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ORIGINAL ARTICLE

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Liver resection or cryotherapy for colorectal liver metastases

A prospective case control study

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Abstract *Background and aims:* While there is promising survival data for cryosurgery of colorectal liver metastases, local recurrence following cryoablation remains a problem. We aimed to compare morbidity and mortality, as well as the recurrence pattern and survival after liver resection and cryotherapy (alone or in combination with resection) for liver metastases. *Patients and methods:* Between 1996 and 2002, 168 patients underwent liver resection alone and 55 patients had cryotherapy (25 in combination with liver resection) for colorectal liver metastases. The patient, tumour and operative details were recorded prospectively and the two patient groups were compared regarding morbidity, survival and recurrence. *Results:* More patients had a prior liver resection, liver metastases were smaller and less frequently synchronous, morbidity was significantly lower and hepatic recurrence was significantly more frequent in the cryotherapy group. Five-year survival rates following resection and cryotherapy were comparable (23 and 26% respectively), while overall and hepatic recurrence-free survival was inferior following cryotherapy. *Conclusion:* Cryotherapy is a valuable treatment option for some patients with non-resectable colorectal liver metastases. While survival is comparable to that after resection, higher hepatic recurrence rates following cryotherapy should caution against the use of cryotherapy for resectable disease until the results of randomized controlled trials are available.

Keywords Colorectal cancer · Liver resection · Cryotherapy · Cryosurgery · Recurrence

Introduction

Liver resection is the treatment of choice for colorectal liver metastases and is associated with 5-year survival rates of 25–50% [1]. However, in only 5–25% of these patients is liver resection feasible [2]. The use of cold temperatures for the destruction of cancerous tissue has been known about for a long time [3]. Increasing knowledge in the field of cryobiology and the use of intraoperative ultrasound for the localization of lesions and monitoring of the freezing process has led to an increased use of cryotherapy in the treatment of non-resectable liver tumours [4–13]. The potential advantages of cryotherapy may lie in the treatment of metastases close to hepatic veins, bilobar metastases or recurrent metastases in the remnant liver following liver resection [6, 10], where resection alone is sometimes not possible. In addition, perioperative morbidity and mortality of cryotherapy in the reported literature compares well with resection and data from animal models gives some evidence that the perioperative secretion of growth factors, which may stimulate the growth of occult micrometastases after surgery is lower following cryotherapy than after resection [14, 15]. However, while there are promising survival data for the use of cryosurgery to treat colorectal liver metastases [16, 17], the reported rates of local recurrence following cryoablation of up to 44% [4, 11, 18] are a strong

argument for limiting cryotherapy strictly to non-resectable disease. There is also some concern that the intraoperative puncture of the metastases with the cryoprobes may lead to the intra-abdominal seeding of tumour cells, which may cause higher rates of peritoneal disease compared with resection.

To assess some of these questions we performed this prospective case control study. We aimed to compare the patient, tumour, and perioperative details, perioperative morbidity and mortality, as well as the recurrence pattern and survival after liver resection and cryotherapy (alone or in combination with resection) for liver metastases.

Patients and methods

Between January 1996 and September 2002, 168 patients underwent liver resection alone and 55 patients had cryotherapy (25 of these in combination with liver resection) for colorectal liver metastases. The patient, tumour and operative details were recorded prospectively.

Preoperative staging included abdominal ultrasound and abdominal CT, chest X-ray, serum analysis of tumour markers, liver function tests and colonoscopy. Recently, we have increasingly used MRI of the liver, particularly for better assessment of the tissue changes following cryotherapy.

Resection was usually performed whenever complete resection of all liver metastases with clear margins and with preservation of a sufficient functional liver reserve in the absence of extrahepatic disease seemed feasible. Cryotherapy was used if complete resection of all liver metastases was not feasible and if no extrahepatic disease was diagnosed. We performed cryosurgery alone or in combination with liver resection if we could assume that all liver metastases may be destroyed completely. Metastases were judged non-resectable, if:

1. They were multiple in both liver lobes
2. They were in an anatomical position that did not allow liver resection without sacrificing an unreasonable amount of liver parenchyma
3. Resection would have involved too high a risk for the patient

In very few patients with resectable lesions who refused to undergo liver resection, cryotherapy was performed, preferably laparoscopically. Postoperatively, most patients were monitored on the intensive care unit, usually for 24 h. Prior to discharge, a CT scan or MRI of the liver was performed in patients who had undergone cryotherapy.

Liver resection was performed via a bilateral subcostal incision. Before resection, inspection and palpation of the abdominal cavity, the liver and the hilar region, including intraoperative ultrasound and frozen section of suspicious lesions was performed to exclude additional disease. For parenchymal transsection we have used different techniques. For cryotherapy we have used a CMS AccuProbe 450-System with single-use cryoprobes with an isolated shaft and a diameter of 3 or 8 mm at the tip. For 3 years, we have preferred to use the Erbokryo CS-6 cryosystem (Erbe Elektromedizin GmbH, Tübingen , Germany) with 3.6-mm probes. Only the probe-tips are cooled, allowing the treatment of central lesions deep within the liver parenchyma without freezing the liver surface. Following laparotomy, exclusion of abdominal extrahepatic disease and intraoperative ultrasound of the liver, the cryoprobe is inserted into the tumour. The probe insertion and the freezing process are controlled by intraoperative ultrasound. All tumours are frozen with a surrounding margin of at least 1 cm of normal tissue and the freezing process is continued for at least 15 min. After a passive thaw of the iceball a second freeze cycle is used to optimize tumour destruction [19]. In five patients with solitary resectable tumours, who were either in a poor general condition or refused to undergo liver resection cryotherapy was performed laparoscopically.

For tumours of up to 4 cm in diameter a single 8-mm CMS probe was used. For larger tumours two or more probes were applied simultaneously. With the Erbe cryoprobes, 3.6-mm single probes were only used for tumours of less than 3 cm in diameter. For larger tumours two or more probes were applied simultaneously (usually three or more).

R0 treatment was assumed when a complete resection or cryo treatment of all visible tumour with adequate margins was achieved. R1 treatment was assumed when all tumours were resected or cryoablated, but the surgeon was concerned about the adequacy of the freezing margin or a resection margin in patients in whom liver resection was histologically involved. R2 treatment was defined as macroscopically detectable untreated tumour (including preoperative imaging) left behind after surgery. The patients did not receive any routine adjuvant treatment, such as chemotherapy. However, in cases of recurrence that could not be treated locally with resection or repeated cryotherapy, palliative systemic chemotherapy was usually given.

Patients were followed up until September 2002 or death. Mean follow-up was 23 months (1–73). Patients had regular 3-monthly follow-up investigations for local recurrence or hepatic recurrence at other locations and extrahepatic recurrence. Local recurrence at the cryosite was assumed when a cryolesion continued to gain size more than 3 months after cryosurgery or when contrast-enhancing tissue was noted again within or immediately next to the cryolesion in follow-up CT scans.

The patient, tumour and operative details for patients undergoing resection alone (group 1) and cryotherapy (±resection; group 2) were compared to assess whether the two groups were similar. To further assess the similarity of the two groups, the “clinical risk score” established by Fong et al. [20] and the “risk groups” as defined by the grading system described by Nordlinger et al. [21]

were calculated for all patients and the distribution of these scores was compared between the two groups. Survival, as well as disease-free and liver disease-free survival were also compared between the two groups. In addition, the same comparisons were made for patients undergoing cryotherapy alone (n=30) and cryotherapy in combination with liver resection (n=25).

Table 1 Distribution of patient, tumour and perioperative parameters within the two groups. *CEA* carcinoembryonal antigen

		Resection (n=168)	Cryotherapy± resection (n=55)	Significance
Age (years)	Mean (SEM)	61.9 (0.8)	61.8 (1.4)	0.95*
Sex (n)	Female	68	24	0.68#
	Male	100	31	
ASA classification (n)	I	4	1	0.73#
	II	72	19	
	III	86	33	
	IV	6	2	
T classification of primary (n)	T1/2	21	10	0.49#
	T3/4	141	44	
	Unknown	6	1	
Nodal involvement at resection of the primary tumour (n)	No involved nodes	49	21	0.31#
	Involved nodes	106	32	
	Unknown	13	2	
Histological differentiation of primary (n)	Well/moderate	108	31	0.66#
	Poor/ undifferentiated	35	14	
	Unknown	25	10	
Prior liver resection (n)	Yes	8	16	<0.001#
	No	159	159	
Time of development of liver metastases (n)	Synchronous	78	17	0.041#
	Metachronous	90	38	
Number of liver metastases (n)	Mean (SEM)	2.35 (0.15)	2.40 (0.29)	0.89*
Diameter of largest liver metastasis (cm)	Mean (SEM)	5.18 (0.23)	3.50 (0.21)	<0.001*
Liver metastases distribution (n)	Unilobar	103	30	0.38#
	Bilobar	65	25	
CEA preoperatively (ng/ml; n)	≤4	39	17	0.19#
	4.01–30	69	27	
	30.01–100	35	7	
	>100	22	4	
	Unknown	3	–	
CEA postoperatively (ng/ml; if preop.>4 ng/ml; n)	≤4	71	26	0.08#
	>4	36	11	
	Unknown or N/A	61	18	
Extrahepatic disease at operation (n)	Yes	34	10	0.71#
	No	134	45	
Intraoperative blood replacement (units red cells)	Mean (SEM)	1.99 (0.34)	1.55 (0.44)	0.09*
Duration of operation (min)	Mean (SEM)	211 (6)	275 (13)	<0.001*
Radicality of surgery (n)	R0	130	47	0.041#
	R1	23	2	
	R2	11	6	
	Unknown	4	–	
Postoperative hospital stay (days)	Mean (SEM)	20 (1)	14 (1)	0.001*

*Mann–Whitney U test
#χ^2 test (likelihood ratio)

Table 2 Distribution of two different scoring systems within the two groups

		Resection (n=168)	Cryotherapy±resection (n=55)	Significance
Clinical risk score [20]	0	6	5	0.21#
	1	37	18	
	2	58	16	
	3	38	10	
	4	26	6	
	5	3	–	
	Mean (SEM)	2.3 (0.1)	1.9 (0.2)	0.025*
Risk groups[a] grading system [21]	Low risk (0–2 factors)	34	20	0.11#
	Intermediate risk (3–4 factors)	65	17	
	High risk (5–7 factors)	7	3	
Number of risk factors[a]	Mean (SEM)	2.9 (0.1)	2.5 (0.2)	0.019*

#χ^2 test (likelihood ratio)
*Mann–Whitney U test
[a]For the Nordlinger system hospital mortality and patients with incomplete resection or extrahepatic disease were excluded

The data are presented as means (±SEM). The Mann–Whitney U test was used to test for significant differences in quantative measures between the two groups and the χ^2 test for qualitative measures. Survival and disease-free intervals were calculated using the Kaplan–Meier method [22]. The log-rank test [23] was used to test for differences between the two groups. A difference was considered significant at $p<0.05$. Statistical analysis was performed using SPSS for Windows, version 10.0.7.

Results

The distribution of patient, tumour and perioperative details of the two groups is summarized in Table 1. Most parameters were comparable between the two groups. However, significantly more patients had a prior liver resection in the cryotherapy group. In addition, liver metastases in the cryotherapy group were smaller and less frequently synchronous. Cryosurgical procedures were longer and a complete resection with clear margins ("R0") was assumed more often.

The distribution of the clinical scores by Fong et al. [20] and Nordlinger et al. [21] in the two groups is summarized in Table 2. For both scoring systems, there was a trend towards higher risk scores or risk groups for the resection group. The mean risk score (Fong et al.) or the mean number of risk factors (Nordlinger et al.) were significantly higher for the resection group (Table 2).

The following liver resections were performed in the resection group: extended hemihepatectomy (n=23); hemihepatectomy (n=44); left lobectomy (n=7); and peripheral or segmental resections (n=64, 31 of these in multiple locations). Thirty patients had combinations of these procedures (for example hemihepatectomy and contralobar peripheral resection etc.). In the cryotherapy group the following additional liver resections were performed in 25 patients: extended hemihepatectomy (n=4); hemihepatectomy (n=3); left lobectomy (n=2); and peripheral or segmental resections (n=16, 9 of these in multiple locations). Perioperative morbidity and mortality in the two groups are summarized in Table 3. Perioperative morbidity was significantly lower following cryotherapy than after liver resection.

The tumour marker carcinoembryonal antigen (CEA) was preoperatively elevated (>4 ng/ml) in 126 patients

Table 3 Perioperative morbidity and mortality in the two groups

	Resection (n=168)	Cryotherapy ± resection (n=55)	Significance
Perioperative mortality, n (%)	8 (5)	1 (2)	0.30#
Perioperative morbidity, n (%)	44 (26)	6 (11)	0.01#
Details of morbidity (n; more than one complication per patient possible)			
Haemorrhage	2	2	
Wound infection	2	–	
Biloma or bile fistula	4	1	
Intra-abdominal abscess	21	1	
Intestinal fistula	3	1	
Peritonitis	1	–	
(Transient) liver failure	6	–	
Gastrointestinal haemorrhage	3	–	
Thrombosis	2	–	
Pulmonary embolus	2	–	
Pneumonia	1	1	
Cardiac morbidity	1	–	
Acute renal failure	1	–	

#χ^2 test (likelihood ratio)

(75%) of the resection group and 38 patients (69%) of the cryotherapy group. A return to the normal range was achieved postoperatively in 71 out of 107 patients (66.4%) in the resection group and 26 out of 37 patients (70.3%) in the cryotherapy group in whom a postoperative serum analysis for CEA was performed.

The recurrence pattern in the two groups is summarized in Table 4. Hepatic recurrence (both inside and outside the cryolesion) and also hepatic recurrence outside the cryolesion only were significantly more frequent following cryosurgery compared with liver resection. The occurrence of lung metastases, peritoneal disease, lymph node metastases, local recurrence of the primary tumour and brain metastases did not differ between the groups, while bone metastases were significantly more frequent following liver resection.

The median survival times and 5-year survival rates following resection and cryotherapy were comparable, with 29 and 29 months and 23 and 26% respectively (Fig. 1). The median disease-free survival times and 5-year disease-free survival rates following resection were superior, with 10 months and 19%, compared with cryotherapy, with 6 months and 12% (p=0.02; Fig. 2). Looking at the disease-free interval in the liver, this difference was even more marked with a median liver disease-free interval of 19 months and a 5-year liver disease-free rate of 33% following resection, compared with 7 months and 15% following cryotherapy (p=0.0015; Fig. 3). The mean local recurrence-free interval at the cryosite for the cryo group was 51 months, with a 3-year local (at the cryosite) recurrence-free survival of 72% (Fig. 4).

We have treated five patients with solitary resectable tumours, who were either in a poor general condition or refused to undergo liver resection, using laparoscopic cryotherapy. The tumour diameters ranged from 2 to 4.5 cm with a median of 3.3 cm. The duration of the procedure ranged from 110 to 360 min with a median of 235 min. No perioperative morbidity or mortality was observed. Complete tumour ablation was achieved in all patients. All five patients are alive at 20, 22, 27, 29 and 48 months postoperatively. Three of the five are disease-free, one has developed a new liver metastasis and one has had recurrence at the cryosite and developed pulmonary metastases.

The distribution of patient, tumour and perioperative details in patients undergoing cryotherapy alone versus cryotherapy and liver resection is summarized in Table 5. Most parameters were comparable between the two groups. However, significantly more patients had a prior liver resection in the cryotherapy only group. In addition, patients in the cryotherapy only group had a smaller number of liver metastases and less frequently bilobar metastases. Cryosurgical procedures were shorter and associated with less blood transfusion intraoperatively, as well as a shorter postoperative hospital stay, than combined procedures. A "R0" treatment was assumed less often and a normalization of preoperatively elevated serum CEA levels was achieved less often in the cryotherapy-only group.

The distribution of the clinical scores by Fong et al. and Nordlinger et al. for patients undergoing cryotherapy alone versus cryotherapy and liver resection is summarized in Table 6. For both scoring systems, there were significantly higher risk scores or risk groups in the cryotherapy and resection group (Table 6).

Perioperative morbidity and mortality in patients undergoing cryotherapy alone versus cryotherapy and liver resection is summarized in Table 7.

Table 4 Distribution of postoperative follow-up and recurrence in the two groups

	Resection (n=168)	Cryotherapy ± resection (n=55)	Significance
Follow up (months), mean (SEM)	22.2 (1)	24.3 (2)	0.50*
Death, n (%)	85 (51)	27 (49)	0.85#
Recurrence, n (%)	102 (61)	42 (76)	0.045#
Involved sites of recurrence (multiple sites per patient possible):			
Liver (total), n (%)	76 (45)	39 (71)	0.001#
Liver at cryosite, n (%)	–	13 (24)	–
Liver other than cryosite, n (%)	76 (45)	38 (69)	0.003#
Lung, n (%)	44 (26)	17 (31)	0.56#
Peritoneal disease, n (%)	14 (8)	7 (13)	0.37#
Lymph nodes, n (%)	24 (14)	9 (16)	0.76#
Local recurrence primary, n (%)	22 (13)	4 (7)	0.20#
Bones, n (%)	13 (8)	0 (–)	0.005#
Brain, n (%)	4 (2)	0 (–)	0.13#
Others, n (%)	11 (7)	4 (7)	0.39#
Locations of recurrence:			
Liver only, n (%)	30 (18)	16 (29)	–
Liver and extrahepatic, n (%)	46 (27)	23 (42)	–
Extrahepatic only, n (%)	26 (16)	3 (6)	–

*χ^2 test (likelihood ratio)
#Mann–Whitney U test

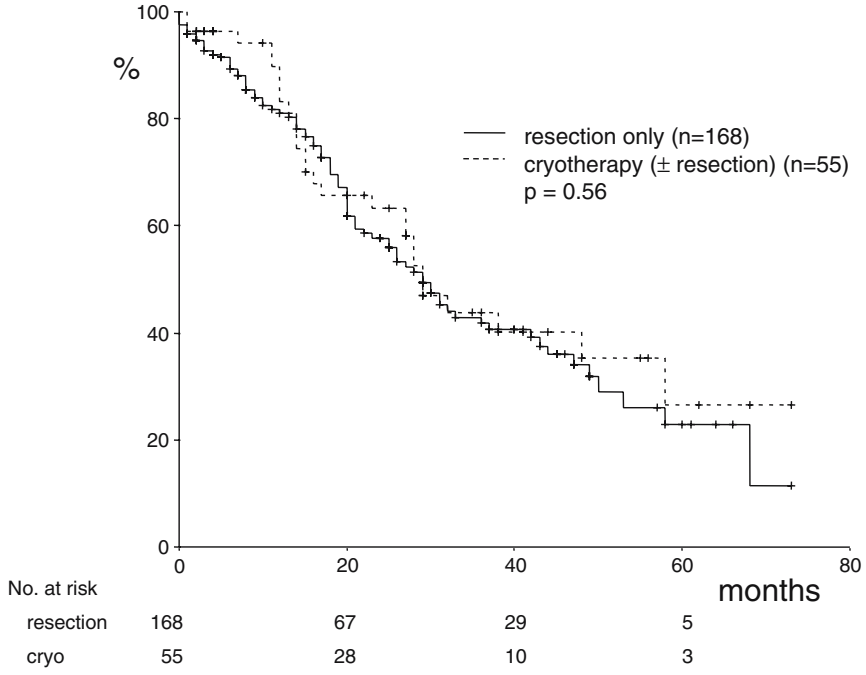

Fig. 1 Survival (Kaplan–Meier) following resection or cryotherapy (± resection) for colorectal liver metastases

The recurrence pattern is summarized in Table 8. There were no significant differences regarding the recurrence pattern in patients undergoing cryotherapy alone or in combination with liver resection. However, a larger proportion of patients were alive following cryotherapy alone, with comparable follow-up times.

Survival following cryotherapy alone was significantly longer than following cryotherapy in combination with resection (Fig. 5). The disease-free survival, as well as disease-free interval in the liver and local recurrence-free interval at the cryosite did not differ significantly between patients undergoing cryotherapy alone or in combination with resection (Figs. 6, 7, 8).

To minimize selection bias in the results of the comparison between resection and cryotherapy (± resection) we have compared survival of patients in comparable risk

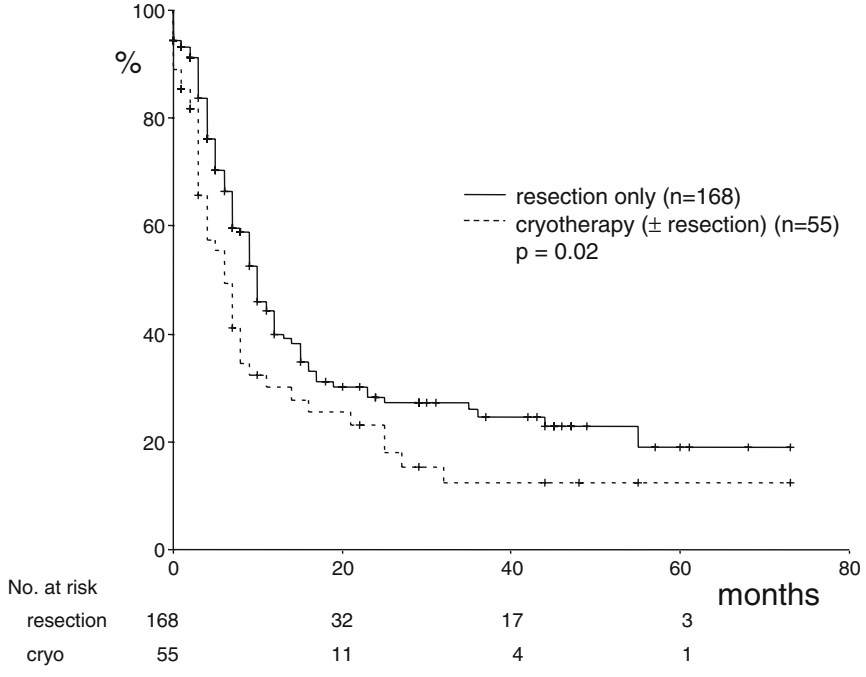

Fig. 2 Disease-free survival (Kaplan–Meier) following resection or cryotherapy (± resection) for colorectal liver metastases

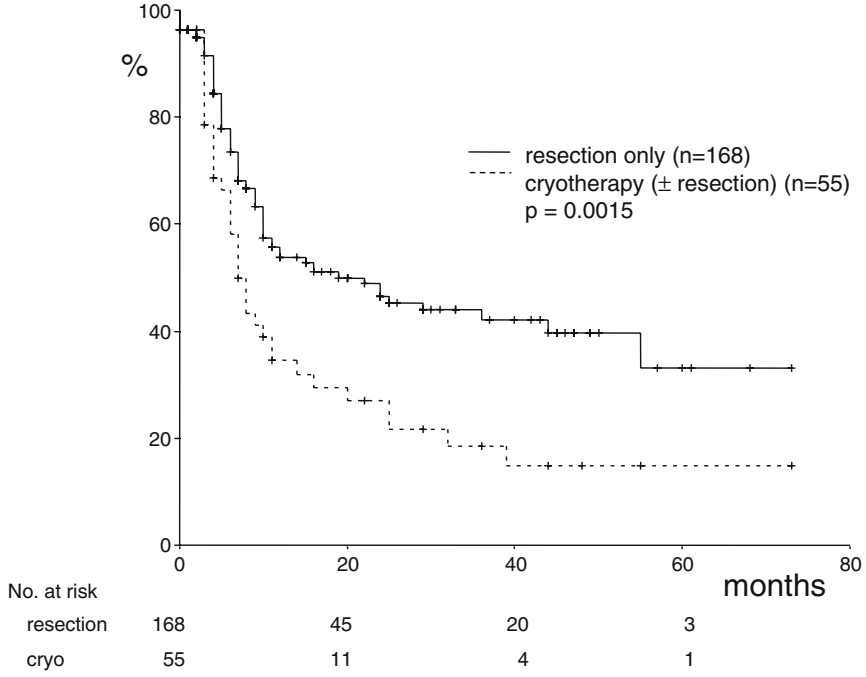

Fig. 3 Liver disease-free survival (Kaplan–Meier) following resection or cryotherapy (± resection) for colorectal liver metastases

groups, as defined by Nordlinger et al. [21]. Neither for low risk (Fig. 9) nor for intermediate risk patients (Fig. 10) was there a significant difference regarding survival.

Discussion

Although we would have expected the cryo group of patients to have more extensive disease, due to our selection criteria for the use of cryotherapy, this was not proven by the comparison with the resection group. There was no difference regarding the number of metastases and the occurrence of bilobar metastases, as well as the preoperative CEA serum levels or the presence of extrahepatic disease at laparotomy, between the two groups. The metastases in the cryo group were smaller, which is certainly due to patient selection. Because of the reported higher risk of local recurrence following cryoablation of tumours greater than 3 cm [18], we have usually avoided cryoablation of much larger lesions. There were less synchro-

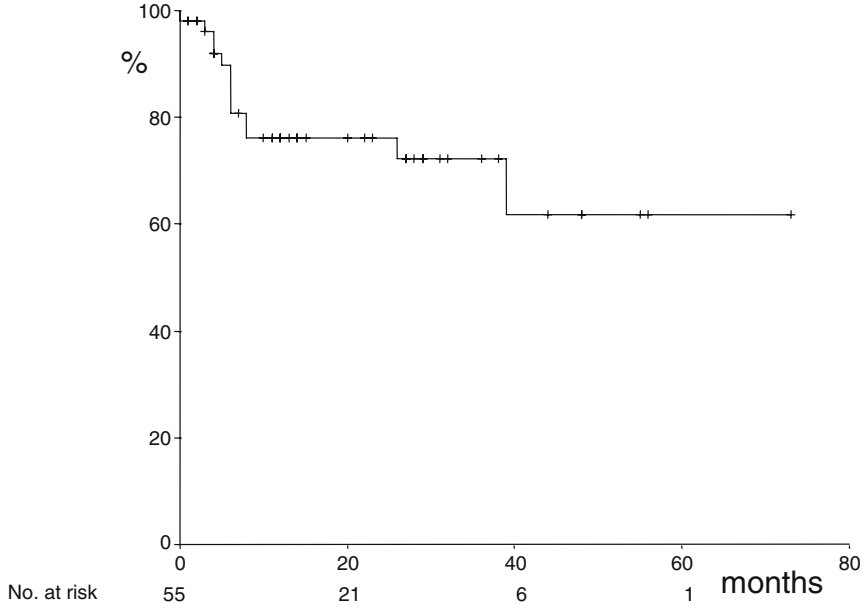

Fig. 4 Cryosite recurrence-free survival (Kaplan–Meier) following cryotherapy (± resection) for colorectal liver metastases

Table 5 Distribution of patient, tumour and perioperative parameters in patients undergoing cryotherapy only versus cryotherapy and liver resection

		Cryotherapy only (n=30)	Cryotherapy+ resection (n=25)	Significance
Age (years)	Mean (SEM)	63.1 (1.9)	60.4 (2.1)	0.32*
Sex (n)	Female	14	10	0.62#
	Male	16	15	
ASA classification (n)	I	1	–	0.15#
	II	9	10	
	III	20	13	
	IV	–	2	
T classification of primary (n)	T1/2	8	2	0.09#
	T3/4	21	23	
	Unknown	1	–	
Nodal involvement at resection of the primary tumour (n)	No involved nodes	12	9	0.95#
	Involved nodes	17	15	
	Unknown	1	1	
Histological differentiation of primary (n)	Well/moderate	14	17	0.22#
	Poor/ undifferentiated	10	4	
	Unknown	6	4	
Prior liver resection (n)	Yes	12	4	0.047#
	No	18	21	
Time of development of liver metastases (n)	Synchronous	8	9	0.46#
	Metachronous	22	16	
Number of liver metastases (n)	Mean (SEM)	1.1 (0.1)	4.0 (0.5)	<0.001*
Diameter of largest liver metastasis (cm)	Mean (SEM)	3.0 (0.2)	4.1 (0.4)	0.10*
Liver metastases distribution (n)	Unilobar	25	5	<0.001#
	Bilobar	5	20	
CEA preoperatively (ng/ml; n)	≤4	9	8	0.45#
	4.01–30	17	10	
	30.01–100	3	4	
	>100	1	3	
	Unknown	–	–	
CEA postoperatively (ng/ml; if preop.>4 ng/ml; (n)	≤4	12	14	<0.001#
	>4	9	2	
	Unknown or N/A	9	9	
Extrahepatic disease at operation (n)	Yes	7	3	0.27#
	No	23	22	
Intraoperative blood replacement (units red cells)	Mean (SEM)	0.7 (0.3)	2.6 (0.9)	0.004*
Duration of operation (min)	Mean (SEM)	240 (16)	318 (18)	0.003*
Radicality of surgery (n)	R0	24	23	0.005#
	R1	–	2	
	R2	6	–	
	Unknown	–	–	
Postoperative hospital stay (days)	Mean (SEM)	13 (0.5)	16 (1.5)	0.033*

*Mann–Whitney U test
#χ^2 test (likelihood ratio)

nous liver metastases treated in the cryo group. This is also due to patient selection, since we were very reluctant to perform cryosurgery of liver metastases combined with resection of the primary tumour because of the increased risk of liver abscess formation at the cryosite [24]. There were more patients who had had a previous liver resection

Table 6 Distribution of two different scoring systems in patients undergoing cryotherapy only versus cryotherapy and liver resection

		Cryotherapy only (n=30)	Cryotherapy + resection (n=25)	Significance
Clinical risk score [20]	0	5	–	<0.001#
	1	14	4	
	2	9	7	
	3	2	8	
	4	–	6	
	5	–	–	
	Mean (SEM)	1.3 (0.2)	2.6 (0.2)	<0.001*
Risk groups[a] grading system [21]	Low risk (0–2 factors)	14	6	0.06#
	Intermediate risk (3–4 factors)	6	11	
	High risk (5–7 factors)	1	2	
Number of risk factors[a]	Mean (SEM)	2.1 (0.3)	2.9 (0.2)	0.018*

#χ^2 test (likelihood ratio)
*Mann–Whitney U test
[a]For the Nordlinger system hospital mortality and patients with incomplete resection or extrahepatic disease were excluded

in the cryo group, since we have used cryotherapy quite frequently to ablate recurrent metastases in the remaining liver after previous liver resection, whenever repeated resection alone was not feasible. The comparison of the groups using the scoring systems of Fong et al. [20] and Nordlinger et al. [21] showed significantly less favorable scores for the resection group (Table 2). If both therapies were of equal short- and long-term efficacy, at least a comparable or even slightly better outcome should therefore be expected for the cryo group.

Table 7 Perioperative morbidity and mortality in patients undergoing cryotherapy only versus cryotherapy and liver resection

	Cryotherapy only (n=30)	Cryotherapy + resection (n=25)
Perioperative mortality (n)	–	1
Perioperative morbidity (n)	2	4
Details of morbidtity (n; more than one complication per patient possible)		
Haemorrhage	1	1
Wound infection	–	–
Biloma or bile fistula	–	1
Intra-abdominal abscess	–	1
Intestinal fistula	–	1
Peritonitis	–	–
(Transient) liver failure	–	–
Gastrointestinal haemorrhage	–	–
Thrombosis	–	–
Pulmonary embolus	–	–
Pneumonia	1	–
Cardiac morbidity	–	–

Morbidity following cryotherapy (± resection) was significantly lower than after resection, and lower following cryotherapy only, than after a combined procedure. This is in accordance with earlier reports in the literature [4, 8, 10]. The immediate efficacy of cryotherapy (± resection) was comparable to liver resection as demonstrated by CEA normalization in 70 versus 66% of patients with a preoperatively elevated CEA serum level, which is in accordance with the findings of other investigators [6, 11, 25–27].

There was no difference in the rate of peritoneal disease between the two groups, therefore peritoneal seeding of tumour cells due to the puncture of the metastases with the cryoprobes does not seem to be a major problem, although we certainly cannot exclude this from occurring occasionally. With the exception of bone metastases, which were less frequent following cryotherapy, there was no difference in the occurrence of extrahepatic recurrence between the two groups. The most frequent extrahepatic site of recurrence was the lung with 31% following cryotherapy (± resection) and 26% following resection. The proposed advantage of cryosurgery over resection, which was seen in some animal models demonstrating lower expression of growth factors [14] or a lesser extent of lung metastases [15] after hepatic cryotherapy compared with liver resection, could not be detected in our series. This is in accordance with the findings of de Jong et al. [28], who have found a similar serum response of hepatocyte growth factor in patients undergoing cryotherapy or resection for colorectal liver metastases.

There were remarkably more patients with hepatic recurrence following cryotherapy compared with resection. This may partly be due to local recurrence at the cryosite, which was observed in 24% of patients, quite comparable

Table 8 Distribution of postoperative follow-up and recurrence for patients undergoing cryotherapy only versus cryotherapy and liver resection

	Cryotherapy only (n=30)	Cryotherapy + resection (n=25)	Significance
Follow-up (months), mean (SEM)	25.2 (3)	23.3 (3)	0.65*
Death, *n* (%)	10 (33)	17 (68)	0.01#
Recurrence, *n* (%)	22 (73)	20 (80)	0.56#
Involved sites of recurrence (multiple sites per patient possible):			
Liver (total), *n* (%)	21 (70)	18 (72)	0.87#
Liver at cryosite, *n* (%)	9 (31)	4 (16)	0.19#
Liver other than cryosite, *n* (%)	20 (67)	18 (72)	0.67#
Lung, *n* (%)	8 (27)	9 (36)	0.46#
Peritoneal disease, *n* (%)	3 (10)	4 (16)	0.51#
Lymph nodes, *n* (%)	5 (17)	4 (16)	0.95#
Local recurrence primary, *n* (%)	1 (3)	3 (12)	0.21#
Bones, *n* (%)	0 (–)	0 (–)	–
Brain, *n* (%)	0 (–)	0 (–)	–
Others, *n* (%)	2 (8)	2 (17)	0.47#
Locations of recurrence:			
Liver only, *n* (%)	9 (30)	7 (28)	
Liver and extrahepatic, *n* (%)	12 (40)	11 (44)	
Extrahepatic only, *n* (%)	1 (3)	2 (8)	

*χ^2 test (likelihood ratio)
#Mann–Whitney *U* test

to results reported by other investigators [4, 10, 18]. We have not recorded the data for resection edge recurrence in the resection group in this study, so we cannot compare the rate of "local treatment failure" of resection with that of cryotherapy. However, looking at the reported results of resection edge recurrence in the literature, this accounts for only 8–25% of all hepatic recurrences following resection of colorectal liver metastases [29, 30]. In a study looking specifically at resection edge recurrence, only 10.4% of all patients undergoing R0 resection developed resection edge recurrence. However, when the macroscopic surgical margin was 5–9, 2–4 or <2 mm, resection edge recurrence developed in 11.3, 11.1 and 20% of patients respectively, over a median follow-up of 29.1 months [31]. Therefore, the local recurrence rate of 24% following cryotherapy is higher than the expected resection edge recurrence rate

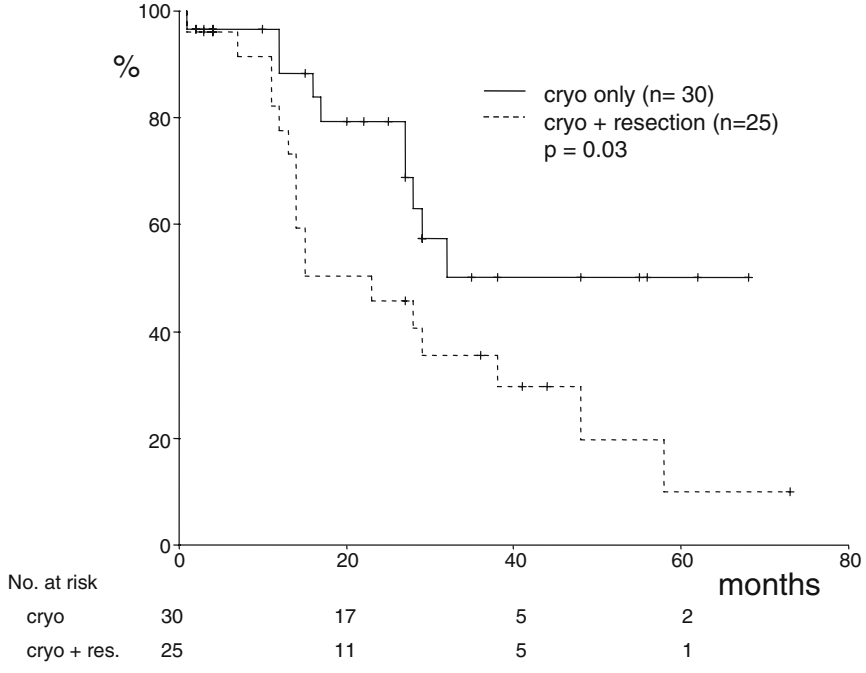

Fig. 5 Survival (Kaplan–Meier) following cryotherapy only or cryotherapy + resection for colorectal liver metastases

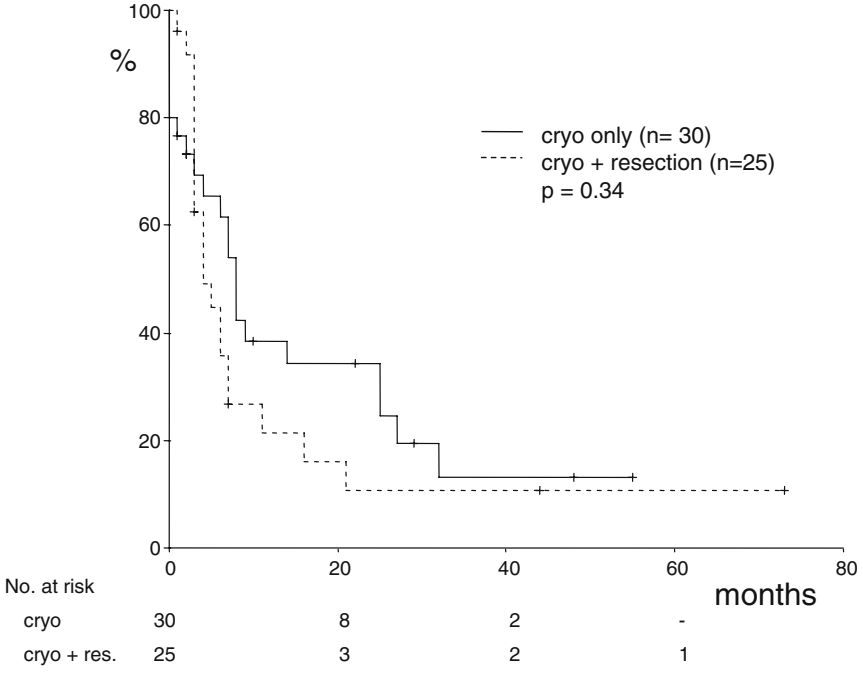

Fig. 6 Disease-free survival (Kaplan–Meier) following cryotherapy only or cryotherapy + resection for colorectal liver metastases

following liver resection. The 3-year cryosite recurrence-free survival was 72% (Fig. 4). Interestingly, local recurrence was seen as late as 39 months following cryotherapy. This is important when assessing other local ablative treatments for liver metastases, since it is demonstrated that a sufficiently long follow-up is necessary to determine the local recurrence rate correctly. However, there was only one patient with hepatic recurrence at the cryosite *only*, the remaining patients all had hepatic recurrence at the cryosite and elsewhere in the liver. Liver disease-free interval and overall disease-free survival were significantly shorter following cryotherapy compared with resection, mainly due to hepatic recurrence. Even if the comparison of the two groups does not reflect major differences in tumour load, the higher hepatic recurrence rate may still be due to patient

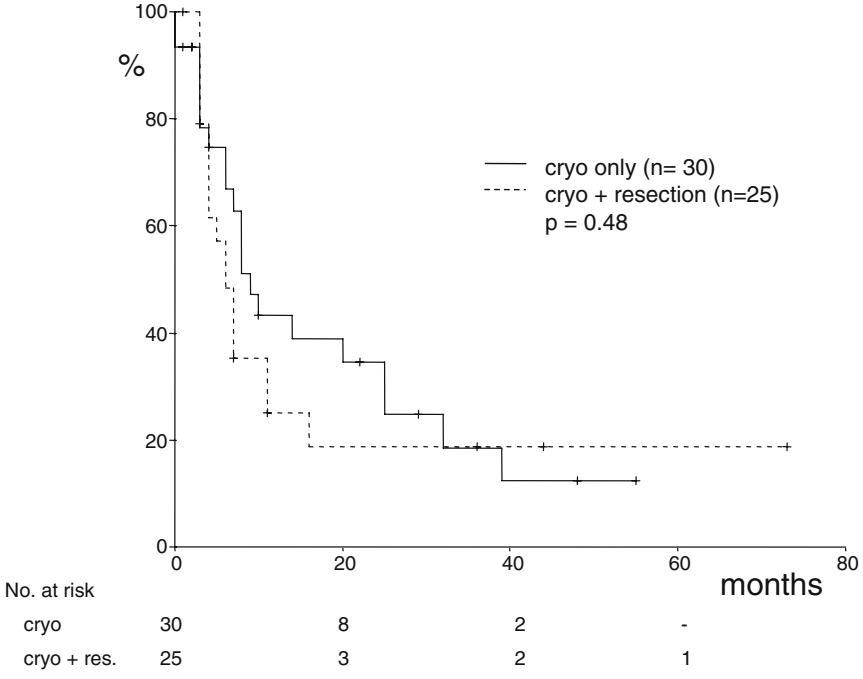

Fig. 7 Liver disease-free survival (Kaplan–Meier) following cryotherapy only or cryotherapy + resection for colorectal liver metastases

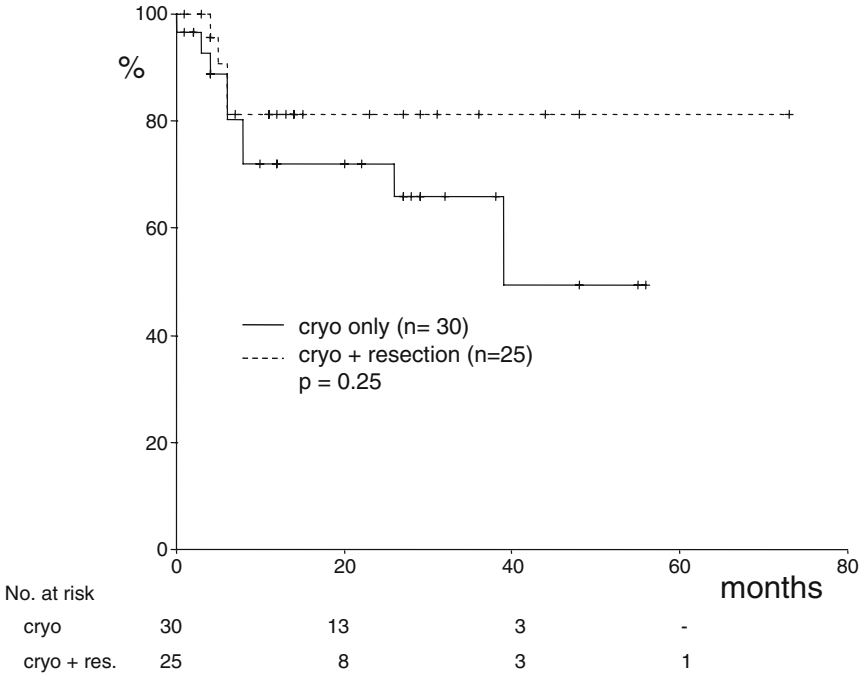

Fig. 8 Cryosite recurrence-free survival (Kaplan–Meier) following cryotherapy only or cryotherapy + resection for colorectal liver metastases

selection. Patients who were felt to have non-resectable disease may have a higher risk of hepatic recurrence.

However, patients who had cryotherapy only mostly had solitary lesions with a mean diameter of only 3 cm. Most of these patients were in the low-risk group according to the Nordlinger grading system and had low Fong clinical risk scores. Even if survival rates were comparable between resection and cryotherapy (± resection), which was also observed in two other studies [32, 33], the markedly higher risk of recurrence in our series—especially in the liver following cryotherapy only, as well as following the combined procedure—which was not assessed in either of the above mentioned studies [32, 33], gives reason to show caution against the use of cryotherapy to treat *resectable* colorectal liver metastases.

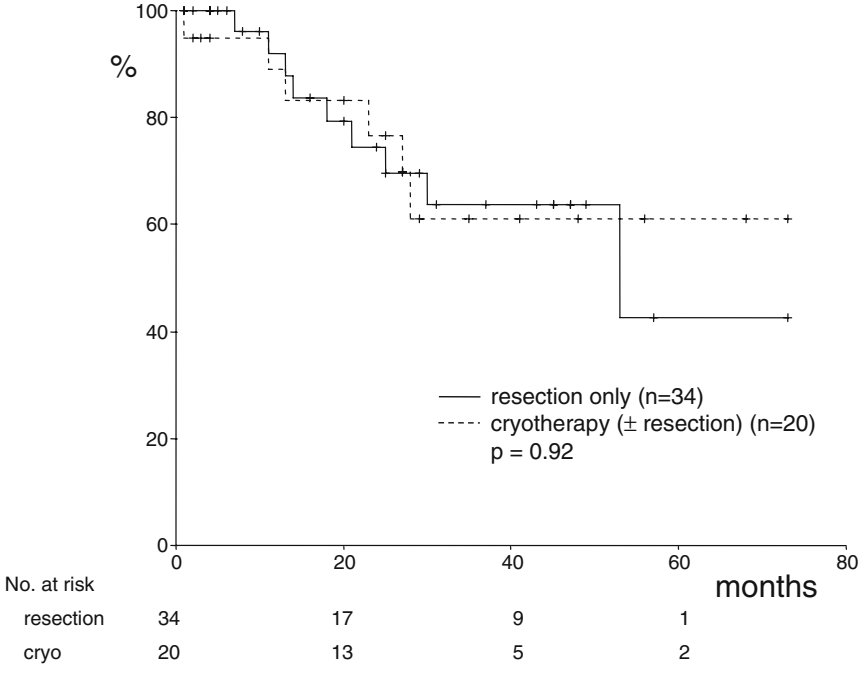

Fig. 9 Survival (Kaplan–Meier) following resection or cryotherapy (± resection) for colorectal liver metastases in patients in the *low* risk group, as defined by the grading system by Nordlinger et al. [21]

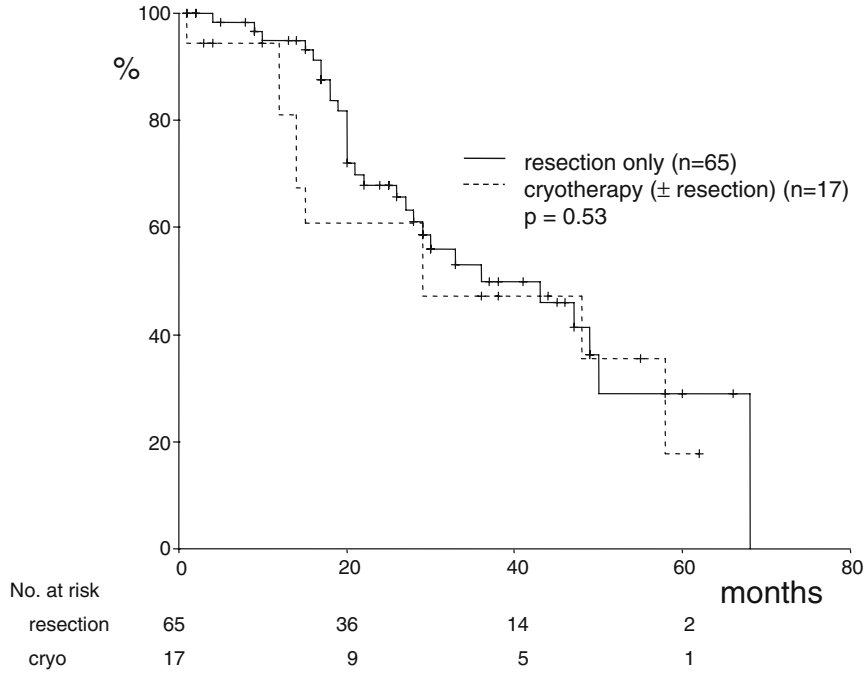

Fig. 10 Survival (Kaplan–Meier) following resection or cryotherapy (± resection) for colorectal liver metastases in patients in the *intermediate* risk group, as defined by the grading system by Nordlinger et al. [21]

Conclusions

Cryotherapy is a valuable treatment option for some patients with non-resectable colorectal liver metastases. In some patients long-term disease-free survival may be achieved, which is an advantage over systemic chemotherapy. However, higher hepatic recurrence rates and a substantial rate of local recurrence following cryotherapy should caution against the use of cryotherapy to treat resectable disease, until the results of randomized controlled trials are available.

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