Dosežki kirurškega zdravljenja bolnikov z jetrnimi zasevki raka debelega črevesa in danke od 2000 do 2020

Achievements in surgical treatment for colorectal liver metastases from 2000 until 2020

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Izvleček

Namen: *Rak debelega črevesa in danke (RDČD) je v svetovnem merilu tretja najpogostejša maligna bolezen in najpogosteje zaseva v jetra. Namen raziskave je predstaviti možnosti kirurškega zdravljenja jetrnih zasevkov in rezultate zdravljenja.*

Metode: *Opravili smo retrospektivni pregled prospektivno vodene datoteke resekcij jetrnih zasevkov RDČD na Kliničnem oddelku za abdominalno in splošno kirurgijo Univerzitetnega kliničnega centra Maribor. Raziskava temelji na principu pristopa k zdravljenju z namenom ozdravitve. Analizirali smo število posegov, ponovne posege, zaplete in preživetje.*

Rezultati: *Od januarja 2000 do decembra 2020 je bilo izvedenih 631 kirurških posegov zaradi jetrnih zasevkov RDČD. 352 (74,4 %) bolnikov je*

Abstract

Purpose: *Colorectal cancer represents the third most frequently occurring malignant disease worldwide that most often disseminates into the liver. The present report describes the treatment possibilities and results of a surgical approach to treat colorectal liver metastases (CLM).*

Methods: *A retrospective review of a prospectively maintained database of patients who underwent surgical treatment for CLM at the Clinical Department of Abdominal and General Surgery of University Medical Centre Maribor in Slovenia was performed. The study was based on the intention-to-treat principle. All procedures, redo procedures, morbidity, and survival were analyzed.*

Results: *The study covered the period between January 2000 and*

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imelo en poseg in 121 (25,6 %) bolnikov več kot enega. Resekcij jeter je bilo 541 (85,7 %), in sicer 389 manjših in 152 velikih resekcij. Radiofrekvenčno ablacijo smo opravili v 61 (9,7 %) in eksploracijo v 29 (4,6 %) primerih. Ponovnih posegov je bilo 138 (21,9 %). Hudi zapleti (stopnja ≥ 3a po klasifikaciji Clavien-Dindo) so se pojavili po 84 (13,3 %) posegih. 90-dnevna pooperativna smrtnost je znašala 3,8 %. Mediano preživetje pri seštevku 0 v Clinical Risk Score je 69 mesecev; 5- in 10-letni preživetji sta 57-% oziroma 38-%.

Zaključek: *Kirurška odstranitev jetrnih zasevkov v celoti in ugodni prognostični dejavniki omogočajo dolgoročno preživetje bolnikov z jetrnimi zasevki RDČD.*

December 2020, during which 631 surgical liver procedures were performed. A total of 352 (74.4%) patients underwent a single procedure, and 121 (25.6%) patients had more than one procedure. The largest portion of surgeries consisted of 541 (85.7%) liver resections (389 minor and 152 major). Radiofrequency ablation was performed in 61 (9.7%) cases and exploration in 29 (4.6%) cases. There were 138 (21.9%) redo procedures. A major morbidity (Clavien-Dindo grade ≥ 3a) was present in 84 (13.3%) cases. The 90-day mortality was 3.8%. In cases with a clinical risk score of 0, the median survival time was 69 months and 5- and 10-year overall survival was 57% and 38%, respectively.

Conclusion: *The complete surgical removal of metastases accompanied by favorable prognostic factors offers long-term survival in CLM patients.*

INTRODUCTION

Colorectal cancer (CRC) currently represents the third most frequently occurring malignant disease affecting 1,800,000 people worldwide (1, 2). At the time of diagnosis, the disease is already metastasized in 15%–25% of patients (2). In addition, 25% of patients develop metachronous colorectal liver metastases. Liver is the most frequent site of distant dissemination (2).

In recent decades, a significant improvement in the survival of patients with colorectal liver metastases (CLM) has been achieved. In the 1990s, the reported two-year overall survival (OS) was just 21% (2). Then, advancements in systemic chemotherapy with better efficacy, improvements in surgical techniques, and enhancement in perioperative care have increased the number of patients treated for CLM and significantly contributed to better outcomes (2).

Different risk scores have been developed for forecasting recurrence and survival (3, 4). The 5-year OS after CLM resection is 35%–40%, but can reach up to 60% in patients with favorable prognostic factors (2). Unfortunately, the disease recurs in 40%–75% of patients, and in half of them it recurs in the liver (2).

The present report describes the evolution of treatment possibilities for CLM at a single tertiary referral center. It also presents treatment results for a surgical approach to CLM.

PATIENTS AND METHODS

Patients

A retrospective review of a prospectively obtained database of patients who underwent surgical treatment for CLM at the Clinical Department of Abdominal and General Surgery of the University Medical Centre Maribor in Slovenia was performed. This department is a specialized referral center for hepato-pancreato-biliary surgeries.

The study covered the period between January 1, 2000 and December 31, 2020. The study was based on the intention-to-treat principle. At the time of their surgery, the patients consented that their anonymized data could be used for research purposes.

The patient records were anonymized and de-identified before the analysis. The ethical approval for the study was obtained from the institutional review board.

Diagnostic and therapeutic workup and follow-up protocol

Available characteristics were obtained from the database and analyzed after the patients underwent a routine diagnostic workup, which included a colonoscopy, blood work, thoracic computed tomography (CT), and abdominal CT with contrast enhancement. If any uncertainties were present, liver-specific contrast magnetic resonance imaging was performed to identify liver lesions. A positron emission tomography (PET) scan was performed when dissemination of the disease was suspected (5).

The patients were presented at a multidisciplinary team meeting (2). Those with metastases confined to the liver were considered for liver resection, radiofrequency ablation (RFA), or a combination of both.

The most frequently utilized chemotherapy schemes were fluorouracil, leucovorin, and oxaliplatin; fluorouracil, leucovorin, and irinotecan; capecitabine plus oxaliplatin; and capecitabine plus irinotecan. These treatment regimens have recently been supplemented with biological agents, such as bevacizumab. The Rat sarcoma virus gene and B-Rapidly accelerated fibrosarcoma gene status was crucial in deciding whether cetuximab therapy would be useful (2). Neoadjuvant chemotherapy was used as a downsizing strategy to transform unresectable CLM into resectable cancer (2).

The follow-up protocol consisted of a carcinoembryonic antigen (CEA) evaluation, chest radiograph or CT, abdominal ultrasound, or magnetic resonance imaging every three months for the first two years and every six months afterwards.

Perioperative considerations and definitions

The preoperative liver function was assessed according to the Child-Pugh classification (6). In addition, the future liver remnant (FLR) was considered when establishing the indications for liver resection. At least 25%–40% of metastasis-free liver parenchyma had to be preserved (5). The CT volumetric analysis was routinely utilized when major liver surgery was planned (2).

When the analysis suggested an insufficient FLR, portal vein embolization (PVE), intraoperative selective portal vein ligation, or the associating liver partition and portal vein ligation (ALPPS) procedure was performed (2, 5). A PVE was followed by atrophy of the embolized hemiliver and hypertrophy of the other hemiliver (5). The two-stage hepatectomy (TSH) was conducted when intraoperative findings were unfavorable (7). In the first stage, the metastasectomy of one hemiliver was performed along with the portal vein ligation for the other hemiliver (7). The effect was similar to that of the preoperative PVE (8). The second stage followed a few weeks later and usually consisted of a major hepatectomy (2, 7). The ALPPS was performed with the same rationale; the difference was the liver parenchyma's transection in the first stage (9, 10).

Local ablation methods were applied when the radical liver resection was not feasible due to the proximity of large vessels (2). RFA was utilized in two ways: the first was percutaneous, which has been used as an independent procedure, and the second was an intraoperative RFA, which was an open and independent procedure or an adjunct to liver resection (2).

The previously established liver anatomy and resection terminology were used (11). Hepatectomies were classified as major when at least three adjacent liver segments were removed. Otherwise, they were defined as minor (11). A histopathological examination

confirmed the final diagnosis. The R0 resection was defined by clear microscopic margins in the case of liver resection (2). Liver resections where a histopathologic examination revealed a tumoral infiltration of surgical margins were defined as R1 (2).

Outcome

The 90-day postoperative morbidity and mortality were graded according to the Clavien-Dindo classification (12).

The 5- and 10-year OS was calculated from the first diagnosis of CLM until death or until the last follow-up visit. Recurrence-free survival (RFS) was calculated from the date of first therapy for CLM until the first radiologic proof of disease recurrence. Hepatic recurrence-free survival (HRFS) was calculated from the date of the first therapy for CLM until the first radiologic proof of disease recurrence in the liver.

The clinical risk score (CRS) by Fong et al. (13) was utilized for prognostication. Its parameters (infiltrated lymph nodes in CRC, number of CLMs > 1, CLM size ≥ 5 cm, CLM appearance in less than one year, and CEA) were calculated for every case. The lowest score was 0, and the highest was 5 (13).

Statistical analysis

The IBM SPSS for Windows Version 26.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analysis. Descriptive statistical methods were used. Categorical variables were expressed as frequencies (percentages). Continuous variables were expressed as medians (minimum-maximum, interquartile range (IQR)). The survival tables with the Wilcoxon test were utilized for the survival analysis.

RESULTS

A total of 631 liver procedures were performed in 473 patients. Of these, 315 (66.6%) were men and 158 (33.4%) were women. At the first CLM diagnosis, the patients' median age was 65.5 years (27–85, IQR 15). At the end of the study, 358 (75.7%) patients were dead, of which 311 (65.8%) died of the disease, 115 (24.3%) patients were alive, 83 (17.5%) patients had no evidence of the disease, and 32 (6.7%) patients were alive with disease. The median follow-up duration was 34 months (0–230, IQR 44).

Characteristics of primary CRC

The primary CRC tumor developed in the right colon in 85 (17.9%) patients. A total of 187 (39.5%) patients had CRC in the left colon. Rectal cancer developed in 188 (39.7%) patients. Thirteen (2.7%) patients had multiple primary CRCs. Regional lymph node metastases were present in 303 (64.1%) patients. According to the tumor-node-metastasis classification, 14 (3.0%), 93 (19.7%), 143 (30.2%), and 223 (47.1%) patients were classified as stage I, II, III, and IV, respectively (14).

Characteristics of colorectal liver metastases

Among 631 liver procedures, unilateral CLM was present in 344 (54.5%) patients and bilateral CLM in 287 (45.5%) patients. The median CLM number was 2 (1–20, IQR 3). The median diameter of the largest CLM was 3.6 cm (0.2–25.0, IQR 2.5). The median CEA value was 12.7 mcg/L (0.30–4237.0, IQR 44.28). Synchronous CLM was present in 223 (47.1%) patients. Three therapeutic strategies were utilized for these cases: the liver-first strategy in 13 (5.9%) patients, simultaneous resection of CRC and CLM in 97 (43.5%) patients, and colorectal-first strategy in 113 (50.6%) patients (15, 16).

A total of 250 (52.9%) patients had metachronous CLM, and the median time from the operation of primary CRC until the detection of CLM was 18 months (6–160, IQR 16). Extrahepatic malignant disease was present in 124 (19.7%) cases.

Surgical treatment and postoperative course

Of the 473 patients, 352 (74.4%) underwent a single procedure, and 121 (25.6%) had more than one procedure. Overall, 95 (20.0%), 19 (4%), five (1.1%), one (0.2%), and one (0.2%) patient had two, three, four, five, and six procedures, respectively. Neoadjuvant chemotherapy was administered in 304 (48.2%) and adjuvant chemotherapy in 432 (68.4%) CLM cases. The diversity of 631 surgical procedures for CLM is shown in Table 1. There were 138 (21.9%) redo procedures. PVE was performed in 23 (3.6%) cases. Ligation of the right portal

vein was necessary in 19 (3.0%) cases, and ALPPS was attempted in three patients. Five patients did not proceed to the second stage due to the disease progression.

When evaluating surgical procedures, explorations accounted for 4.6% (29 cases) and RFA for 9.7% (61 cases) of all surgeries. The largest portion of the procedures consisted of 541 (85.7%) liver resections (Table 2). An R0 resection was performed in 430 (79.4%) cases. There were a total of 93 (17.1%) re-resections. Since 2017, 74 patients underwent a liver resection for CLM, which were performed laparoscopically in 35 (47.3%) patients (17-19).

The morbidity and mortality rates are shown in Table 3. The cause of death was multi-organ failure in ten (1.6%), sepsis in six (1.0%), cardio-respiratory failure in three (0.5%), pulmonary embolism in three (0.5%), and liver failure in two (0.3%) patients. The median hospital stay was nine (1–162, IQR 6) days.

Survival analysis

The 5- and 10-year OS in patients treated with a different surgical method is shown in Table 4. The difference between groups was statistically significant (Wilcoxon test, $P < 0.001$). The 5- and 10-year OS based on the CRS is represented in Table 5. The 5- and 10-year RFS and HRFS in patients based on the CRS are shown in Table 6. Finally, an overview of morbidity, mortality, and survival from other centers is demonstrated in Table 7.

DISCUSSION

Thirty years ago, the primary objective of stage IV CRC treatment was palliative care, and the patients' OS was poor. Understanding tumor biology, the arrival of effective systemic chemotherapy treatment, and extension of the frontiers of surgical indications have transformed CLM management and improved

Table 1. *Summary of 631 surgical procedures for colorectal liver metastasis*

Surgical procedure	N of procedures	%	Surgical procedure	N of procedures	%
One-stage liver procedures–first procedure	**454**	**71.9**	**One-stage liver procedures–redo procedure**	**138**	**21.9**
First hepatectomy	383	60.7	Second hepatectomy	75	11.9
Open RFA	27	4.3	Open RFA	17	2.7
Hepatectomy and RFA	21	3.3	Percutaneous RFA	17	2.7
Exploration	18	2.9	Exploration	11	1.7
Percutaneous RFA	5	0.8	Third hepatectomy	8	1.3
TSH	**39**	**6.2**	Hepatectomy and RFA	8	1.3
First stage	22	3.6	Fourth hepatectomy	2	0.3
Second stage	17	2.6			

RFA – radiofrequency ablation, TSH – two-stage hepatectomy

the OS since then (2). Nevertheless, improvements in diagnostics highly impacted the patients' selection. The PET scanner has been available in Slovenia since 2002 in Splošna bolnišnica Maribor (20). Four years later, the Institute of Oncology Ljubljana was supplied with a PET-CT machine, which started operating in September 2007 (21). Since 2017, a PET-CT apparatus has also been available in the University Medical Centre Maribor (20).

Metastases develop after dissociation of the tumoral cells from the primary CRC tumor and their entrance into lymph vessels and portal circulation (2). CRCs arising in the middle or lower rectal third have venous outflow into the inferior vena cava, which promotes systemic spreading (22). In the present cohort, 17.9% of patients had the primary CRC in the right colon and 39.5% in the left colon. Rectal cancer developed in 39.7% of patients. In the study by McCracken et al., 37% of primary CRCs were in the right colon, 36% in the left colon, and 27% in the rectum (23). The prognosis of the right-sided CRC was worse (23, 24).

Furthermore, the target tissue microenvironment and the circulating tumor cell organotropism also define the metastatic site (25, 26). Micro-RNAs are short RNA molecules compatible with parts of mRNA. Micro-RNAs specifically bind to these mRNA portions and diminish the transcription into proteins. This alters the metabolism in the target organ. For example, CLM patients have a low expression of miR-31-5p, whereas it is high in peritoneal carcinomatosis of CRC (25). This can explain why CRC metastases in certain patients develop only in the liver. Therefore, re-resections or/and RFA were performed in 20.2% of our patients. The reported rates of liver re-resections are 38% by Engstrand et al. (27) and 36.6% by Vigano et al. (28), whereas the present study rate is 17.1%.

When performing a liver resection for CLM, the principle is to be "radical but conservative", that is, radical in oncological terms and conservative in preserving non-tumoral liver parenchyma (29). This principle is reflected in the present results because 61.1% of all procedures were minor liver resections.

Table 2. *Minor and major liver resections, their frequency, and percentages in 631 procedures*

Minor resections	N=389	61.6%	Major resections	N=152	23.0%
ALPPS – first stage	3	0.5	Trisegmentectomy	14	2.2
Metastasectomy	136	21.6	Trisegmentectomy and metastasectomy	6	1.0
			Right hemihepatectomy	79	12.5
Segmentectomy	75	11.9	Extended right hepatectomy	8	1.3
Segmentectomy and metastasectomy	22	3.5	Left hemihepatectomy	29	4.6
Bisegmentectomy	73	11.6	Extended left hepatectomy	4	0.6
Bisegmentectomy and metastasectomy	46	7.3	Central resection	6	1.0
Minor resection and RFA	34	5.4	Major resection and RFA	6	1.1

ALPPS – associating liver partition and portal vein ligation; RFA – radiofrequency ablation

Similarly, Gasser et al. (24) have reported 69% as a rate of minor resections.

A two-stage procedure was carried out when an extended hepatectomy was indicated, and the volumetric analysis suggested an insufficient FLR (2). Enhancement of liver hypertrophy via portal vein ligation were first described by Cantlie et al. in 1897 and Rous et al. in 1920, and then developed by Honjo et al. in 1975 (2, 30, 31). PVE was introduced in the late 1980s by Kinoshita et al. (32) and Makuuci et al. (2, 33). In 2002, Broering et al. have compared both methods (8) and found that PVE results in a significantly more efficient increase in liver volume and shorter hospital stay. Adam et al. (7) have proposed a two-stage hepatectomy in 2000. Our first two-stage hepatectomy for CLM was performed in 2006. ALPPS was introduced in 2012 (9), and our first procedure for CLM was carried out in 2016.

The first guidelines for laparoscopic liver resection (LLR) were published in 2008 (34), which was also when the University Medical Centre Maribor in Slovenia first began performing the procedure. The first LLR for CLM was carried out in 2012 (15). The first treatment results for 12 patients were presented in 2017 (15). Our first propensity score matching study of simultaneous resection of CLM and primary tumors in 20 patients was published in 2018 (16) and was internationally acknowledged (35-37). Since 2017, 74 patients underwent liver resection for CLM, which was performed laparoscopically in 35 (47.3%) patients (17-19).

Severe morbidity in liver surgery occurs due to bleeding, bile leakage, or liver insufficiency (24). Anastomotic dehiscence was the major cause of severe morbidity when a simultaneous colorectal resection was performed (24). The severe morbidity and mortality rates were 13.3% and 3.8%, respectively, which are comparable to rates at other high-volume centers (Table 7).

Finally, the advancements in systemic therapy, surgical technique, and perioperative care contributed to the 5-year OS reaching 35%–40% (2). The 5- and 10-year OS values for different surgical treatment modalities are represented in Table 4. Furthermore, survival rates were up to 60% (2, 13, 38) when the most favorable prognostic factors were considered (CRS 0), which

Table 3. *Morbidity and mortality after 631 surgical procedures for colorectal liver metastases*

Morbidity grades	N	%
Without morbidity	375	59.4
CD 1 – any deviation from normal postoperative course	4	0.6
CD 2 – mild deviations requiring antibiotics, blood transfusion, or parenteral nutrition	144	22.8
Major morbidity	84	13.3
CD 3a – intervention without general anesthesia	43	6.8
CD 3b – intervention under general anesthesia	27	4.3
CD 4a – single-organ dysfunction	4	0.6
CD 4b – multi-organ dysfunction	10	1.6
CD 5 – mortality	24	3.8

Grading according to the Clavien-Dindo classification (12)

Table 4. *Five- and 10-year overall survival in patients with colorectal liver metastases treated with different surgical methods*

	N of patients	Median survival time (months)	5-year OS (%)	10-year OS (%)
Liver resection R0	334	41	33	10
Percutaneous RFA	5	30	20	NR
Open RFA	20	24	15	15
Liver resection R1	49	27	10	NR
Liver resection and RFA	20	21	5	NR
Liver resection R2	3	21	NR	NR
Exploration only – no liver resection	19	17	NR	NR

RFA – radiofrequency ablation; NR – not reached; OS – overall survival.

Table 5. *Five- and 10-year overall survival and clinical risk score (13)*

Surgical procedure	N of patients	CRS	Median survival (months)	5-year OS (%)	10-year OS (%)
Liver resection R0	21	0	69	57	38
	67	1	56	46	19
	107	2	43	31	7
	80	3	35	28	5
	23	4	33	22	9
	2	5	24	NR	NR
Liver resection R1	1	0	42	NR	NR
	2	1	96	50	NR
	12	2	30	NR	NR
	17	3	35	24	NR
	6	4	20	NR	NR
	2	5	18	NR	NR
Open RFA	8	2	36	38	38
	2	3	36	NR	NR
	4	4	24	NR	NR
Percutaneous RFA	1	0	66	100	NR
	2	2	24	NR	NR
Liver resection and RFA	3	2	27	NR	NR
	7	3	22	NR	NR
	4	4	20	NR	NR
	1	5	18	NR	NR

CRS – clinical risk score; RFA – radiofrequency ablation; NR – not reached; OS – overall survival

was reflected in the present results (Tables 5, 6). For patients whose CRS was 0, the median survival time was 69 months or 5.75 years, while the 5- and 10-year OS was 57% and 38%, respectively. Median survival time was 3.9 years for the delayed resection group and 5.9 years for the simultaneous resection group in the study by the METASYNC study group in France (39). The median survival time was 4.9 years at the Memorial Sloan Kettering Cancer Center in New York (40). The 5-year OS in the OSLO-COMET trial in Norway was 54% in the laparoscopic group and 55% in the open resection group (41). The 10-year OS in the Memorial Sloan Kettering Cancer Center was 24% (40). More data on OS, RFS, and survival intervals from these centers are presented in Table 7. In conclusion, redo procedures are important for the treatment of CLM. Morbidity and mortality rates are comparable among high-volume centers specialized in liver surgery worldwide. The R0 resection accompanied by favorable prognostic factors offers long-term survival in patients with CLM.

Table 6. *Five-year and 10-year recurrence-free and hepatic recurrence-free survival and CRS (13)*

Surgical procedure	N of patients	CRS	Median recurrence-free interval (months)	5-year RFS	10-year RFS	Median hepatic recurrence-free interval (months)	5-year HRFS	10-year HRFS
Liver resection R0	21	0	54	43	38	57	48	38
	67	1	34	31	13	41	34	13
	107	2	23	18	7	29	20	7
	80	3	21	13	3	21	14	3
	23	4	16	17	9	18	17	9
	2	5	12	NR	NR	12	NR	NR
Liver resection R1	1	0	42	NR	NR	42	NR	NR
	12	2	17	NR	NR	19	NR	NR
	17	3	16	NR	NR	17	NR	NR
	6	4	16	NR	NR	16	NR	NR
Open RFA	8	2	24	25	25	24	38	38
	2	3	12	NR	NR	12	NR	NR
Liver resection and RFA	3	2	15	NR	NR	15	NR	NR
	7	3	11	NR	NR	11	NR	NR
	4	4	20	NR	NR	20	NR	NR
	1	5	18	NR	NR	18	NR	NR

CRS – clinical risk score; HRFS – hepatic recurrence-free survival; RFA – radiofrequency ablation; NR – not reached; RFS – recurrence-free survival.

Table 7. *Overview of reported morbidity, mortality, and survival analysis in selected centers*

Authors, year	Study period, N of patients	Subgroups	Morbidity	Mortality	Survival analysis
MEMORIAL SLOAN KETTERING CANCER CENTER, NEW YORK, USA					
Kingham et al. (42), 2015	1993–2012	1993–1999	53%	5%	Not researched
		2000–2006	34%	2.3%	
		2007– 2012	20%	1.6%	
Creasy et al. (40), 2018	1992–2004 1211	Not researched.			10-year OS: 24% Med. survival: 4.9 y 10-year RFS: 20%
METASYNC STUDY GROUP, FRANCE					
Boudjema et al. (39), 2021	2006–2015	simultaneous resection	Overall 49%, Colorectal 28%, liver 15%.	7.4%	Med. OS: 5.9 y Med. DFS 1.3 y
		delayed resection	Overall 46%, colorectal 13%, liver 17%.	3.2%	Med. OS: 3.9 y Med. DFS: 1.0 y
OSLO-COMET TRIAL, NORWAY					
Fretland et al. (43), 2018; Aghayan et al. (41), 2021	2012–2016	laparoscopic group	19%	0%	5-y OS: 54% 5-y RFS: 30%
		open group	31%	0.7%	5-y OS: 55% 5-y RFS: 36%
THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTRE, HOUSTON, TEXAS, USA					
Lillemoe et al. (44), 2018	2003–2016 137	23%, at either stage of TSH		Not reported.	Med. RFS after TSH was 12 months. Med. OS in recurrence: resection: 143 months, no resection: 49 months.

DSF – disease-free survival; Med. – median; OS – overall survival; OSLO-COMET – Oslo Randomized Laparoscopic Versus Open Liver Resection for Colorectal Metastases Trial; RFS – recurrence-free survival; TSH – two-stage hepatectomy; UK – United Kingdom; USA – United States of America; y – year

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