher rate of local recurrence was observed in both of our treatment groups, particularly following PCS. An explanation may be related to our definition of local recurrence. Indeed, it is often difficult to differentiate a local from a hepatic recurrence. We deliberately chose to define local recurrence as revascularization appearing not only within the previous tumor site but also at its periphery. As expected, this expanded definition will tend to increase to some extent the rate of local recurrence.

Another explanation may be related to the percutaneous approach of treatment. The percutaneous approach has the advantage of being minimally invasive and allows for a rapid recovery, as shown by the short hospital stays observed in our study. However, the limitations of preoperative imaging narrow the ability to fully detect the presence of other disease not identified at percutaneous treatment. Considering these limitations, it is possible that either unrecognized extrahepatic disease or undetected hepatic disease existed in some of our patients. Bilchik and colleagues[8] found that, despite extensive preoperative imaging before laparoscopic radiofrequency or cryosurgery, 12% to 13% of patients had extrahepatic disease and 30% to 33% had additional intrahepatic tumors detected on intraoperative ultrasonography. However, in the present study, neither the presence of an untreated hepatic tumor nor the presence of extrahepatic metastases influenced the incidence of local recurrence. Although it is reasonable to state that unrecognized hepatic or extrahepatic disease influences overall recurrence, the impact of such undetected disease on local recurrence needs to be established.

Furthermore, this difference may exist because of the higher accuracy of the procedure of tumor destruction by laparotomy compared with percutaneous approaches. Certainly, tumor localization by echography is enhanced by the open rather than the percutaneous approach. Thus, the outcome of treatment may be affected. However, there exist certain groups of patients who cannot be approached by laparotomy or laparoscopy, but who are candidates for a percutaneous approach. These patients include those following previous hepatic resection, those with severe hepatic cirrhosis, and those unable to withstand general anesthesia. In these groups of patients, a percutaneous approach is feasible and safe.

In the present study, the differences in the rates of local recurrence were amplified following treatment for METS (10 [71%] of 14 and 3 [19%] of 16 for tumors and 7 [78%] of 9 and 2 [18%] of 11 for patients following PCS and PRF, respectively), while the differences following treatment for HCC were not significant (6 [38%] of 16 and 3 [17%] of 18 for tumors and 5 [45%] of 11 and 2 [14%] of 14 for patients following PCS and PRF, respectively). High rates of treatment failure after PRF of METS have also been reported by others.[31,32] In the study by Solbiati and colleagues,[31] an incomplete response was observed in 42% of tumors and in 50% of patients. In the study by Rossi and colleagues,[32] 6 (55%) of 11 patients did not achieve total necrosis on dynamic CT or histological examination during posttreatment follow-up. Furthermore, by multivariate analysis, treatment by cryotherapy had an independent influence on local recurrence. This is consistent with the findings that metastatic tumors treated by open cryosurgery tend to have a higher local recurrence, up to 44%, compared with primary hepatic tumors (0%).[10] A difference in the sensitivity of tumoral tissue to cryosurgery may explain the disparity in recurrence rates.

Our policy is that of an aggressive approach to resection for patients with hepatic malignancies. Thus, those patients who we identify as unresectable are a group of patients who already have advanced disease, particularly those with metastatic disease. This was demonstrated because many of our patients, 20 (65%) of 31 treated by PCS (HCC, 9 [50%] of 18; and METS, 11 [85%] of 13) and 18 (55%) of 33 treated by PRF (HCC, 4 [22%] of 18; and METS, 14 [93%] of 15), were treated previously by hepatic resection. Adjuvant therapies, such as chemotherapy and chemoembolization, were also widely used to control the tumoral disease. The results of the present study may be reflective of the patients to whom we had offered this local treatment. The advanced stage of disease is also reflective in the high rate of hepatic-only or extrahepatic recurrence we found following treatment. However, 4 (13%) of 31 patients who underwent PCS and 5 (15%) of 33 patients who underwent PRF are alive without recurrence. This group of patients offers promise that survival may be improved.

Overall, the risk of recurrence after percutaneous tumor destruction stresses the need to consider liver resection whenever possible, because it is a more definitive tumor treatment, and to restrict the indications of in situ tumor destruction to patients with unresectable disease. We believe it is premature to compare liver resection with in situ tumor destruction in patients with resectable disease, particularly for those with metastases. Minimally invasive therapy does not mean better results for tumor control.

In conclusion, PCS and PRF are safe and effective methods with which to control unresectable hepatic malignancies. However, despite successful initial tumor devascularization, many tumors recur, in local, hepatic, or extrahepatic sites. Percutaneous radiofrequency results in a lower rate of local recurrence than PCS, particularly in those with metastatic malignancies. These retrospective results open the way to a prospective randomized trial comparing the 2 treatments to state definitively the suggested superiority of radiofrequency. It is further expected that the more recent advancements in the area of radiofrequency probes, which allow the creation of up to a 7-cm destruction area (Rita Medical Systems, Inc), will further lower the rate of local recurrence by helping to reduce the requirement for overlapping ablations during the treatment of larger tumors.

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