

Clinical research review

Meta-analysis of clinical outcome after first and second liver resection for colorectal metastases

Anthony Antoniou, FRCS,^a Richard E. Lovegrove, MRCS,^a Henry S. Tilney, MRCS,^a
Alexander G. Heriot, MD, FRCS,^a Timothy G. John, MD, FRCS,^b Myrddin Rees, MS, FRCS,^b
Paris P. Tekkis, MD, FRCS,^a and Fenella K.S. Welsh, MD, FRCS,^b London and Basingstoke,
United Kingdom

Background. The perioperative risk and long-term survival benefit of repeat hepatectomy for patients with liver metastases from colorectal cancer, compared with that of a first liver resection, has been reported with varying results in the literature.

Methods. The literature was searched using Medline, Embase, Ovid, and Cochrane databases for all studies published from 1992 to 2006. Two authors independently extracted data using the following outcomes: postoperative complications and mortality; disease recurrence; and long-term survival. Trials were assessed using the modified Newcastle-Ottawa Score. Random-effect meta-analytical techniques were used for analysis.

Results. Twenty-one studies met the inclusion criteria, comprising 3,741 patients. The use of adjuvant chemotherapy was similar in both groups (odds ratio [OR] = 0.97; 95% confidence interval [CI] = 0.54, 1.74; $P = .92$), as was the number of hepatic nodules present at the time of first or second resection (weighted mean difference [WMD] = 0.18; 95% CI = -0.22, 0.57; $P = .380$). Wedge resection was carried out less often at first hepatectomy (39% vs 46%; OR = 0.66; 95% CI = 0.44, 1.00; $P = .05$). There was significantly less blood loss in patients undergoing first versus second hepatectomy (WMD = 238 ml; 95% CI = 90, 385; $P = .002$). There was no difference in perioperative morbidity (OR = 1.01; 95% CI = 0.65, 1.55; $P = .98$), mortality (OR = 1.01; 95% CI = 0.18, 5.72; $P = .99$) or long-term survival (HR = 0.90; 95% CI = .66, 1.24; $P = .530$) between groups.

Conclusions. Repeat hepatectomy for patients with colorectal cancer metastases is safe and provides survival benefit equal to that of a first liver resection. (*Surgery* 2007;141:9-18.)

From the Imperial College London, Department of Biosurgery and Surgical Technology, St. Mary's Hospital, London, and the Department of Hepatobiliary Surgery, North Hampshire Hospitals NHS Trust, Basingstoke, United Kingdom

COLORECTAL CANCER is common, with 34,000 new cases per annum in the United Kingdom and

145,000 in the United States. Half of these patients will either present with or develop metastatic disease during their lifetime, most commonly within the liver.¹⁻⁴ Of the patients with liver metastases, 20% to 30% have potentially resectable disease,² leading to 5-year survival rates of 25% to 44%.^{1,5-10} Despite hepatic resection with curative intent, however, 60% of patients will develop recurrent intra- or extra-hepatic disease. Of these, approximately 20% are potentially amenable to re-resection.¹¹

Despite favorable accounts of repeat hepatic resections for patients with recurrent colorectal liver metastases, there remains controversy regarding the optimal treatment for such patients. Moreover,

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Reprint requests: Paris P. Tekkis, MD, FRCS, Senior Lecturer/Consultant Colorectal Surgeon, Imperial College London, Department of Biosurgery and Surgical Technology, St. Mary's Hospital, 10th Floor QEOM Building, Praed Street, London W2 1NY, United Kingdom. E-mail: p.tekkis@imperial.ac.uk

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the advent of minimally invasive therapies such as radiofrequency ablation (RFA) or microwave ablation that potentially offer less procedure-associated morbidity and mortality, has further fueled this debate.¹² A keen concern, however, is the variable rate of local recurrence that can follow such targeted therapies.¹³ How this impacts on long-term outcome is as yet unclear and emphasizes the importance of determining the benchmark as represented by repeat liver resection.

The present study uses meta-analytical techniques to achieve consensus regarding the perioperative risk and long-term survival benefit of repeat hepatectomy for patients with liver metastases from colorectal cancer, compared with that of a first liver resection.

MATERIALS AND METHODS

Study selection. The literature was searched using Medline, Embase, Ovid, and Cochrane databases for studies published up to 2006 comparing outcomes after first and second liver resections for colorectal metastases. The following MeSH search headings were used: “colorectal neoplasms,” “neoplasm metastasis,” “liver,” “hepatectomy,” and “reoperation.” The following text searches and search headings and their combinations were used: “colorectal cancer,” “liver resection,” “liver metastasis,” “first,” “second,” and “redo.” The “related articles” function was used to broaden the search, and all abstracts, studies, and citations scanned were reviewed. No language restrictions were made.

Data extraction. Two reviewers (R.E.L. and A.A.) independently carried out the search, as well as reviewing and extracting the following data according to a pre-specified protocol. First author, year of publication, study population characteristics, study design, inclusion, and exclusion criteria, number of subjects, length of follow-up, short-term, and long-term outcomes were extracted.

Inclusion criteria. Studies had to (1) compare outcomes between first and second liver resection; and (2) report on at least one of the outcomes mentioned below. Furthermore, when 2 studies were reported by the same institution, either the one of better quality or the most recent publication was included, unless the study outcomes were mutually exclusive or measured at different time intervals.

Exclusion criteria. Non-comparative studies were excluded. If end-points were not comparable, or if it was impossible to calculate them from the published results, then the assessed study was excluded. Studies that displayed a “zero cell” for an outcome of interest in both groups were excluded

from the analysis of that outcome but were taken into consideration when considering its total sample size.

Outcomes of Interest and Definitions The following outcomes of interest were used to compare the 2 operative techniques.

Short-term adverse events: Post-operative mortality defined as occurring within 30 days of operation from any cause. All complications were recorded including wound infection (defined as the presence of inflammation, or purulent discharge, or positive wound swab for bacterial growth), bile leak and fistula, subphrenic abscess, pleural effusion, hepatic insufficiency, and postoperative hemorrhage.

Disease recurrence: Recurrence of cancer within the liver with and without extrahepatic disease was recorded. Where stated the disease free-interval (DFI) was also noted.

Survival: Cancer-specific survival data was compared between patients undergoing first or second liver resection. The published survival curves had to commence censoring at the time of the first or second resection. Those studies using identical patient populations for outcomes of first versus second resection were excluded from survival analysis to eliminate bias. Bias would be introduced because those patients undergoing a first resection would survive long enough to require a second resection, and this would be reflected in the survival curves.

Statistical analysis. Meta-analysis was carried out in line with recommendations from the Cochrane Collaboration ‘The Quality of Reporting of Meta-Analyses’ (QUORUM) guidelines.^{14,15} The effect measures estimated were odds ratio (OR) for dichotomous data and weighted mean difference (WMD) for continuous data, both reported with 95% confidence intervals (CI).¹⁶ This ratio represented the odds of an adverse event occurring in a “control” group compared with a “treatment” group. The analysis was undertaken by comparing first resection to second resection with an OR of more than “one” favoring the second resection group. The point estimate of the OR was considered statistically significant at the *P* less than .05 level if the 95% CI did not include “one.” Studies that contained a “zero” in 1 cell for the number of events of interest in 1 of 2 groups resulted in problems with the computation of ratio measurement. To overcome this problem the Haldane correction was applied, whereby a value of 0.5 was added in both groups from that particular study.¹⁷

For categorical variables the OR were combined with the Mantel-Haenszel chi-square method using a “random effect” meta-analytical technique.¹⁸ In a

random effect model it is assumed that there is variation between studies and the calculated OR thus has a more conservative value.^{19,20} In operative research, meta-analysis using the random effect model is preferable particularly because patients that are operated on in different centers have varying risk profiles and selection criteria for each operative technique. In the tabulation of the results, squares indicate point estimates of treatment effect (OR), with the size of the square representing the weight attributed to each study and 95% CI indicated by horizontal bars. The diamond represents the summary OR from the pooled studies with 95% CI. For studies that presented continuous data as mean and range values, the standard deviation (SD) was calculated using statistical algorithms and checked using “bootstrap” re-sampling techniques. Thus all continuous data were standardized for the analysis. Meta-analysis of survival data was undertaken by extracting cumulative survival data from published Kaplan-Meier plots and calculating the log hazard ratio (HR) and standard error (SE), as described by Parmar et al.²¹ An HR of less than “one” represented a survival benefit favoring the second resection group, whereas an HR greater than “one” represented a survival benefit favoring the first resection group.

The quality of the randomized and non-randomized studies was assessed by using the Newcastle-Ottawa Scale (NOS) with some modifications to match the needs of this study.²² The quality of the studies was evaluated by examining three items: patient selection, comparability of the 2 study groups, and assessment of outcome. “High quality” studies were defined as those achieving 7 or more stars on this quality assessment.

Two strategies were used to quantitatively assess heterogeneity: (1) graphic exploration with funnel plots was used to evaluate publication bias^{16,23}; and (2) sensitivity analysis was undertaken for the following subgroups: (i) year of publication 2000 onward; (ii) studies of high quality; and (iii) study size more than 100 patients total.

Analysis was conducted by using the statistical software Stata version 9.1 SE for Windows (StataCorp, College Station, Tex) and Review Manager Version 4.2 (The Cochrane Collaboration, Software Update, Oxford, UK).

RESULTS

Studies selected. The literature search identified 24 comparable studies that met the selection criteria.^{9,10,24-45} One study was excluded as it became apparent that this was a review article.²⁶ Another was excluded to prevent overlap with another arti-

cle from the same institution.²⁹ A third exclusion was made because the article was a single-patient case report.³⁰ The remaining 21 studies were included for analysis. All included studies were retrospective, and 13 had matched groups of patients who had undergone a first then second hepatic resection.^{9,24,25,27,28,31,32,35,37-39,43,44} On review of the extracted data there was 100% agreement between the 2 reviewers.

A total of 3,741 patients in 21 studies underwent primary liver resection for colorectal liver metastasis between 1971 and 2005. Table I presents a summary of these studies. Of these, 892 (23.8%) underwent a repeat liver resection for recurrence of intrahepatic disease. When the 8 studies with different patients in the first and second resection groups were considered, 277 (8.9%) of 3,126 patients underwent a re-resection. Where gender was discussed there were 1,312 (40.7%) women from 3,225 patients undergoing primary liver resection and 264 (39.9%) from 662 patients undergoing repeat resection. Age at primary operation ranged from 23 to 87 years. There was no significant difference in the number of liver nodules at the time of first and second liver resection (WMD = 0.18; 95% CI = -0.22, 0.57; $P = .380$). Follow-up ranged from 0 to 175 months after first resection and 0 to 199 months after second resection.

Although more patients (93/512 [18.2%]) had extra-hepatic metastases at the time of second liver resection, compared with patients undergoing first liver resection (308/2,314 [13.3%]), this was not statistically significant (OR = 0.55; 95% CI = 0.15, 1.98; $P = .36$). There was, however, significant heterogeneity ($P < .001$) between the 7 published studies that reported this finding. There was no difference in the percentage of patients in either group who received chemotherapy during their management (560/1,636 [34.2%] first resection vs 233/615 [37.9%] second resection; OR = 0.97; 95% CI = 0.54, 1.74; $P = .920$). With regard to operative procedure, there were significantly less wedge resections carried out in patients undergoing their first liver resection (1,034/2,654 [39%]) compared with those undergoing repeat liver operation (321/692 [46%]); OR = 0.66; 95% CI = 0.44, 1.00; $P = .050$). The remaining patients underwent an anatomic resection. Operating time, recorded in 5 articles, did not differ significantly between first and second resections, with the first resection being a mean of 28 minutes shorter than the second ($P = .140$). Mean blood loss was significantly lower (WMD = 238 ml; 95% CI = 90, 385) during the first resection compared with the second ($P = .002$).

Table I. Characteristics of included studies

Study (y)	Study type	Cases		Age at first resection (years)	Matching	Follow-up (mo)	Study quality
		1st	2nd				
Adam (1997) ²⁴	Retro	64	64	56 (31-73)	2,7	—	*****
Bozzetti (1992) ²⁵	Retro	11	11	58 ± 8.7	2,4,7	16.6 ± 11.8	*****
Chiappa (1999) ²⁷	Retro	10	10	62 ± 9	2,3,4,7	—	*****
Chu (1997) ²⁸	Retro	9	9	50 ± 11	2,6,7	—	*****
Kin (1998) ³¹	Retro	15	15	—	2,3,7	—	*****
Muratore (2001) ³²	Retro	29	29	61 (50-70)	2,7	—	*****
Nagakura (2002) ³³	Retro	100	17	63 (32-87)*	2	—	*****
Nordlinger (1994) ³⁴	Retro	1,818	116	59 (32-80)	1,2,5	20 (0-121)	*****
Pessaux (2006) ³⁵	Retro	42	42	64 (24-80)	2,7	56	*****
Petrowsky (2002) ⁹	Retro	126	126	62 (34-82)*	2,7	58.8*	*****
Pinson (1996) ³⁶	Retro	95	10	53 ± 10.2	3,5,6	33 ± 27	*****
Shaw (2006) ¹⁰	Retro	718	66	63 (26-86)	2,3,4,6	32 (5.2-199)	*****
Sugarbaker (1999) ³⁷	Retro	170	170	58 (28-84)	7	29 (1-128)	*****
Sugawara (2005) ³⁸	Retro	27	27	59 ± 8.5	2,3,4,6,7	41 ± 22	*****
Suzuki (2001) ³⁹	Retro	26	26	55 (30-76)	2,4,7	—	*****
Takahashi (2003) ⁴⁰	Retro	120	23	60 (23-78)	3	23 (1-69)*	*****
Tanaka (2004) ⁴¹	Retro	193	26	—	6	32 (1-125)	*****
Tascheri (2003) ⁴²	Retro	26	5	54 (30-69)	—	—	*****
Yamada (2001) ⁴³	Retro	11	11	—	3,7	42.9 ± 27.3	*****
Yamamoto (1999) ⁴⁴	Retro	75	75	—	2,7	24 (2.4-121)*	*****
Zacharias (2004) ⁴⁵	Retro	56	14	74 (70-81)*	1,3,6	—	*****

Mean age and follow-up (±SD or range). Matching criteria: 1, age; 2, gender; 3, number of liver nodules; 4, chemotherapy; 5, follow-up; 6, resection type; 7, number of patients in each group.

*Median (interquartile range).

Meta-analysis of adverse events. Sixteen studies reported on postoperative adverse events.^{9,10,24,25,28,32,34-42,45} There were no significant differences between any of the adverse outcomes analyzed in the 2 groups. There were 29 (2.4%) episodes of postoperative hemorrhage in 1,221 patients after primary liver resection and 25 (4.8%) episodes in 524 patients after second resection ($P = .580$). Biliary leak or fistula occurred in 21 (2.1%) of 1,005 patients undergoing primary resection and 15 (3.2%) of 469 patients undergoing repeat resection ($P = .520$). Meta-analysis of the 20 studies^{9,10,24,25,27,28,31-36,38-45} that reported perioperative mortality showed no difference between the 2 groups, with 15 deaths in 1,732 patients (0.87%) after first liver resection and 6 deaths in 690 patients (0.87%) undergoing repeat resection (OR = 1.01; 95% CI = 0.18, 5.72; $P = .990$). Overall complications occurred in 345 of 1,468 patients (23.5%) undergoing first liver resection and 119 of 598 patients (19.9%) undergoing repeat resection ($P = .980$) (Fig 1).

Disease recurrence. Recurrence of tumor was reported in 1,377 of 2,348 patients (58.6%) after first resection and 126 of 191 patients (66.0%) after second resection. The time to tumor recurrence after first and second resections did not differ sig-

nificantly with a WMD of 3.27 months between the groups ($P = .310$) (Table II).

Meta-analysis of survival data. Meta-analysis of survival data extracted from Kaplan-Meier plots was possible in 7 studies.^{10,24,28,31,33,36,40} Analysis of survival after first and second resections (Fig 2) showed that there was no significant difference between the 2 groups, with an HR of 0.90 (95% CI = 0.66, 1.24; $P = .530$).

Sensitivity analysis. Sensitivity analysis was carried out by comparing outcomes between first and second liver resections for high quality studies (≥ 7 stars), studies published since 2000 and those studies with more than 100 patients (Table III). It reinforces the finding that there is no significant difference in the incidence of adverse events after first or second liver resection. Perioperative blood loss remained significantly less in those patients undergoing their first liver resection in all but the analysis of high quality studies. Analysis of the 4 studies published from the year 2000 that reported on operating time showed that the first liver resection was quicker than a repeat hepatectomy by almost 46 minutes ($P = .002$). The only study with more than 100 patients that documented operating time also showed a similar trend ($P = .07$).⁴¹ Sen-

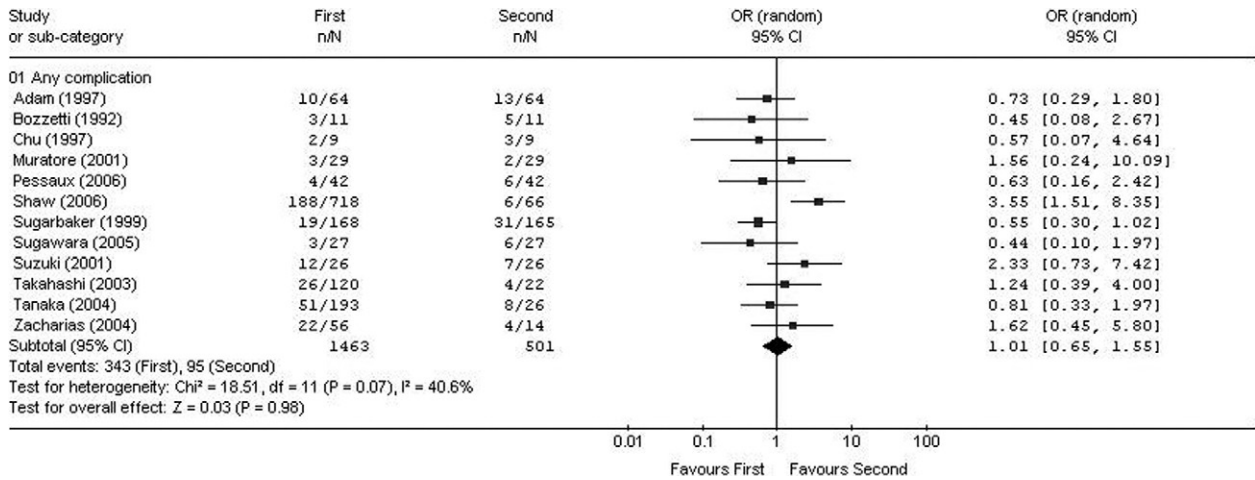


Fig 1. Forrest plot of complications after first and second liver resection.

Table II. Treatment and outcomes for first and second liver resections of colorectal metastases

Outcome	No. patients	No. studies	OR/WMD*/HR ⁺ (95% CI)	P value	HG P value
Perioperative treatment					
Wedge resection	2,654	14	0.66 (0.44,1.00)	.050	.001
Chemotherapy	1,474	11	0.97 (0.54,1.74)	.920	<.001
Operating time (min)	332	5	-27.5 (-63.9, 8.9)*	.140	.090
Blood loss (ml)	1,005	6	-238 (-385, -90)*	.002	.230
Length of stay (d)	1,016	5	0.7 (-2.8,4.3)*	.680	.008
Postoperative complications					
Perioperative mortality	1,126	4	1.01 (0.18,5.72)	.990	.770
Hemorrhage	1,028	5	1.19 (0.64,2.21)	.580	.900
Pleural effusion	36	2	1.01 (0.10,10.28)	1.000	.320
Bile leak/fistula	1,005	7	0.72 (0.26,1.96)	.520	.950
Hepatic insufficiency	849	3	0.73 (0.09,5.64)	.760	.170
Subphrenic abscess	76	3	0.89 (0.15,5.21)	.890	.720
Wound infection	203	3	0.65 (0.20,2.05)	.460	.990
Any complication	1,463	12	1.01 (0.65,1.55)	.980	.070
Disease recurrence					
Intrahepatic recurrence	2,322	5	0.69 (0.42,1.14)	.150	.120
Extrahepatic ± intrahepatic recurrence	2,222	4	0.71 (0.42,1.19)	.200	.170
Overall recurrence	2,322	5	0.79 (0.58,1.08)	.150	.620
Disease free	409	3	0.99 (0.56,1.74)	.970	.970
Disease-free interval (mo)	20	2	-3.27 (-9.65,3.10)*	.310	.750
Survival					
First vs second resection	1,417	7	0.90 (0.66, 1.24) ⁺	.530	.060

CI, confidence interval; HG, heterogeneity; HR, hazard ratio (values <1 favor second resection, values >1 favor first resection); OR, odds ratio (values <1 favor first resection, >1 favor second resection); WMD, weighted mean difference) (negative values favor first resection, positive values favor second resection). Numbers in bold represent statistically significant P values.

sitivity analysis of survival data showed that the survival benefit of a first liver resection was matched by repeat resection.

Publication bias. A “funnel plot” of the studies comparing first and second liver resections, focusing on the peri-operative complications is shown in Figure 3. This is a scatter plot of the treatment

effects estimated from individual studies plotted on the horizontal axis (OR), against the SE of the log of the estimate shown on the vertical axis SE (Log OR). Two of 12 studies lie outside of the 95% CI limits as reflected by the trend toward heterogeneity in this outcome (P = .070). When only high quality studies are considered it is found that all of

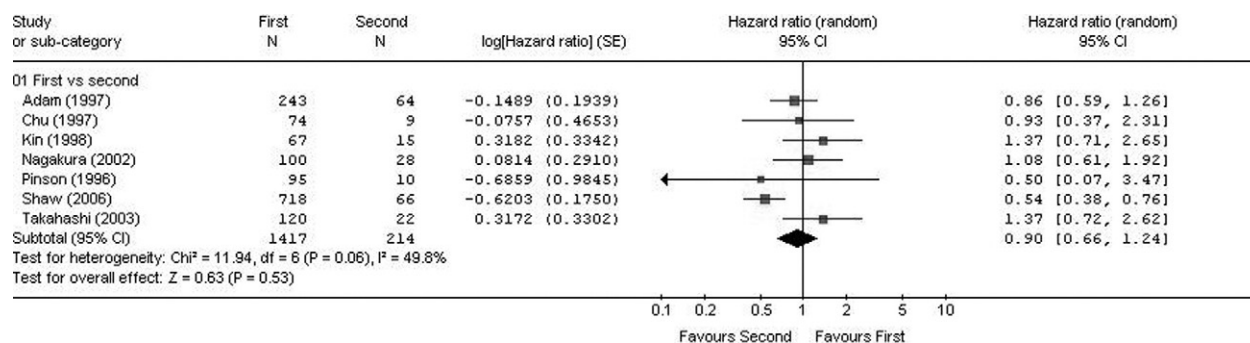


Fig 2. Meta-analysis of survival data after first and second liver resections.

Table III. Subgroup analysis of selected outcomes

Outcome	No. patients	No. studies	OR/WMD*HR ⁺ (95% CI)	P value	HG P value
Studies published $\geq 2,000$					
Wedge resection	547	7	0.56 (0.32,1.00)	.050	.080
Intrahepatic recurrence	409	3	0.88 (0.51,1.51)	.640	.470
Bile leak/fistula	921	4	0.99 (0.27,3.62)	.990	.890
Any complication	1,211	8	1.34 (0.80,2.26)	.260	.160
Blood loss (ml)	906	4	-252 (-395,-110)*	<.001	.250
Operating time (min)	317	4	-45.9 (-74.7,-17.1)*	.002	.920
1st vs 2nd survival	938	3	0.89 (0.48,1.64) ⁺	.700	.010
High quality studies (≥ 7 stars)					
Wedge resection	1,982	9	0.65 (0.40,1.06)	.080	.230
Intrahepatic recurrence	1,913	2	0.59 (0.23,1.51)	.270	.140
Bile leak/fistula	821	5	0.75 (0.20,2.76)	.670	.920
Any complication	847	6	1.34 (0.63,2.88)	.450	.090
Blood loss (ml)	770	4	-204 (-459,52)*	.120	.260
Operating time (min)	97	3	-10.5 (-65.6,44.7)*	.710	.080
1st vs 2nd survival	954	4	0.79 (0.45,1.39) ⁺	.420	.080
Studies with ≥ 100 patients					
Wedge resection	2,397	5	0.65 (0.33,1.31)	.230	<.001
Intrahepatic recurrence	2,227	4	0.65 (0.38,1.11)	.110	.110
Bile leak/fistula	838	2	1.51 (0.27,8.40)	.640	.820
Any complication	1,199	4	1.15 (0.48,2.79)	.750	.005
Blood loss (ml)	838	2	-261 (-496,-27)*	.030	.180
Operating time (min)	193	1	-59.0 (-121.8,3.8)*	.070	—
1st vs 2nd survival	938	3	0.89 (0.48,1.64) ⁺	.700	.010

CI, confidence interval; HG, heterogeneity; HR, hazard ratio (values <1 favor second resection, values >1 favor first resection); OR, odds ratio (values <1 favor first resection, >1 favor second resection); WMD, weighted mean difference) (negative values favor first resection, positive values favor second resection). Numbers in bold represent statistically significant P values.

the studies now lie within the 95% CI limits, and this is reflected by the heterogeneity being non-significant ($P = .450$).

DISCUSSION

The optimal therapy for patients with recurrent colorectal liver metastases remains under debate.

This meta-analysis attempted to assess whether repeat hepatectomy for recurrent colorectal liver metastases can achieve clinical outcomes comparable to a first hepatectomy. In the 21 studies that met the inclusion criteria, the patients undergoing a first or second liver resection had similar demographic characteristics. The operative procedure,

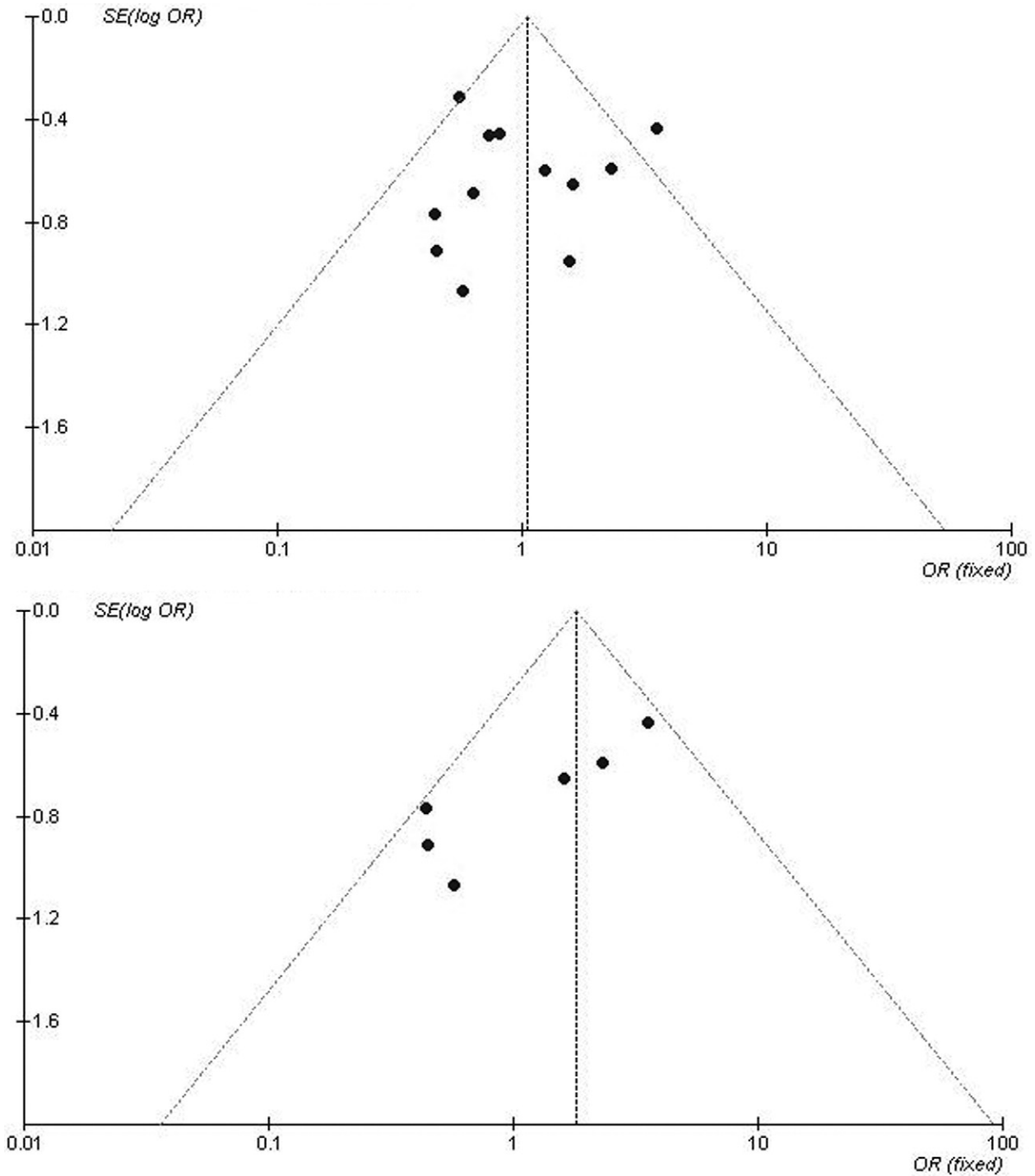


Fig 3. Funnel plot of any complications. All studies (**top**) and high quality studies (**bottom**). The dots represent individual studies and the lines 95% CI.

however, seemed to differ between the first and second resection groups. As might be expected, an increased percentage of wedge resections was carried out in the repeat hepatectomy group, probably reflecting the need for a parenchymal-sparing ap-

proach in re-do hepatic operation. This seems to be oncologically justifiable as there was no difference in the incidence of recurrent disease or survival between the 2 groups. In contrast, wedge resections have been shown previously as having an increased

risk of a positive operative margin,^{41,46} with margin positivity being associated with a higher incidence of recurrent disease⁴¹ and reduced survival.⁴⁶ The impact of positive margins has been critically analyzed in a more recent study that looked at pathologic margin status per se in 557 patients undergoing hepatic resection for colorectal metastases.⁴⁷ They found that a positive operative margin was associated with a significantly higher incidence of recurrent disease and a shorter median survival compared with patients with margins of 1 to 4 mm, 5 to 9 mm, and more than 10 mm. There was no difference in recurrence rate or survival in these 3 latter groups of margin-negative patients, emphasizing that it is the margin involvement rather than the type of resection, that impacts on long-term outcome. There was insufficient data to comment on resection margin involvement in this meta-analysis, with only one study reporting on this.²⁸

The overall data indicate that the operating time for a first liver resection was 30 minutes faster than a repeat resection. Subgroup analysis of the 4 most recent studies showed, however, that the repeat hepatectomies took significantly longer. This was consistent with the authors' own experience and that of others⁴⁸ that re-do liver operation is potentially more lengthy and challenging than a first-time resection. There are a number of reasons for this: (1) exposure of the liver is more difficult due to extensive peri-hepatic adhesions; (2) there may be altered intra-hepatic and portal anatomy due to hypertrophy of the liver remnant and subsequent rotation of the porta hepatis; and (3) the texture and consistency of the liver parenchyma may be altered, leading to a longer duration of clamping of the hepatic pedicle and increased blood loss.⁴⁸ This later factor was supported by the consistent finding that perioperative blood loss is significantly greater during repeat hepatectomy ($P = .002$, HG $P = .23$).

This meta-analysis showed that repeat hepatectomy can be carried out with a morbidity and mortality equal to that of a first hepatectomy. There was no significant difference in specific or overall complications between the 2 groups and this result remained robust on sensitivity analysis. Mortality rates of less than 1% in both groups are a testament to advances in operative and anesthetic techniques,⁴⁹ the use of low CVP anesthesia,^{50,51} and the advent of modern chemotherapeutic agents that can potentially down-size critically-placed lesions.^{52,53}

Comprehensive evidence that repeat hepatectomy matches the survival benefit of a first hepatectomy is provided here. Although there is some

heterogeneity between survival data as shown by sensitivity analysis, this probably reflects differences in patient selection between series and also the expanding criteria for resectability in the past 20 years. In the early years, only lesions that were unilateral or small in number were tackled operatively. In contrast, the current accepted criteria for resectability are that there must be a treatment strategy for every lesion (resection + ablation) to remove all macroscopic disease with clear resection margins, while leaving sufficient liver parenchyma to support function.⁵⁴ The favorable survival data for patients after both a first and second liver resection supports this current aggressive approach. Eighteen percent of patients undergoing repeat hepatectomy had extra-hepatic disease, compared with 13% of patients undergoing a first resection. Although this result was not significantly different ($P = .36$), there was considerable lack of consistency between the studies (HG $P < .001$), probably reflecting differences in patient selection. A number of early studies have shown that the presence of extra-hepatic disease is a poor prognostic factor for patients undergoing either primary⁵ or repeat liver resection.^{11,44} Five-year survival rates of 50% have been shown for patients undergoing sequential liver and lung resection for colorectal metastases.⁵⁵ More recently, Elias and colleagues reported a series of 111 patients who underwent hepatectomy with concurrent resection of hilar lymph nodes, adrenals, ovaries, or peritoneal disease (with intra-peritoneal chemotherapy), or subsequent (within 2 months) lung resection.⁵⁶ They reported an overall 5-year survival rate of 20%, increasing to 29% in the 75 patients who had an R0 resection. The present study supports current evidence^{54,57} that treatable extra-hepatic disease should not be a contra-indication to hepatic resection, repeat, or otherwise.

There are, to date, no published, randomized, controlled trials comparing the outcome of repeat hepatectomy to potential alternatives such as RFA; indeed, the role of such ablative therapies is still being defined.⁵⁸ Certainly there are no randomized data to support the use of RFA in preference to repeat hepatectomy.¹² Lesions treated with RFA have local recurrence rates of 4% to 55%.¹³ Moreover, the procedure is not without risk⁵⁹ and usually requires general anesthesia and multiple treatment episodes. As discussed above, ablation may be used in conjunction with operative resection to increase resectability rates. In a series of 418 consecutive patients with colorectal liver metastases from the MD Anderson Cancer Center, 45% underwent resection only, 24% RFA and resection, 14% RFA only, and 17% chemotherapy only. It was

found that the 4-year survival after resection (65%) was better than after RFA and resection (36%) or RFA only (22%) ($P < .0001$). Survival for “unresectable” patients treated with RFA and resection or RFA only was greater than those treated with palliative chemotherapy only ($P = .0017$).⁶⁰ A further large published case series of 117 patients treated with RFA who were unfit for or unsuitable for resection reported 3-year survival rates of 46%.⁶¹

The current meta-analysis has shown that repeat hepatectomy for resectable colorectal metastases can be carried out with morbidity, mortality, and long-term survival benefit equal to that of a first hepatectomy. These promising data rely on intensive surveillance after the first hepatectomy, early referral to a specialist hepatobiliary surgeon, and meticulous operative treatment and perioperative care. In the absence of other proven therapies, repeat hepatectomy is the treatment of choice for resectable disease.

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REFERENCES

1. Scheele J, Stang R, Altendorf-Hofmann A, Paul M. Resection of colorectal liver metastases. *World J Surg* 1995;19:59-71.
2. Stangl R, Altendorf-Hofmann A, Charnley RM, Scheele J. Factors influencing the natural history of colorectal liver metastases. *Lancet* 1994;343:1405-10.
3. Scheele J, Stangl R, Altendorf-Hofmann A. Hepatic metastases from colorectal carcinoma: impact of surgical resection on the natural history. *Br J Surg* 1990;77:1241-6.
4. Sugarbaker PH. Surgical decision making for large bowel cancer metastatic to the liver. *Radiology* 1990;174:621-6.
5. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999;230:309-18.
6. Rees M, Plant G, Bygrave S. Late results justify resection for multiple hepatic metastases from colorectal cancer. *Br J Surg* 1997;84:1136-40.
7. Adam R, Huguet E, Azoulay D, Castaing D, Kunstlinger F, Levi F, et al. Hepatic resection after down-staging of unresectable hepatic colorectal metastases. *Surg Oncol Clin N Am* 2003;12:211-20.
8. Neeleman N, Andersson R. Repeated liver resection for recurrent liver cancer. *Br J Surg* 1996;83:893-901.
9. Petrowsky H, Gonen M, Jarnagin W, Lorenz M, DeMatteo R, Heinrich S, et al. Second liver resections are safe and effective treatment for recurrent hepatic metastases from colorectal cancer: a bi-institutional analysis. *Ann Surg* 2002;235:863-71.
10. Shaw IM, Rees M, Welsh FK, Bygrave S, John TG. Repeat hepatic resection for recurrent colorectal liver metastases is associated with favorable long-term survival. *Br J Surg* 2006;93:457-64.
11. Wanebo HJ, Chu QD, Avradopoulos KA, Vezeridis MP. Current perspectives on repeat hepatic resection for colorectal carcinoma: a review. *Surgery* 1996;119:361-71.
12. Elias D, De Baere T, Smayra T, Ouellet JF, Roche A, Lasser P. Percutaneous radiofrequency thermoablation as an alternative to surgery for treatment of liver tumor recurrence after hepatectomy. *Br J Surg* 2002;89:752-6.
13. Sutherland LM, Williams JA, Padbury RT, Gotley DC, Stokes B, Maddern GJ. Radiofrequency ablation of liver tumors: a systematic review. *Arch Surg* 2006;141:181-90.
14. Clarke M, Horton R. Bringing it all together: Lancet-Cochrane collaborate on systematic reviews. *Lancet* 2001;357:1728.
15. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008-12.
16. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.
17. Haldane JB. The estimation and significance of the logarithm of a ratio of frequencies. *Ann Hum Genet* 1956;20:309-11.
18. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959;22:719-48.
19. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.
20. Sterne JA, Davey Smith G. Sifting the evidence-what's wrong with significance tests? *BMJ* 2001;322:226-31.
21. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med* 1998;17:2815-34.
22. Athanasiou T, Al-Ruzzeh S, Kumar P, Crossman MC, Amrani M, Pepper JR, et al. Off-pump myocardial revascularization is associated with less incidence of stroke in elderly patients. *Ann Thorac Surg* 2004;77:745-53.
23. Egger M, Smith GD. Misleading meta-analysis. *BMJ* 1995;311:753-4.
24. Adam R, Bismuth H, Castaing D, Waechter F, Navarro F, Abascal A, et al. Repeat hepatectomy for colorectal liver metastases. *Ann Surg* 1997;225:51-60.
25. Bozzetti F, Bignami P, Montalto F, Doci R, Gennari L. Repeated hepatic resection for recurrent metastases from colorectal cancer. *Br J Surg* 1992;79:146-8.
26. Bismuth H, Adam R, Navarro F, Castaing D, Engerran L, Abascal A. Re-resection for colorectal liver metastasis. *Surg Oncol Clin N Am* 1996;5:353-64.
27. Chiappa A, Zbar AP, Biella F, Staudacher C. Survival after repeat hepatic resection for recurrent colorectal metastases. *Hepatogastroenterology* 1999;46:1065-70.
28. Chu QD, Vezeridis MP, Avradopoulos KA, Wanebo HJ. Repeat hepatic resection for recurrent colorectal cancer. *World J Surg* 1997;21:292-6.
29. Fong Y, Blumgart LH, Cohen A, Fortner J, Brennan MF. Repeat hepatic resections for metastatic colorectal cancer. *Ann Surg* 1994;220:657-62.
30. Imamura H, Sano K, Harihara Y, Noie T, Hasegawa K, Minagawa M, et al. Complete remission of disease for 5 years following initial and repeat resection of the liver for the removal of 22 metastases of colorectal origin. *J Hepatobiliary Pancreat Surg* 2003;10:321-4.
31. Kin T, Nakajima Y, Kanehiro H, Hisanaga M, Ohyama T, Nishio K, et al. Repeat hepatectomy for recurrent colorectal metastases. *World J Surg* 1998;22:1087-91.

32. Muratore A, Polastri R, Bouzari H, Vergara V, Ferrero A, Capussotti L. Repeat hepatectomy for colorectal liver metastases: a worthwhile operation? *J Surg Oncol* 2001;76:127-32.
33. Nagakura S, Shirai Y, Suda T, Hatakeyama K. Multiple repeat resections of intra- and extrahepatic recurrences in patients undergoing initial hepatectomy for colorectal carcinoma metastases. *World J Surg* 2002;26:141-7.
34. Nordlinger B, Vaillant JC, Guiguet M, Balladur P, Paris F, Bachellier P, et al. Survival benefit of repeat liver resections for recurrent colorectal metastases: 143 cases. *Association Francaise de Chirurgie. J Clin Oncol* 1994;12:1491-6.
35. Pessaux P, Lermite E, Brehant O, Tuech JJ, Lorimier G, Arnaud JP. Repeat hepatectomy for recurrent colorectal liver metastases. *J Surg Oncol* 2006;93:1-7.
36. Pinson CW, Wright JK, Chapman WC, Garrard CL, Blair TK, Sawyers JL. Repeat hepatic surgery for colorectal cancer metastasis to the liver. *Ann Surg* 1996;223:765-73.
37. Sugarbaker PH. Repeat hepatectomy for colorectal metastases. *J Hepatobiliary Pancreat Surg* 1999;6:30-8.
38. Sugawara G, Isogai M, Kaneoka Y, Suzuki M, Yamaguchi A. Repeat hepatectomy for recurrent colorectal metastases. *Surg Today* 2005;35:282-9.
39. Suzuki S, Sakaguchi T, Yokoi Y, Kurachi K, Okamoto K, Okumura T, et al. Impact of repeat hepatectomy on recurrent colorectal liver metastases. *Surgery* 2001;129:421-8.
40. Takahashi S, Inoue K, Konishi M, Nakagouri T, Kinoshita T. Prognostic factors for poor survival after repeat hepatectomy in patients with colorectal liver metastases. *Surgery* 2003;133:627-34.
41. Tanaka K, Shimada H, Ohta M, Togo S, Saitou S, Yamaguchi S, et al. Procedures of choice for resection of primary and recurrent liver metastases from colorectal cancer. *World J Surg* 2004;28:482-7.
42. Taschieri AM, Elli M, Vignati GA, Montecamozzo G, Danelli PG, Kurihara H, et al. Repeated liver resection for recurrent metastases from colorectal cancer. *Hepatogastroenterology* 2003;50:472-4.
43. Yamada H, Katoh H, Kondo S, Okushiba S, Morikawa T. Repeat hepatectomy for recurrent hepatic metastases from colorectal cancer. *Hepatogastroenterology* 2001;48:828-30.
44. Yamamoto J, Kosuge T, Shimada K, Yamasaki S, Moriya Y, Sugihara K. Repeat liver resection for recurrent colorectal liver metastases. *Am J Surg* 1999;178:275-81.
45. Zacharias T, Jaeck D, Oussoultzoglou E, Bachellier P, Weber JC. First and repeat resection of colorectal liver metastases in elderly patients. *Ann Surg* 2004;240:858-65.
46. DeMatteo RP, Palese C, Jarnagin WR, Sun RL, Blumgart LH, Fong Y. Anatomic segmental hepatic resection is superior to wedge resection as an oncologic operation for colorectal liver metastases. *J Gastrointest Surg* 2000;4:178-84.
47. Pawlik TM, Scoggins CR, Zorzi D, Abdalla EK, Andres A, Eng C, et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. *Ann Surg* 2005;241:715-22.
48. Elias D, Lasser P, Hoang JM, Leclere J, Debaene B, Bognel C, et al. Repeat hepatectomy for cancer. *Br J Surg* 1993;80:1557-62.
49. Rees M, Plant G, Wells J, Bygrave S. One hundred and fifty hepatic resections: evolution of technique towards bloodless surgery. *Br J Surg* 1996;83:1526-9.
50. Chen H, Merchant NB, Didolkar MS. Hepatic resection using intermittent vascular inflow occlusion and low central venous pressure anesthesia improves morbidity and mortality. *J Gastrointest Surg* 2000;4:162-7.
51. Jones RM, Moulton CE, Hardy KJ. Central venous pressure and its effect on blood loss during liver resection. *Br J Surg* 1998;85:1058-60.
52. Adam R, Avisar E, Ariche A, Giachetti S, Azoulay D, Castaing D, et al. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal. *Ann Surg Oncol* 2001;8:347-53.
53. Bismuth H, Adam R, Levi F, Farabos C, Waechter F, Castaing D, et al. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. *Ann Surg* 1996;224:509-20.
54. Garden OJ, Rees M, Poston GJ, Mirza D, Saunders M, Ledermann J, et al. Guidelines for resection of colorectal cancer liver metastases. *Gut* 2006;55(53):iii1-8.
55. Ike H, Shimada H, Togo S, Yamaguchi S, Ichikawa Y, Tanaka K. Sequential resection of lung metastasis following partial hepatectomy for colorectal cancer. *Br J Surg* 2002;89:1164-8.
56. Elias D, Ouellet JF, Bellon N, Pignon JP, Pocard M, Lasser P. Extrahepatic disease does not contraindicate hepatectomy for colorectal liver metastases. *Br J Surg* 2003;90:567-74.
57. Reddy RH, Kumar B, Shah R, Mirsadraee S, Papagiannopoulos K, Lodge P, et al. Staged pulmonary and hepatic metastasectomy in colorectal cancer—is it worth it? *Eur J Cardiothorac Surg* 2004;25:151-4.
58. Lau TN, Lo RH, Tan BS. Colorectal hepatic metastases: role of radiofrequency ablation. *Ann Acad Med Singapore* 2003;32:212-8.
59. de Baere T, Risse O, Kuoch V, Dromain C, Sengel C, Smayra T, et al. Adverse events during radiofrequency treatment of 582 hepatic tumors. *Am J Roentgenol* 2003;181:695-700.
60. Abdalla EK, Vauthey JN, Ellis LM, Ellis V, Pollock R, Broglio KR, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Ann Surg* 2004;239:818-25.; discussion 25-7.
61. Solbiati L, Livraghi T, Goldberg SN, Ierace T, Meloni F, Dellanoce M, et al. Percutaneous radio-frequency ablation of hepatic metastases from colorectal cancer: long-term results in 117 patients. *Radiology* 2001;221:159-66.