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Liver

Outcomes of *ex vivo* liver resection and autotransplantation: A systematic review and meta-analysis

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ABSTRACT

Background: Many patients with hepatic tumors cannot benefit from resection owing to the difficult anatomic sites of their lesions. Some of these patients might be eligible for *ex vivo* liver resection and autotransplantation. This procedure consists of complete hepatectomy, extracorporeal liver resection, and autotransplantation of the remnant liver.

Methods: Four databases were searched for studies reporting cases of *ex vivo* liver resection and autotransplantation. Outcomes of this procedure were evaluated by meta-analysis of proportions with random effects model and individual participant data analysis.

Results: Fifty-three studies were assessed. Meta-analysis revealed an R0 resection rate of 93.4% (95% confidence interval: 81.0–97.9%, $I^2 = 0\%$), a frequency of major surgical complications of 24.5% (95% confidence interval, 16.9–34.3%, $I^2 = 26\%$), a 30-day mortality of 9.5% (95% confidence interval: 5.9–14.9%, $I^2 = 0\%$), and a 1-year survival of 78.4% (95% confidence interval: 62.2–88.8%, $I^2 = 64\%$). We were able to obtain the individual participant data in 244 patients; R0 resection was achieved in 98.6%, with no obvious difference between analyzed subgroups. The 30-day mortality and 1-year survivals were 7.9% and 82.1%, respectively. For groups with malignant and nonmalignant tumors, the 30-day mortalities were 11.3% vs. 6.3% ($P = .181$), and 1-year survivals were 65.0% vs. 89.7% ($P < .001$). When comparing those with malignant versus those with nonmalignant lesions, major surgical complications occurred in 50.0% vs. 21.0%; $P < .001$). Regression analysis revealed that outcomes of patients with benign tumors were better compared with those with malignant tumors (1-year survival, odds ratio: 4.629; 95% confidence interval: 2.181–10.097, $P < .001$).

Conclusion: Ex vivo liver resection and autotransplantation facilitates radical treatment in selected patients with conventionally unresectable hepatic tumors and normal liver function. The outcomes of treatment of malignant lesions appear to be less satisfactory.

Introduction

Liver and intrahepatic bile duct cancers as well as hepatic metastases from other malignancies are among the most prevalent human tumors. Resection is the best method to treat the vast majority of those conditions and to provide long-term survival.[1] Unfortunately, not all patients are eligible for resection by conventional techniques, even after portal vein embolization or with the use of the associating liver partition and portal vein ligation for staged hepatectomy (ALPPS procedure). This applies mainly to those with poor liver function and with lesions in difficult anatomic sites, especially with the involvement of large blood vessels. Another possible treatment of malignant hepatic lesions is allogeneic liver transplantation, although patients with those lesions are less likely to benefit from this procedure owing to organ shortage and unsatisfactory outcomes.[2]

Nevertheless, progress in hepatobiliary and transplantation surgery in recent decades has brought about alternative options.[3] Selected cases of conventionally unresectable liver tumors might be treated *in situ in vivo* (the technique of total vascular exclusion

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[TVE]), *ex situ in vivo* (*ante-situm* resection), or *ex situ ex vivo*.[4] TVE involves clamping of the supra- and infrahepatic inferior vena cava (IVC) as well as the hepatic pedicle, leading to total vascular isolation allowing resection with restricted blood loss. TVE can be supplemented by *in situ* hypothermic perfusion, as originally described by Fortner et al. (1974).[5] *Ante-situm* resection, first implemented by Hannoun et al. (1991)[6] is a more advanced technique, which, in addition to the previously described vascular isolation, facilitates partial mobilization of the liver by the division of the suprahepatic IVC. *Ex vivo* liver resection and autotransplantation (ERAT) is a procedure involving complete hepatectomy and extracorporeal liver resection followed by autologous transplantation of the remnant hepatic parenchyma. In contrast to the *ante-situm* resection, ERAT requires division and subsequent anastomosis of the hepatic artery, portal vein, and biliary tree. The resection is performed by bench surgery on an externally cooled organ. ERAT was first performed by Pichlmayr et al. (1988).[7] Since then, the technique has been described in many patients with various types of liver tumors, including malignancies (e.g., hepatocellular carcinoma [HCC], cholangiocarcinoma [CCC], and colorectal cancer metastases [CRM]) as well as nonmalignant lesions, such as hepatic alveolar echinococcosis, focal nodular hyperplasia (FNH), and hemangioma.

ERAT is a technique used for curative intent in patients with conventionally unresectable liver tumors; its main principle is to achieve a radical (R0) resection in these demanding cases.[8,9] We conducted a systematic literature review and meta-analysis of studies reporting ERAT to investigate outcomes of this method.

Material and methods

We registered the protocol for this study prospectively on PROSPERO (CRD42020156811). The reporting of its results conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[10]

Literature search

We searched (last update on 25 March 2020) PubMed, Embase, Scopus, and Web of Science databases for eligible studies. Peer-reviewed search queries, dates of searches, their results, and other relevant details are reported in Table S1 in the Supplementary Content.

Inclusion and exclusion criteria

Reports of human cases of ERAT were considered eligible for the meta-analysis. We included only full-text, English-language articles. Unpublished data, book chapters, or conference abstracts were excluded. No dates of coverage restrictions were applied.

Data extraction

Two reviewers independently screened the results of the search. Discrepancies were infrequent and were resolved by discussion. The following variables from the analyzed articles were entered in a standardized spreadsheet as follows: type of a study, years of publication and operation, number of patients who underwent ERAT, their demographics (age, sex), and type of resected tumor(s) and their number and localization. The use of techniques designed to augment the future liver remnant and the use of neoadjuvant treatment were evaluated. Operative details, including the maximal diameter of the largest lesion, preservation fluid used, resected liver segments (in compliance with the Brisbane terminology[11]), application of major hepatic resection (defined as resection of 4 or more segments[12]), remnant liver-to-standard volume ratio (RLV/SLV), cold and warm ischemic times, total anhepatic time, duration of operation, and blood loss were retrieved. Outcomes including R0 resection status and the presence of major operative complications (IIIa or greater according to the Clavien-Dindo classification[13]) and their description, as well as 30-day, 90-day, and in-hospital mortality, together with 1-year survival rates were extracted. Additionally, information on any need for subsequent allogeneic liver transplantation, details about tumor recurrences, follow-up periods, and durations of hospital stay were collected.

Quality assessment

We followed recommendations provided by Murad et al. (2018)[14] when assessing the validity and risk of bias of the analyzed studies. The presence of potential publication bias was evaluated with a funnel plot and Egger regression analysis; the latter was not performed for analyzes including fewer than 10 studies.[15]

Statistical analysis

Continuous variables are presented as means (with standard deviations) and/or medians (with ranges). For categorical variables, frequencies of categories were provided. Estimated results from the studies that included at least four ERAT patients were evaluated by a meta-analysis of proportions with random effects model. A meta-analysis of individual participant data was performed to assess outcomes of ERAT in the sample of all of the collected cases, as well in two subgroups defined by the malignant or nonmalignant character of the lesion. Logistic regression models were developed to evaluate factors affecting the outcomes of ERAT. Linear regression analysis was used to calculate the association between tumor size and operative time. In all the analyses, the pairwise deletion was implemented (i.e., missing data were not imputed). $P < .05$ was considered statistically significant. All analyses and plots were done using the tidyverse,[16] the metafor,[17] and the meta[18] packages in R 3.6.3 environment (R Core Team, 2020).[19]

Results

Study selection and characteristics

Our search in PubMed, Embase, Scopus, and Web of Science databases yielded 5,806 publications. Manual review of their reference sections resulted in adding 3 more records. After deduplication, primary screening, and full-text evaluation, we included a total number of 53 studies in the final meta-analysis (Fig 1, Table I).

Risk of bias and study quality

Analyzed articles consisted mainly of case reports and case series with the exceptions of an observational study[20] and a prospective study.[21] The field of research on ERAT lacks good, evidence-based data or studies of reliable statistical significance. We found no randomized controlled trials.

Meta-analysis of proportions with random effects model conducted for reports with at least 4 patients revealed minimal heterogeneity for the pooled prevalence of 3 of the 4 primary outcomes: R0 resection ($I^2 = 0\%$), major operative complications ($I^2 = 26\%$), and 30-day mortality ($I^2 = 0\%$). A substantial inconsistency between those studies was found when assessing 1-year survival rates ($I^2 = 64\%$).

The funnel plot and Egger regression test revealed that publication bias was unlikely for the analysis concerning 30-day mortality (Fig S1, Supplementary Content). For the rest of the primary

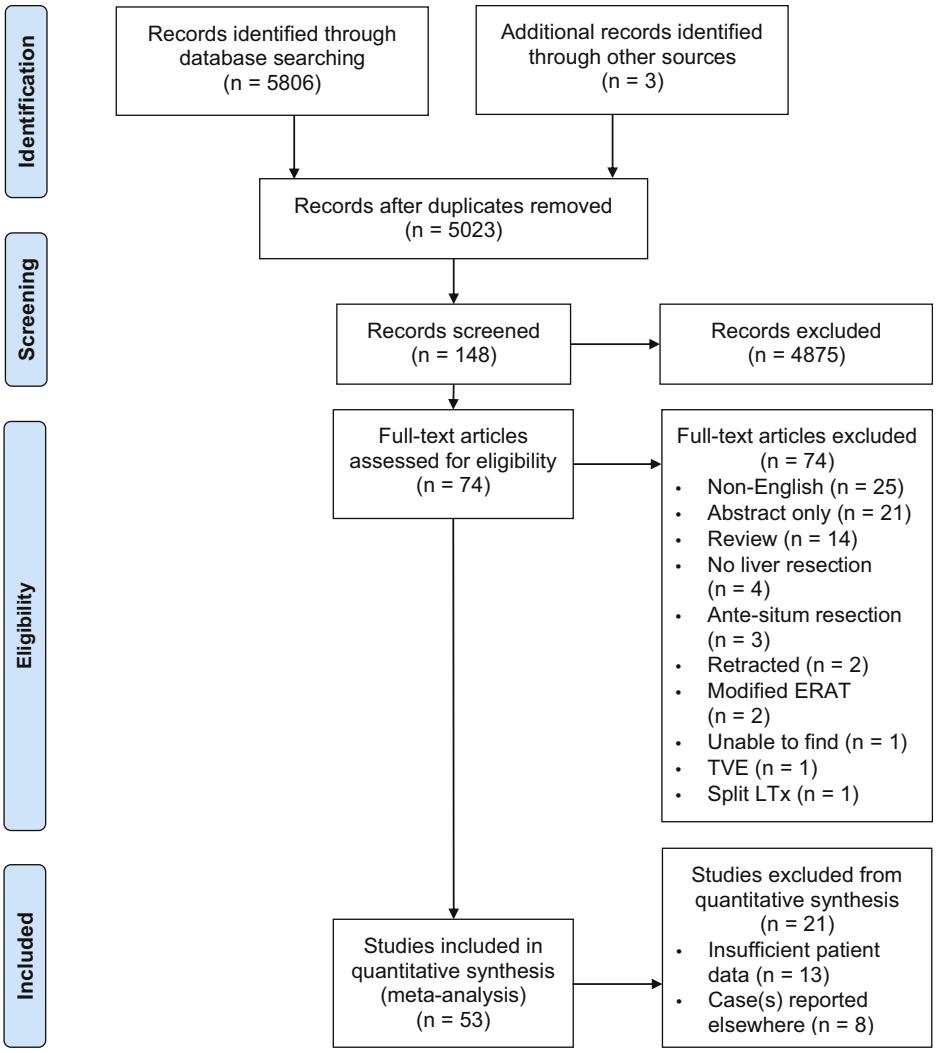


Fig 1. PRISMA flow chart of the study screening and selection for the meta-analysis. *LTx*, liver transplantation.

outcomes, we could not determine the risk of bias owing to the inclusion of fewer than 10 studies in this part of the analysis (Figs S2, S3, and S4, Supplementary Content).

Patients' characteristics and preoperative management

Meta-analysis of the individual participant data was performed. A total of 244 patients who underwent ERAT were extracted from all the 53 evaluated studies. Among them, 160 (65.6%) were assigned to the nonmalignant subgroup. The malignant group consisted of 84 (34.4%) patients. The most common diagnoses included: hepatic alveolar echinococcosis (63.5%), CRM (11.5%), and CCC (9.4%, Table S2, Supplementary Content).

The median age for the studied group was 37 (5–84), consisting of 55.2% women, with no statistically significant difference between the analyzed subgroups (49.3% in the malignant group and 57.9% in the nonmalignant group), $\chi^2\,(1, n = 232) = 1.48$, $P = .224$. In 41.0% of individuals with malignant disease, neoadjuvant therapy had been given. Some form of neoadjuvant therapy was also used in 36.1% of patients with nonmalignant tumors, $\chi^2\,(1, n = 161) = 0.311$, $P = .577$, usually involving albendazole for hepatic alveolar echinococcosis before ERAT. One person from the nonmalignant group with a giant hepatic hemangioma underwent transcatheter arterial embolization.[22]

There were 6 patients (2.6%) in whom some procedure aimed to increase their future liver remnant was performed, involving either portal vein embolization[21,23] or associating liver partition and portal vein ligation for staged hepatectomy.[1,8] Most patients had normal liver function and no history of cirrhosis. All patients' details and characteristics are presented in Tables I and II.

Operative procedure

ERAT was performed most commonly in patients with bilobar neoplasms (72.6%) and with invasion of the major vascular structures in the hepatic hilum, hepatic veins, or the IVC (85.1%). The median maximal diameter of the resected lesion was 15.0 cm (2.7–23.5). Major hepatic resection was performed in 89.5% of cases; the frequency of major hepatic resection was greater in patients with nonmalignant disease (96.6% vs. 79.8%), χ^2 (1, n = 200) = 14.6, $P < .001$.

Two main preservation fluids were used to store and flush resected organs on the back table: histidine-tryptophan-ketoglutarate (49.5%) or University of Wisconsin solution (49.1%). Ringer's lactate solution containing 2% albumin was utilized in 1 case.[24] LaQuaglia et al. (2018)[25] used cold saline during resection in a pediatric patient. Celsior solution was also chosen once.[26]

Table I
Studies eligible for the meta-analysis, patients' details and characteristics

Ref.	No of ERAT cases	Diagnosis	No of major hepatic resection cases*	Maximal diameter of the largest lesion, mean/median (SD) [range], mm	Total anhepatic time, mean/median (SD) [range], min	Follow-up, mean/median (SD) [range], months	F/M	Age, mean/median (SD) [range], y
Cancerous tumors (primary hepatic or biliary cancers, metastatic tumors, or other lesions infiltrating on the liver)								
41	8	Met. LMS, CRM, CCC × 5, CRC	6/8	-	352.5 (98.5)	2.9 (3.3)	-	52.1 (7.2)
53	2	CRM × 2	1/2	-	232 (110.3)	16 (8.5)	1/1	49 (0)
57	1	CCC	1/1	-	328	8	1/0	50
48	1	IMT	1/1	-	-	8	1/0	5
58	1	Met. LMS	1/1	-	-	18	1/0	55
59	1	CRM	0/1	-	110	1	0/1	50
51	1	Neuroendocrine tumor	1/1	22	135	24	1/0	46
27	4	CRM × 4	4/4	11.3 (7.5)	222.5 (39.5)	13.8 (11.8)	2/2	57 (13.6)
28	20	Met. LMS × 3, CRM × 9, CCC × 5, HCC × 3	16/20	-	348 (84)	11.5 (11.6)	5/15	51.6 (9.3)
60	2	HCC, CRM	2/2	-	140	22 (25.5)	-	-
61	1	HCC	1/1	12	330	12	1/0	40
44	1	CCC	1/1	3	330	17	1/0	26
9	2	HCC, CRM	2/2	-	140	38 (48.1)	-	-
33	2	CCC, LMS	2/2	-	240 (134.4)	11.7 (16)	0/2	49.5 (12)
50	1	PCC	0/1	7.8	-	6	1/0	15
52	1	CRM	1/1	-	240	3	0/1	42
62	1	HCC	1/1	19.5	364	28	1/0	17
63	6	HCC × 2, CRM × 4	5/6	-	-	22.6 (28.3)	3/3	63.2 (14.2)
26	1	Met. PB	0/1	2.7	412	8	1/0	38
64, 65	1	Myxoid liposarcoma	1/1	23.5	-	62	0/1	71
49	2	CCC × 2	2/2	5.5 (0.7)	204 (50.9)	8.7 (11.8)	0/2	59.5 (6.4)
66	3	HCC × 3	3/3	14.3 (6.5)	193.7 (29.7)	25.7 (2.5)	0/3	66 (5.6)
67	1	CCC	1/1	6.6	-	3	1/0	66
68	1	GIST	1/1	19	353	12	1/0	60
69	1	Pancreatic head GN	0/1	-	280	60	1/0	31
70	1	Met. HAC	1/1	13	240	20	0/1	56
71	1	LMS	0/1	8.8	166	14	1/0	53
72	1	ACC	0/1	15	-	0.6	1/0	22
73	1	CCC	1/1	10	-	1	1/0	63
23	1	CCC	1/1	7	270	36	0/1	51
74	1	CRM	0/1	6.9	-	-	1/0	41
25	1	HCC	1/1	17.1	-	50	0/1	13
1	1	CCC	1/1	11.6	-	7	1/0	73
8	2	CRM, CCC	2/2	12 (1)	-	8.5 (4.9)	2/0	57 (22.6)
37	1	LMS	0/1	13.5	120	24	1/0	58
75	1	CCC	1/1	-	289	0.5	0/1	79
43	2	CCC × 2	2/2	-	-	21 (4.2)	1/1	48 (11.3)
24	2	CCC, HCC-CCC	1/2	16 (5.7)	-	-	1/1	60.5 (10.6)
31	1	SFT	1/1	19.5	300	3	1/0	32
76	1	HCC	1/1	120	135	48	0/1	24
Noncancerous tumors (HAE, FNH, hemangioma)								
41	1	FNH	0/1	-	240	-	-	30
28	2	FNH × 2	1/2	-	240 (0)	84 (33.9)	2/0	42 (17)
49	1	hemangioma	1/1	20	228	22	1/0	60
22	1	hemangioma	1/1	-	401	8	1/0	39
39	1	HAE	1/1	18	342	2	1/0	24
35	6	HAE × 6	6/6	-	-	[18–30]	4/2	39 (7.8)
34	15	HAE × 15	13/15	-	-	[5–37]	7/8	32
77	1	HAE	1/1	12.7	102	5	1/0	44
36	15	HAE × 15	15/15	-	280.3 (67.5)	18.9 (11.2)	8/7	34.2 (14.1)
78	1	HAE	1/1	-	270	3	1/0	63
21	69	HAE × 69	69/69	-	360 [104–879]	22.5 [14–89]	37/32	37 [15–62]
79	8	HAE × 8	-	-	-	20 [13.5–33]	3/5	37.1 (11.5)
45	2	HAE × 2	2/2	-	337 (55.2)	9.5 (0.7)	1/1	39 (2.8)
80	1	HAE	1/1	16	-	-	0/1	20
40, 81	35	HAE × 35	-	15.9 [11.3–22.0]	309 [180–480]	-	24/11	33 [17–57]
82	1	HAE	-	-	-	18	1/0	20

ACC, adrenocortical carcinoma; *F*, female patient; *GIST*, gastrointestinal stromal tumor; *GN*, ganglioneuroma; *HAC*, hepatoid adenocarcinoma; *HAE*, hepatic alveolar echinococcosis; *IMT*, inflammatory myofibroblastic tumor; *LMS*, leiomyosarcoma; *M*, male patient; *Met.*, metastatic; *No*, number; *PB*, pancreatoblastoma; *PCC*, pheochromocytoma; *Ref.*, reference; SD, standard deviation; *SFT*, solitary fibrous tumor.

* Four or more liver segments.

Table II
Patients' details and characteristics (analysis of the individual participant data)

Variable (n/missing)	All patients (244)	Subgroup		*P* value
		Nonmalignant ($n = 160$)	Malignant ($n = 84$)	
Age (240/4)	37 [5–84]*	37 [15–63]	52.5 [5–84]	<.001
Sex (232/12)				
Female patients, *n*,%	128 (55.2%)	92 (57.9%)	36 (49.3%)	.224
Male patients, *n*,%	104 (44.8%)	67 (42.1%)	37 (50.7%)	
Number of lesions (103/141)				
1 lesion, *n*,%	79 (76.7%)	36 (80.0%)	43 (74.1%)	.485
Multiple lesions, *n*,%	24 (23.3%)	9 (20.0%)	15 (25.9%)	
Liver lobes involved (117/127)				
Unilobar, *n*,%	32 (27.4%)	8 (24.2%)	24 (28.6%)	.636
Bilobar, *n*,%	85 (72.6%)	25 (75.8%)	60 (71.4%)	
Invasion into major vessels (194/50)				
No major vessels involved, *n*,%	29 (14.9%)	29 (22.8%)	0 (0.0%)	< .001
With invasion to major vessels, *n*,%	165 (85.1%)	98 (77.2%)	67 (100%)	
Maximal diameter of the largest lesion, cm (75/169)	15.0 [2.7–23.5]	15.9 [11.3–22.0]	12.0 [2.7–23.5]	.003
Neoadjuvant treatment (161/83)				
No neoadjuvant treatment, *n*,%	101 (62.7%)	78 (63.9%)	23 (59.0%)	.577
After neoadjuvant treatment, *n*,%	60 (37.3%)	44 (36.1%)	16 (41.0%)	
Use of techniques of augmentation of the future liver remnant (230/14)				
No FLR augmentation, *n*,%	224 (97.4%)	149 (98.0%)	75 (96.2%)	.410
After FLR augmentation, *n*,%	6 (2.6%)	3 (2.0%)	3 (3.8%)	
Portal vein embolization (230/14)				
Without PVE, *n*,%	226 (98.3%)	149 (98.0%)	77 (98.7%)	1.000
After PVE, *n*,%	4 (1.7%)	3 (2.0%)	1 (1.3%)	
Associating liver partition and portal vein ligation for staged hepatectomy (230/14)				
Without ALPPS, *n*,%	228 (99.1%)	152 (100%)	76 (97.4%)	.114
After ALPPS, *n*,%	2 (0.9%)	0 (0.0%)	2 (2.6%)	
Transarterial chemoembolization (210/34)				
Without TACE, *n*,%	205 (97.6%)	156 (99.4%)	49 (92.5%)	.015
After TACE, *n*,%	5 (2.4%)	1 (0.6%)	4 (7.5%)	

ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; *FLR,* future liver remnant; *PVE,* portal vein embolization; *TACE,* transarterial chemoembolization.
* For quantitative variables we report medians with ranges in the square brackets.

The median duration of the operation was 16.0 hours (6.4–31.0) and was greater in the nonmalignant group (16.0 hours [6.6–24.0] vs. 13.3 hours [6.4–31.0]); $P = .005$. We performed a linear regression analysis to predict operative time based on the maximal diameter of the largest lesion (Fig 2). We found statistically significant regression equations when assessing the whole group, $F(1, 50) = 9.73$, $P = .003$ ($R^2 = 0.163$), as well as the malignant subgroup only, $F(1, 12) = 12.8$, $P = .004$ ($R^2 = 0.475$). A patient's predicted operative time (measured in hours) was equal to 7.954 + 0.337 (lesion diameter in cm) in the first case, and 5.750 + 0.601 (lesion diameter in cm) in the second. The duration of operation increased by 20 minutes or 36 minutes for each cm of tumor diameter, respectively.

During the procedure, patients lost 1,000 mL (400–78,910) of blood and required 6 units (0–39.5) of packed red blood cells. Blood loss was greater in the malignant subgroup (median of 6,500 mL [1,500–78,910] vs. 1,000 mL [400–32,455]); $P < .001$. More details about the operative procedures are provided in Table III.

Primary outcomes

Meta-analysis of proportions revealed that R0 resection was achieved in 93.4% (95% confidence interval [CI]: 81.0–97.9%; $I^2 = 0\%$) of ERAT cases, 30-day mortality was 9.5% (95% CI: 5.9–14.9%; $I^2 = 0\%$), 1-year survival was 78.4% (95% CI: 62.2–88.8%; $I^2 = 64\%$), and major operative complications was 24.5% (95% CI: 16.9–34.3%; $I^2 = 26\%$) as shown in the forest plots (Fig 3).

The outcomes obtained from the analysis of the individual participant data are summarized in Table IV. R0 resection status confirmed by pathologic examination, however, was reported clearly in only 70 patients and was achieved in 98.6% of them. We identified 1 case with CRM in which the resection margin was involved.[27] There were 19 (7.9%) deaths in the first 30 postoperative days (POD), with no difference between the malignant and nonmalignant subgroups (11.3% vs. 6.3%), χ^2 (1, $n = 239$) = 1.79, $P = .181$. The 90-day and in-hospital mortality of 12.5% and 8.2%, respectively, were more prevalent after ERAT for malignant tumors; 90-day mortality: 21.6% vs. 8.2%, χ^2 (1, $n = 232$) = 8.27, $P = .004$ and for in-hospital mortality: 18.3% vs. 2.7%, χ^2 (1, $n = 232$) = 17.2, $P < .001$. Survival of the first postoperative year was noted in 161 (82.1%) patients, with worse results for those with malignant disease (65.0% vs. 89.7%), χ^2 (1, $n = 196$) = 17.3, $P < .001$.

Major operative complications occurred in 29.0% of cases, less commonly in those with nonmalignant lesions (21.0% vs. 50.0%), χ^2 (1, $n = 217$) = 17.7, $P < .001$. Bile leakage was the most frequent complication (16.0%). Severe bleeding occurred in 11.3% of ERAT operations. The malignant subgroup was more prone to post-hepatectomy liver failure (23.0% vs. 8.9%), $\chi^2(1, n = 197) = 7.46$, $P = .006$.

We performed logistic regression analysis to evaluate factors affecting the outcomes of ERAT (Table V). Nonmalignant disease was a positive predictor of 1-year survival (odds ratio [OR]: 4.692, 95% CI: 2.181–10.097, $P < .001$) and a negative predictor of both 90-day mortality (OR: 0.325, 95% CI: 0.147–0.718, $P = .005$) and major operative complications (OR: 0.266, 95% CI: 0.141–0.502, $P < .001$). Odds of 30-day mortality were less for individuals without a history of liver failure after ERAT (OR: 0.174, 95% CI: 0.059–0.517, $P = .002$).

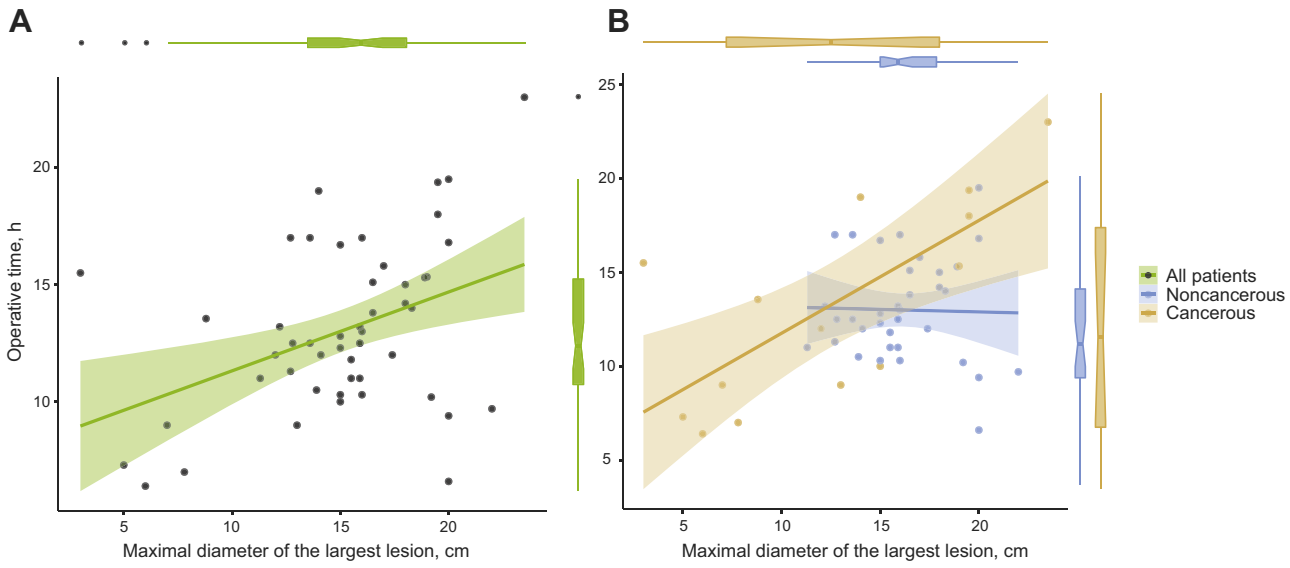


Fig 2. Linear regression model for operative time as function of the maximal diameter of the largest lesion. (*A*) Plot of the model evaluating all patients: F (1, 50) = 9.73, $P = .003$, $R^2 = 0.163$. (*B*) Plot of the subgroup analysis data. For the patients with malignant disease: F (1, 12) = 12.8, $P = .004$, $R^2 = 0.475$. For the nonmalignant subgroup: F (1, 36) = 0.0224, $P = .882$, $R^2 = -0.0271$.

Secondary outcomes

Some additional outcomes were analyzed. Among all of the patients included in the study, 10 cases (4.1%) of allotransplantation rescue were described, all in the malignant subgroup ($P < .001$). Disease recurrence was reported in 22 (12.4%) cases, all involving patients with malignant tumors (34.4%); 10 patients (32.3%) developed recurrent disease in the first year of follow-up. All outcomes as well as recurrence patterns are presented in Table IV.

Outcomes of treatment of selected malignant tumors

Hepatocellular carcinoma

We collected 14 (5.7%) cases of HCC in noncirrhotic livers treated with ERAT. Their median age was 42 years (13–73). They had up to 2, usually bilobar (78.6%), lesions with radiologically confirmed invasion into major vascular structures (present in all 11 individuals for whom the data were available), with a median maximal diameter of 17.1 cm (6.8–19.5). We identified 2 cases of 30-day, in-hospital deaths and 11 of patients who survived the first post-transplant year. One 39-year-old man required allogeneic liver transplantation on the 14th POD owing to severe ischemia caused by arterial bleeding.[28] Tumor recurrence was present in 5 cases.

Cholangiocarcinoma

CCCs were resected in 23 (9.4%) patients. Their median age was 54 years (26–79). All were single tumors. The CCCs involved both liver lobes in 18 of the 23 patients and invaded major vessels in 21. The maximal diameter of the removed lesions was 10.0 cm (3.0–20.0). There were 4 (17.4%) cases of 30-day mortality and 8 reported 12-month survivors. In 3 patients, tumor recurrence was confirmed. Liver allotransplantation was performed in 8 (34.8%) patients.

Table III
Operative details of the ERAT procedures (analysis of the individual participant data)

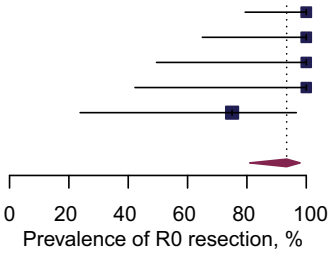
Variable (*n*/missing)	All patients	Subgroup		*P* value
		Nonmalignant ($n = 160$)	Malignant ($n = 84$)	
Operative time, h (175/69)	16.0 [6.4–31.0]*	16.0 [6.6–24.0]	13.3 [6.4–31.0]	.005
RLV/SLV, % (139/105)	71 [34.5–125.0]	71 [36.0–125.0]	51 [34.5–52.6]	<.001
Major hepatic resection (220/44)				
Minor resection, *n*,%	21 (10.5%)	4 (3.4%)	17 (20.2%)	<.001
Major resection, *n*,%	179 (89.5%)	112 (96.6%)	67 (79.8%)	
Blood loss, mL (122/122)	1,000 [400–78,910]	1,000 [400–32,455]	6,500 [1,500–78,910]	<.001
PRBC units transfused (135/109)	6 [0–39.5]	6 [0–39.5]	9 [0–25.0]	.853
Cold ischemic time, min (28/216)	240 [85–480]	300 [180–480]	134 [85–368]	.004
Warm ischemic time, min (40/204)	19.5 [2–65]	3 [2–46]	40 [3–65]	<.001
Total anhepatic time, min (194/50)	314 [102–879]	368 [102–879]	289 [110–540]	<.001
Preservation fluid (220/24)				
HTK, *n*,%	109 (49.5%)	73 (48.7%)	36 (51.4%)	.137
UW, *n*,%	108 (49.1%)	77 (51.3%)	31 (44.3%)	
Celsior, *n*,%	1 (0.5%)	0 (0.0%)	1 (1.4%)	
5% ringer lactate containing 2% Albumin, *n*,%	1 (0.5%)	0 (0.0%)	1 (1.4%)	
Saline, *n*,%	1 (0.5%)	0 (0.0%)	1 (1.4%)	
Time of hospital stay, d (188/56)	34 [7–128]	34 [7–128]	23 [7–61]	.086

HTK, histidine-tryptophan-ketoglutarate solution; *PRBC,* packed red blood cells; *UW,* University of Wisconsin solution.
* For quantitative variables we report medians with ranges in the square brackets.

A Prevalence of R0 resection.

Study	Cases	Total	Prevalence, %	95% CI
Yang *et al.* (2017)	31	31	100.0	[79.4; 99.9]
Wen *et al.* (2015)	15	15	100.0	[65.0; 99.8]
Du *et al.* (2019)	8	8	100.0	[49.5; 99.7]
Wang *et al.* (2012)	6	6	100.0	[42.3; 99.6]
Lodge *et al.* (2000)	3	4	75.0	[23.8; 96.6]
Random effects model		**64**	**93.4**	**[81.0; 97.9]**

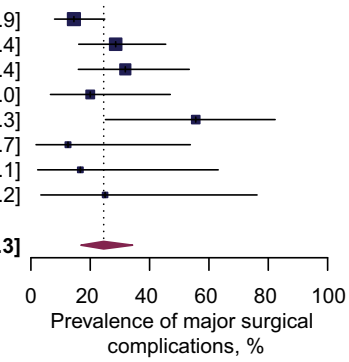
Heterogeneity: I^2 = 0%, τ^2 = 0, χ^2_4 = 3.22 (P = .52)



B Prevalence of major surgical complications.

Study	Cases	Total	Prevalence, %	95% CI
Aji *et al.* (2018)	10	69	14.5	[8.0; 24.9]
Shen *et al.* (2019)	10	35	28.6	[16.1; 45.4]
Oldhafer *et al.* (2000)	7	22	31.8	[16.0; 53.4]
Wen *et al.* (2015)	3	15	20.0	[6.6; 47.0]
Pichlmayr *et al.* (1990)	5	9	55.6	[25.1; 82.3]
Du *et al.* (2019)	1	8	12.5	[1.7; 53.7]
Wang *et al.* (2012)	1	6	16.7	[2.3; 63.1]
Lodge *et al.* (2000)	1	4	25.0	[3.4; 76.2]
Random effects model		**168**	**24.5**	**[16.9; 34.3]**

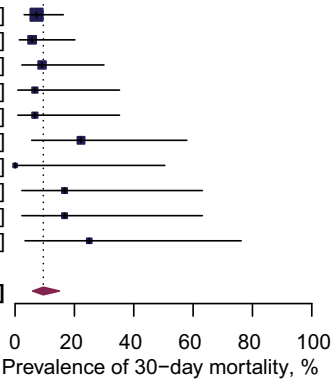
Heterogeneity: I^2 = 26%, τ^2 = 0.1149, χ^2_7 = 9.50 (*P* = .22)



C Prevalence of 30-day mortality.

Study	Cases	Total	Prevalence, %	95% CI
Aji *et al.* (2018)	5	69	7.2	[3.0; 16.3]
Shen *et al.* (2019)	2	35	5.7	[1.4; 20.2]
Oldhafer *et al.* (2000)	2	22	9.1	[2.3; 30.0]
Wen *et al.* (2015)	1	15	6.7	[0.9; 35.2]
He *et al.* (2015)	1	15	6.7	[0.9; 35.2]
Pichlmayr *et al.* (1990)	2	9	22.2	[5.6; 57.9]
Du *et al.* (2019)	0	8	0.0	[0.3; 50.5]
Wang *et al.* (2012)	1	6	16.7	[2.3; 63.1]
Malde *et al.* (2011)	1	6	16.7	[2.3; 63.1]
Lodge *et al.* (2000)	1	4	25.0	[3.4; 76.2]
Random effects model		**189**	**9.5**	**[5.9; 14.9]**

Heterogeneity: I^2 = 0%, τ^2 = 0, χ^2_9 = 4.67 (P = .86)



D Prevalence of 1-year survival.

Study	Cases	Total	Prevalence, %	95% CI
Aji *et al.* (2018)	60	69	87.0	[76.8; 93.1]
Shen *et al.* (2019)	32	35	91.4	[76.6; 97.2]
Oldhafer *et al.* (2000)	12	22	54.5	[34.1; 73.5]
Wen *et al.* (2015)	11	15	73.3	[46.7; 89.6]
Du *et al.* (2019)	8	8	100.0	[49.5; 99.7]
Wang *et al.* (2012)	5	6	83.3	[36.9; 97.7]
Malde *et al.* (2011)	3	6	50.0	[16.8; 83.2]
Random effects model		**161**	**78.4**	**[62.2; 88.8]**

Heterogeneity: I^2 = 64%, τ^2 = 0.6405, χ^2_6 = 16.69 (P = .01)

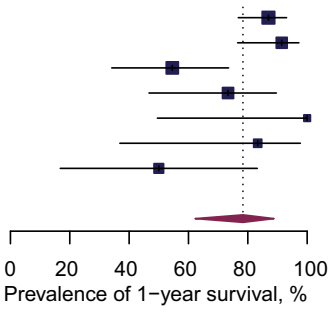


Fig 3. Forest plots of the primary ERAT outcomes (meta-analysis of proportions).

Table IV
Outcomes of *ex vivo* liver resection and autotransplantation (analysis of the individual participant data)

Variable (*n*/missing)	All patients	Subgroup		*P* value
		Nonmalignant ($n = 160$)	Malignant ($n = 84$)	
Follow-up, months (200/44)	22.0 [0–108]*	22.5 [0–108]	13.0 [0–76]	<.001
R0 resection status (70/174)				
Not radical resection, *n*,%	1 (1.4%)	0 (0.0%)	1 (2.7%)	1.000
R0 resection, *n*,%	69 (98.6%)	33 (100%)	36 (97.3%)	
Occurrence of major operative complications (217/27)				
No MSCs reported, *n*,%	154 (71.0%)	124 (79.0%)	30 (50.0%)	<.001
With MSC, *n*,%	63 (29.0%)	33 (21.0%)	30 (50.0%)	
30-day mortality (239/5)				
Alive after 30 PODs, *n*,%	220 (92.1%)	149 (93.7%)	71 (88.8%)	.181
Died within 30 PODs, *n*,%	19 (7.9%)	10 (6.3%)	9 (11.3%)	
90-day mortality (232/12)				
Alive after 90 PODs, *n*,%	203 (87.5%)	145 (91.8%)	58 (78.4%)	.004
Died within 90 PODs, *n*,%	29 (12.5%)	13 (8.2%)	16 (21.6%)	
In-hospital mortality (232/12)				
Discharged alive, *n*,%	213 (91.8%)	146 (97.3%)	67 (81.7%)	<.001
Died in hospital, *n*,%	19 (8.2%)	4 (2.7%)	15 (18.3%)	
1-year survival (196/48)				
Died at 1-year follow-up, *n*,%	35 (17.9%)	14 (10.3%)	21 (35.0%)	<.001
Survived 1 year, *n*,%	161 (82.1%)	122 (89.7%)	39 (65.0%)	
Bleeding complication (151/93)				
No major bleeding, *n*,%	134 (88.7%)	86 (90.5%)	48 (85.7%)	.366
Major bleeding complication, *n*,%	17 (11.3%)	9 (9.5%)	8 (14.3%)	
Bile leakage (213/31)				
No leakage reported, *n*,%	179 (84.0%)	128 (81.5%)	51 (81.1%)	.094
With bile leakage, *n*,%	34 (16.0%)	29 (18.5%)	5 (8.9%)	
Liver failure (197/47)				
No liver failure, *n*,%	169 (85.8%)	112 (91.1%)	57 (77.0%)	.006
With liver failure, *n*,%	28 (14.2%)	11 (8.9%)	17 (23.0%)	
Need for liver allotransplantation (244/0)				
No allotransplantation, *n*,%	234 (95.9%)	160 (100%)	74 (88.1%)	<.001
Allograft needed, *n*,%	10 (4.1%)	0 (0.0%)	10 (11.9%)	
Recurrence during follow-up (177/67)				
No recurrence, *n*,%	155 (87.6%)	113 (100%)	42 (65.6%)	<.001
Tumor recurrence, *n*,%	22 (12.4%)	0 (0.0%)	22 (34.4%)	
Recurrence at 1-year follow-up (120/124)				
No recurrence, *n*,%	110 (91.7%)	89 (100.0%)	21 (67.7%)	<.001
Tumor recurrence, *n*,%	10 (8.3%)	0 (0.0%)	10 (32.3%)	
Time to recurrence, months (13/9)	10 [3–48]	-	10 [3–48]	-
Recurrence pattern (12/10)				
Locoregional, *n*,%	7 (58.3%)	-	7 (58.3%)	-
Distant, *n*,%	3 (25.0%)	-	3 (25.0%)	
Both, *n*,%	2 (16.7%)	-	2 (16.7%)	

MSC, major surgical complication.
* For quantitative variables we report medians with ranges in the square brackets.

Table V
Logistic regression analysis (analysis of the individual participant data)

Predictor variables	Regression coefficient	SE	Z	*P* value	OR	95% CI	
						Lower	Upper
Model for major operative complication as a dependent variable							
Intercept	1.32	0.196	6.76	<.001	3.758	2.560	5.516
Nonmalignant lesion	−1.32	0.324	−4.08	<.001	0.266	0.141	0.502
R^2_{McF}: 0.064; AIC: 249; Accuracy: 71.0%; Overall model test, χ^2: 16.8, df: 1, $P < .001$							
Model for 30-d mortality as a dependent variable							
Intercept	2.85	0.343	8.30	<.001	17.222	8.795	33.724
No liver failure	−1.75	0.555	−3.15	.002	0.174	0.059	0.517
R^2_{McF}: 0.081; AIC: 105; Accuracy: 91.7%; Overall model test, χ^2: 8.91, df: 1, $P = .003$							
Model for 90-d mortality as a dependent variable							
Intercept	2.41	0.290	8.33	<.001	11.154	6.324	19.673
Nonmalignant lesion	−1.12	0.404	−2.78	.005	0.325	0.147	0.718
R^2_{McF}: 0.044; AIC: 171; Accuracy: 87.5%; Overall model test, χ^2: 7.72, df: 1, $P = .005$							
Model for 1-y survival as a dependent variable							
Intercept	−2.16	0.282	−7.67	<.001	0.115	0.066	0.200
Nonmalignant lesion	1.55	0.391	3.95	<.001	4.692	2.181	10.097
R^2_{McF}: 0.087; AIC: 172; Accuracy: 82.1%; Overall model test, χ^2: 16.1, df: 1, $P < .001$							

AIC, Akaike information criterion; R^2_{McF}, McFadden's R^2; *SE,* standard error.

Discussion

In this systematic review and meta-analysis, we evaluated the outcomes of ERAT. Liver back-table resection followed by autotransplantation is a technically demanding procedure performed in patients with hepatic tumors in whom conventional resection is not feasible. By combining data from 53 studies, including 244 liver bench surgery cases, we calculated that this approach facilitates radical resection in 98.6% (pooled rate of 93.4%, 95% CI: 81.0–97.9%, $I^2 = 0\%$). Mortality within the first 30 PODs occurred in 7.9% (combined prevalence of 9.5%, 95% CI: 5.9–14.9%, $I^2 = 0\%$), 1-year survival was present in 82.1% (meta-analysis of proportions revealed this frequency to be equal to 78.4%, 95% CI: 62.2–88.8%, $I^2 = 64\%$), and major operative complications occurred in 29.0% (pooled result: 24.5%, 95% CI:16.9–34.3%, $I^2 = 26\%$).

We compared patients with malignant and benign tumors. As a result, we showed that outcomes for the benign group are much more promising owing to less 30-day and in-hospital mortality rates (8.2% vs. 21.6% and 2.7% vs. 18.3%, respectively). Furthermore, 1-year survival was observed in 89.7% (65.0% in the malignant subgroup). A similar observation was reported by Oldhafer et al. (2000)[28] who concluded that the long-term results of the procedure were unsatisfactory, because only 7 of their 22 patients survived at least 18 months, including 2 with a nonmalignant disease (FNH).

Cheng et al. (2018)[29] described their experience with anesthesia management of 43 patients with either HCC or CCC treated with ERAT. They noted lesser durations of the operation (8.2 ± 2.3 hours) and total anhepatic time (250 ± 45 minutes) than those in the malignant subgroup from our study. Observed blood loss was 1,587 ± 434 mL, and in-hospital mortality was 20.9%. The rate did not differ much from our data (18.3%). The deaths in the series of Cheng et al. were caused by liver failure in 5 patients, sepsis in 3, and renal insufficiency in 1.

In the largest published series of 69 cases of hepatic alveolar echinococcosis resected with the bench approach, 30-day and 90-day mortality occurred in 5 (7.2%) and 8 (11.6%) of patients, respectively. One-year survival was reported in 60 (87.0%).[21] When we analyzed our data for the individuals with hepatic alveolar echinococcosis, we observed the rate of 6.5% for deaths within 30 PODs and 8.4% within 90 PODs. The one-year survival was noted in 89.5% of the ill. Median operative time, duration of the anhepatic phase, and blood loss were similar to those we calculated for the nonmalignant subgroup (15.9 [8–24] hours, 360 [104–879] minutes, and 1,000 [400–15,000] mL, respectively).

Hibi et al. (2019)[30] illustrated the concept of transplant oncology to which ERAT undoubtedly belongs. One of the four main purposes mentioned in the context of transplant oncology was to extend the limits of conventional surgery by applying transplantation techniques. Several problems arising from standard hepatectomy or allotransplantation could be overcome in selected cases by bench surgery. In comparison to *in situ* hepatectomy, ERAT increases the chances of obtaining negative margins while still maximizing the residual liver volume owing to more precise extracorporeal resection.[9,31] Additionally, the back-table resection facilitates the reconstruction of blood vessels without the pressure of time constraints *in situ*, whereas conventional surgery performed in a bleeding operative field might be time-consuming and, therefore, leading to undesirably prolonged warm ischemia time.[9,32,33] Autotransplantation helps to avoid the issue of donor shortage, an ongoing problem of transplant surgery. Moreover, allotransplantation is generally not favored in surgical oncology, because it requires immunosuppressive therapy, which may carry a risk of malignant growth of cancer cells.[34–36] Buchholz et al. (2019)[37] pointed out that during the bench surgery there is an opportunity to use *ex situ* radiotherapy for malignant lesions. What is worth mentioning is that He et al. (2015)[34] indicated that the total cost of treatment might be less with ERAT in comparison with allotransplantation. Furthermore, Beldi et al. (2019)[38] suggested that survival time in the group of ERAT patients is greater than in those who underwent allogeneic transplantation for hepatic alveolar echinococcosis.

ERAT is a technically demanding procedure that requires a multidisciplinary approach, including a surgical team experienced in liver transplantation and complex perioperative anesthesia management.[21,29,33,35,39] Despite increasing progress and experience with ERAT in patients with various tumor types, an increased risk of perioperative failure and mortality still exists.[24] It is no longer an experimental surgery but an established procedure, which can play a clinically important role in selected situations. ERAT may be considered as a treatment of last resort when other types of therapies are inapplicable. ERAT is reserved for noncirrhotic patients with normal liver function diagnosed with hepatic lesions that are conventionally unresectable.[40,41] ERAT may be most appropriate for tumors of large size and/or difficult anatomic locations, including a severe compression against or infiltration on large vascular or biliary structures (e.g., the retrohepatic IVC, portal structures, hepatic veins, and the hepatocaval confluence).[9,31,35,37,42,43] Furthermore, ERAT is reasonable when previous resections were unsuccessful or when there is a very high operative risk for *in situ* resections, such as large unstoppable hemorrhage (e.g., in case of hemangioma) or probable liver failure caused by the need for a prolonged operative time with subsequent prolonged warm ischemia injury.[21,22,24,33,42,44] ERAT can only be performed when a sufficient residual liver volume can be ensured after the resection.[34,37] The use of techniques of augmentation of the future liver remnant may be considered to prevent treatment failure.[8,21]

ERAT is contraindicated for a number of conditions (i.e., cirrhosis, cholestasis, Budd-Chiari syndrome, extrahepatic metastases [of both hepatic alveolar echinococcosis and malignant tumors], severe invasion of hepatic structures, and an insufficient [less than 40%] RLV/SLV).[21,36,45–48] Multiorgan alveolar echinococcosis with extrahepatic lesions controllable with albendazole is not necessarily an absolute contraindication.[36] Limited extrahepatic metastases might be managed with ERAT as contemporary advancements in chemo- and radiotherapy enable effective treatment of the disease or provide long palliative effect.[43,45] Impaired liver function, as manifested by obstructive jaundice, secondary sclerosing cholangitis, or portal hypertension, and severe damage of the intrahepatic biliary tree make the procedure infeasible.[40] Therefore, these patients should also meet the functional and anatomic criteria to be eligible for ERAT: (1) preoperative expectation of RLV/SLV is at least 35% to 40%; (2) total bilirubin less than twice of the upper limit of normal in patients with obstructive jaundice; and (3) a routine percutaneous transhepatic cholangial drainage must be performed in patients with obstructive jaundice.[1,21,36,40] Operative planning is likely to be helpful in determining the most suitable resection planes and avoiding complications. The RLV should be assessed quantitatively and qualitatively prior to operation as well as before the back bench resection phase to avoid small-for-size liver syndrome and to ensure postoperative maintenance of normal liver function.[34]

We calculated that major operative complications occur in about 1 in 4 ERAT cases. Among the most prevalent postoperative complications are biliary leakage, liver failure, bleeding, pleural effusion, renal insufficiency, wound infection, and sepsis.[21,31,34,40,42] Because of the technical difficulty, the risk of operative complications, and the defined operative mortality, ERAT should be considered as the treatment of last resort.

An ongoing debate concerns the risk of allotransplantation rescue in case of postresection hepatic insufficiency after ERAT.[21] We found 10 such cases.[28,41,48,49] Among them, 7 deaths occurred within the first 90 PODs and 8 occurred in patients diagnosed with CCC. This leads to a major ethical dilemma, because such cases would not be eligible for liver transplantation beforehand.[50] It is not possible to keep a hepatic graft available in case of failure, as described by Pichlmayr et al. (1990)[41] in one of his patients with FNH. Precise preoperative assessment and the recognition of the need to prevent intraoperative warm ischemia could help to moderate the need for allotransplantation after the bench procedure.

Although ERAT has been known since 1988, it is performed rarely; indeed, many patients do not meet the criteria for this procedure. Its position seems to be well established in the treatment of hepatic alveolar echinococcosis for which most cases are described and promising outcomes are reported.[21] Taking into account the worrisome prevalence of early deaths in patients with malignant tumors, high recurrence rates, and an alarming number of liver failures requiring allotransplantation, as seen in CCC, we believe that the use of ERAT in the group of patients with malignant tumors is questionable. Each person should be evaluated appropriately for ERAT individually until strong evidence from randomized controlled trials is available. All of that might be the reason why institutions that specialize in liver bench surgery usually perform hundreds of conventional resections per every ERAT.[51–53]

Although ERAT is not a popular treatment option, its use has been increasing over the years, and it might see some further improvements or even applications. As shown in a case reported by Boggi et al. (2006),[54] liver resection performed with the *ex vivo* technique might not only be reserved for elective treatment of hepatic tumors but can also be implemented in emergency settings such as blunt abdominal trauma.

Limitations

Some limitations might result from a low level of evidence of the included studies because of the absence of high-quality research in this field. Taking into account that synthesis of case series and case reports is recommended and justified for evaluation of evidence for rare and highly specialized operative procedures,[14] we believe that our approach of a systematic review and meta-analysis is the best available method to facilitate substantial progress in understanding the role of ERAT in modern hepatobiliary surgery. Furthermore, the meta-analysis of the individual participant data was applied to decrease the heterogeneity of the results in the included studies.[55] The presence of missing data was another limitation. We addressed this problem by available-case analysis to provide evidence-based practitioners with the most comprehensive information. Our study did not consider the effect of various types of hepatectomies.

In conclusion, ERAT is a complex operative procedure that in selected patients with conventionally unresectable liver tumors can facilitate a potentially curative radical treatment. It is the last resort therapy reserved for a small, select group of patients with normal hepatic function and a sufficient predicted residual liver volume after the hepatic resection. ERAT minimizes warm ischemia injury and allows resection of the tumor(s) in a bloodless field with time pressure decreased. Although the experience with the procedure evolves, some controversies are still present, including the possible need for liver allotransplantation. The strongest evidence is present for hepatic alveolar echinococcosis with the most cases reported. Outcomes for patients with malignant disease seem to be disappointing owing to the high recurrence rate and worrisome prevalence of 30-day, 90-day, and in-hospital mortality.

Supplementary Materials

Supplementary data to this article include Supplementary Content which contains the summary of search strategy, written in compliance with the PRISMA-Search extension to the PRISMA statement[56], a table with frequencies of diagnoses, and funnel plots created to evaluate the presence of publication bias.

Conflict of interest/Disclosures

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.surg.2020.05.036.

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