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(Review Article)

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Robotic surgery for colorectal liver metastases (CRLM): A systematic literature review with meta-analysis.

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Abstract

Colorectal Cancer (CRC) is the third most prevalent cancer (10.2%) with the second highest mortality (9.2%).[1] Up to 14.5% of patients present with synchronous metastases and 12.8% will develop metachronous metastases within 5 years. The treatment for these metastases is resection. [2] In this study we perform a systematic search of the literature about robotic versus laparoscopic liver resections of colorectal liver metastases (CLRM). We include 16 studies. We describe the patient and tumor characteristics. We also describe operation characteristics (rate of major resections, operation time, usage and duration of Pringle, conversion rate, complication rate, R0 margin rate, estimated blood loss, length of stay, mortality and recurrence.

Using this data we perform a meta-analysis: no significant difference in operation time was found between robotic and laparoscopic liver resections. There was significantly lower conversion rate, significantly higher R0 margin rate, significantly lower blood loss in the robotic group.

We conclude that robotic surgery is promising in the therapy of CRLM. In the future there is need for RCT to compare robotic versus laparoscopic liver surgery for CRLM. Furthermore a longer follow-up is needed.

Keywords Robotic surgery; Colorectal liver metastases (CLRM); Literature review; Meta-analysis; Liver surgery; Hepatobiliary surgery

1 Introduction

In this paper we intend to discover the current status of robotic surgery in the field of surgery for Colorectal Liver Metastases (CRLM).

In a report published in 2018, Colorectal Cancer (CRC) is the third most prevalent cancer (10.2%) with the second highest mortality (9.2%).[1] Up to 14.5% of patients has synchronous metastases at the time of diagnosis, 76.8% of which are located in the liver. In 12.8% of patients liver metastases will develop during a 5 year follow-up (so-called metachronous metastases).[2]

To provide the best chance for cure for patients with CRC, the primary tumor and its metastases must be removed. Given that the liver is the most affected site for metastases, the field of liver resections has grown significantly over time.

In recent decades, the use of laparoscopic liver surgery is increased, with proven benefits over open surgery (reduced blood loss, reduced Pringle time, reduced overall and liver-specific complication rate, reduced postoperative ileus and reduced length of stay).[3,4] Meanwhile oncologic outcomes are proven to be the same as compared to open surgery. [3,4] This was investigated for both Hepatocellular carcinoma (HCC) [5] and for CRLM [6–8].

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More recently robotic surgery is also being applied in the field of liver surgery. The goal of this study is to compile a comprehensive literature review concerning the use of robotic surgery for the resection of CRLMs. It has been theorised that robotic surgery gives added benefits over laparoscopic surgery: magnified 3-dimensional vision, tremor control, intuitive wrist like movements allowing to perform delicate dissection and precise intracorporeal suturing, articulating instruments with 7° of freedom allowing easier access to the posterior liver segments, better ergonomics reducing surgeon fatigue.[9] The downsides of robotic surgery is the cost, lack of tactile feedback and the learning curve for the surgeon.[9]

2 Methods

For this study we searched for relevant literature written in English on robotic surgery specifically for CRLM in the Pubmed database up until august 2022, using the aftermentioned searches.

By checking all references of selected papers, two more papers were also included (Chiow *et al.* and Yang *et al.*). During the process of writing this review (after closing our search process) 1 extra paper was published: Gumbs *et al*, 2022[10].

Several search results were excluded based on:

- The language (1 French, 1 Danish, 1 Chinese, 1 Hungarian, 1 German),
- Study design (e.g. One study researched the overall survival after multiple redo resections of relapsed liver metastases, one compared the learning curve of a starting HPB centre, while including almost no robotic surgery),
- Some results were reviews themselves,
- Some results had the wrong publication type (e.g. Case reports, editorials, expert opinions),
- Some papers studied a different therapy/intervention (e.g. The use of ultrasound preoperatively, the use of ICG-fluorescence, robotic assisted placement of a hepatic artery infusion pump, robot-assisted radiosurgery: Percutaneous radiofrequency ablation (RFA).) Robotic ALPPS was excluded in the scope of this study. 3 studies included synchronous resections of the CRLM combined with the colon resection.

We performed a literature search using 2 search queries*:* one using filters searching for specific medical subject headings (MeSH) in the title and abstract *“(("colorectal liver metastases"[Title/Abstract]) OR ("CRLM"[Title/Abstract])) AND (("robot surgery"[Title/Abstract]) OR ("robotic surgery"[Title/Abstract]) OR ("robotic"[Title/Abstract]))”* and one broader search without filters *“laparoscopic liver resection AND robotic liver resection AND colorectal liver metastases”.* The former search yielded 42 hits and the latter yielded 55. The search was performed by 1 person, the study itself was later double checked by the above mentioned authors.

These searches were uploaded to the Rayyan software. This software helps to detect duplicates and to screen the abstracts. This application was used to decide to include or exclude the different search hits and to keep track of the reasons for exclusion.

Both searches yielded a total of 97 search hits. After eliminating the duplicates, 73 studies remained. Of these, 60 were excluded: 5 based on language, 2 based on study design, 6 of these were systematic reviews themselves, 19 were of a different publication type, 25 results were excluded because the different therapy/intervention was studied, 3 results researched surgery combining liver and colorectal surgeries.

As a result of this a total of 16 studies were included (supplemental Figure 1).

The following results were extracted from the selected papers: author, study type, population size, patient demographics, tumor size, operative characteristics (number of major resections, operation time, usage of Pringle manoeuvre, duration of Pringle manoeuvre, conversion rate, complication rate, rate of R0 resections, resection margin width, intraoperative blood loss, transfusion rate), postoperative stay (days of hospital stay, days of IC stay), mortality and survival rates and recurrence rates.

3 Results

3.1 Overview of included studies

A total of 16 studies are included (supplemental Table 1). There are multiple case series: Guilianoti *et al*; Croner *et al*; Guerra *et al.*; Guadagni *et al;* Araujo *et al;* Birgin *et al*.

Furthermore there are multiple cohort studies. Rahimli *et al;* Shapera *et al;* Masetti *et al.*

Multiple research groups combine propensity score matching (PSM) to a cohort study to better unify the difference in groups to reduce bias.

Currently we could find 1 randomized controlled trial: Li *et al.* compares 112 patients, 61 robotic versus 61 laparoscopic CRLM resections.

3.2 Patient and tumor characteristics

Supplemental Table 2 shows patient and tumor characteristics. The ratio male/female differed drastically over studies. Araujo *et al.* had no men in their case series of n=5. Birgin *et al.* had a ratio of 9:1 M:F in their case series. There were never statistical differences.

There was less variability in mean age: lowest median age (55 years old) was described in Guilianotti *et al;* but that was including benign pathologies. Li *et al.* had a mean age of 57 years in both groups. Oldest median age (66 years old) was noted in Guadagni *et al.* and Birgin *et al*. Because mean and median data was compiled, no averages could be calculated.

Many studies showed data for both CRLM and HCC, whereas this study only focuses on the CRLM data provided. The smallest mean lesion size was 20mm in the robotic group of Shapera *et al.* The smallest individual tumor overall was 4mm in a patient in the study of Guerra *et al.* The biggest tumor was 290mm in the study of Gumbs *et al.* If we compile the robotic data, the weighted average (weighted to the population size) was 26.5 mm, the weighted average of the laparoscopic groups (Beard *et al*; Rahimli *et al*; an Li *et al.*) was 25.2 mm.

3.3 Operation characteristics

Supplemental Table 3 shows the operation characteristics.

3.3.1 Rate of major resections

Within the case series there is a wide range of the rates of major resections (defined as ≥ 3 couinaud's liver segments). Ranging from 0% (Croner *et al*; Guadagni *et al*; Araojo *et al.*), to low rates (Guerra *et al*. had 5/59 (6.7%)), to 100% (Guilianotti *et al*; Succandi *et al.* and Birgin *et al.*)

No cohort studies had a statistical difference in distribution of major/minor rates in both groups. Chiow *et al*. investigated right posterior sectionectomy operations, although complex operations, following the definition of as ≥ 3 liver segments, we regard this as minor resections. Following this train of thought we consider the right anterior sectionectomy described by Yang *et al*. as minor and the central hepatectomy as major resections. The RCT of Li *et al*. didn't describe how many segments were resected.

3.3.2 Operation time

Shortest operation times (OT) were reported by Guadagni *et al*. with a mean OT of 198 minutes, this group performed only wedge resections. Longest times (disregarding the above mentioned) of 428 min were reported by Birgin *et al*. who performed all major resections.

Rahimli *et al*. found that in their population robotic surgery took significantly longer than laparoscopic surgery: 342 min versus 200 min (p=0.004). Shapera *et al*. showed that robotic surgery took significantly longer than open surgery: 375 min versus 269 min (p=0.05). Other cohort studies found no significant differences.

The RCT of Li *et al*. however proved that robotic surgery was significantly shorter than laparoscopic: 156 min versus 184 min (p=<0.001).

3.3.3 Meta-analysis of the data of operation time

We used operation time data to perform a meta-analysis. We could only use those studies that provided mean, standard deviation (SD) and sample size for each arm of the study: robotic vs. laparoscopic (or open). We selected the following studies:

Table 1 Meta-analysis of the data of the operation time: study inclusion

Study	**Type**	**Mean**	**SD**	**n**
Beard	R	272	115	115
	L	253	118	514
Sucandy	R	302	131.5	42
	O	300	115.6	42
Gumbs	R	271.5	106.3	36
	L	209.7	116	462
Chiow	R	272	150	96
	L	310	121	244
Yang	R	339	207	48
	L	298	110	185
Shapera	R	358	130.5	42
	O	279	113.3	14

We calculated the fixed and random effects model.

Table 2 Meta-analysis of the data of the operation time: effect size

	Robotic			**Laparoscopic**					
Study	n	Mean	SD	n	Mean	SD	Pooled SD	ES	SE
Beard	115	272	115	514	253	118	117.46	0.16	0.10
Sucandy	42	302	131.5	42	300	115.6	123.81	0.02	0.22
Gumbs	36	271.5	106.3	462	209.7	116	115.34	0.54	0.17
Chiow	96	272	150	244	310	121	129.81	-0.29	0.12
Yang	48	339	207	185	298	110	135.49	0.30	0.16
Shapera	42	358	130.5	14	279	113.3	126.57	0.62	0.32

ES = Effect Size; SE = Standard Error

For the Robotic Group, we obtained:

Table 3 Meta-analysis of the data of the operation time: effect analysis, robotic

Fixed Effect Analysis	**Random Effect Analysis**
Overall Mean = 288.2 (SE = 6.7)	Random Effect = 868.7
95% CI[275.01, 301.34]	Overall Mean = 298.2 (SE = 14.3)
z-score = 42.90 (p = 0.0000)	95% CI[270.23, 326.21]
Homogeneity analysis	z-score = 20.88 (p = 0.0000)
Q = 19.66 df = 5 p = 0.0014	
I^2 = 74.6% (Moderate heterogeneity)	

Under the fixed effect model we assume that there is one true effect size, which is shared by all included studies. By contrast, under the random effects model, we allow that the true effect could vary from study to study. For example, the effect size might be a little higher if the subjects are older, or more educated, or healthier and so on. The studies included in the meta-analysis are assumed to be a random sample of the relevant distribution of effects, and the combined effect estimates the mean effect in this distribution.

The Q-statistics represents the total variance, that is the sum of the weighted squared deviations of each study mean from the combined mean. I^2 statistic is a measure of heterogeneity and is defined as $I^2 = 100\% \times (Q - df)/Q$, where Q is Cochran's heterogeneity statistic and df the degrees of freedom. Negative values of I^2 should be set equal to zero, so that I^2 lies between 0% and 100%.

For the Laparoscopic Group, we have:

Table 4 Meta-analysis of the data of the operation time: effect analysis, laparoscopic

Fixed Effect Analysis	**Random Effect Analysis**
Overall Mean = 256.0 (SE = 3.1)	Random Effect = 1915.5
95% CI[250.07, 262.03]	Overall Mean = 274.0 (SE = 18.8)
z-score = 83.93 (p = 0.0000)	95% CI[237.18, 310.73]
Homogeneity analysis	z-score = 14.60 (p = 0.0000)
Q = 156.16 df = 5 p = 0.0000	
I^2 = 96.8% (High heterogeneity)	

Comparing the two groups, we have:

Table 5 Meta-analysis of the data of the operation time: effect analysis, comparing robotic and laparoscopic

Fixed Effect Analysis	**Random Effect Analysis**
Overall Mean = 0.11 (SE = 0.06)	Random Effect = 0.08
95% CI[-0.009, 0.232]	Overall Mean = 0.19 (SE = 0.14)
z-score = 1.82 (p = 0.0689)	95% CI[-0.09, 0.46]
Homogeneity analysis	z-score = 1.34 (p = 0.1792)
Q = 21.90 df = 6 p = 0.0005	
I^2 = 77.2% (High heterogeneity)	

Note: the overall mean difference is standardized with the standard deviation.

The overall standardized mean difference in the random effects model is 0.19 (SE = 0.14) with 95%CI [-0.19; 0.46] (p = 0.1792) showing that there is no significant difference in operation time between robotic and laparoscopic surgery.

Performing the meta-analysis on all pooled data, we have:

Table 6 Meta-analysis of the data of the operation time: effect analysis, all data

Fixed Effect Analysis	**Random Effect Analysis**
Overall Mean = 261.5 (SE = 2.8)	Random Effect = 1749.4

95% CI[256.10, 266.99]	Overall Mean = 286.3 (SE = 13.0)
z-score = 94.15 (p = 0.0000)	95% CI[260.83, 311.79]
Homogeneity analysis	z-score = 22.03 (p = 0.0000)
Q = 194.78 df = 11 p = 0.0000	
I^2 = 94.4% (High heterogeneity)	

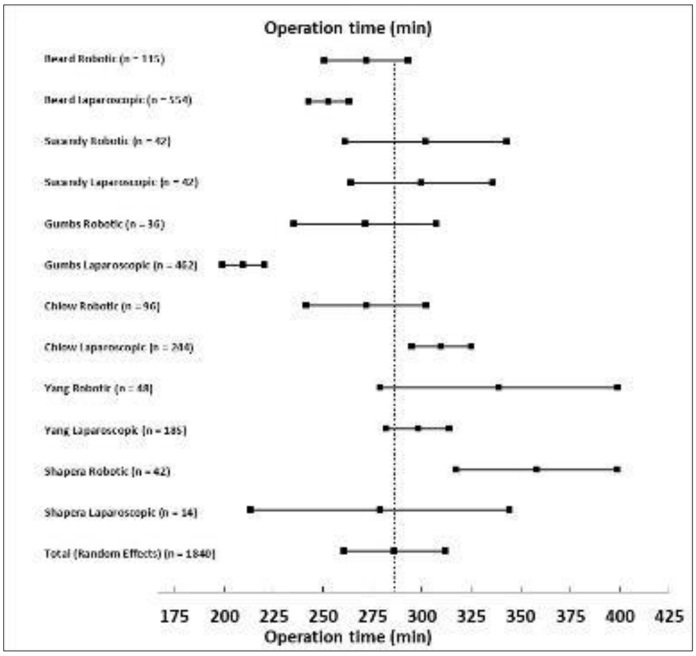


Figure 1 Forest plot of the data of operation time

The vertical dotted line is the overall mean operation time.

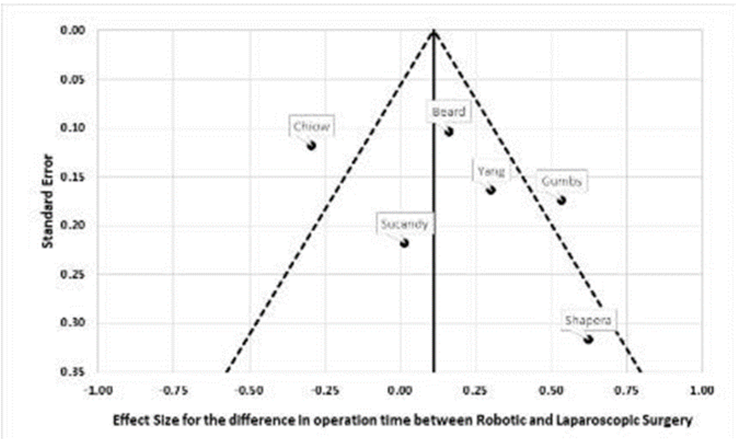


Figure 2 Funnel plot for data of operation time

The contours are obtained using the significance level of 0.05.

A funnel plot is a graphical tool for detecting bias in meta-analysis. Treatment effect is plotted on the horizontal axis and standard error is plotted on the vertical axis. The vertical line represents the summary effect estimated derived using fixed-effect meta-analysis and the diagonal lines represent the 95%CIs (effect ± 1.96 SE) around the summary effect for each standard error on the vertical axis. In the absence of heterogeneity 95% of the studies should lie within the funnel defined by these diagonal lines. Publication bias results in asymmetry of the funnel plot.

Conclusion: although there is large heterogeneity between studies, there seems to be no significant difference in operation time between robotic and laparoscopic surgery.

3.3.4 Usage and duration of Pringle manoeuvre

The usage of the Pringle manoeuvre ranged from 0% to approximately 60%.

In the study of Masetti *et al*. there was significantly less usage of the Pringle manoeuvre in the robotic minimal invasive liver surgery group compared to the laparoscopic group: 55.5% vs. 27.3%, respectively ($p < 0.001$). Also the intermittent usage of Pringle was significantly lower: 54.5% vs. 27.3%, ($p = 0.001$).

Only 3 studies reported duration of clamping: ranging from 39 min to 63 min. Neither of them showed a significant difference shown.

Meta-analysis of the data of Pringle manoeuvre

Table 7 Meta-analysis of the data of Pringle manoeuvre: effect size

	Robotic			**Laparoscopic**					
Study	n	Prop	SD	n	Prop	SD	Pooled SD	Risk diff	SE
Rahimli	12	0	0	13	0	0	0.00	0.00	0.000
Chiow	88	0.625	0.051608	88	0.636364	0.05128	0.05	-0.01	0.073
Yang	40	0.525	0.078958	40	0.8	0.063246	0.07	-0.28	0.101
Masetti	77	0.272727	0.050754	953	0.555089	0.016098	0.02	-0.28	0.053
Gumbs	21	0	0	21	0.190476	0.085689	0.06	-0.19	0.086

Note that two authors report 0% use of Pringle.

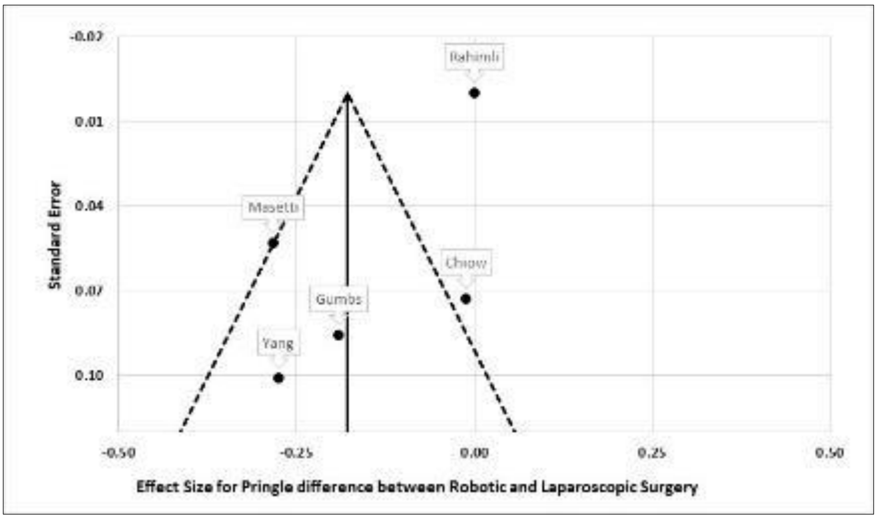


Figure 3 Funnel plot for Pringle use

Funnel plot for Pringle proportion difference. Most authors report less use of Pringle with the robotic method, although Rahimli did not use Pringle at all, and Chiow reports very similar (63%) application in both methods.

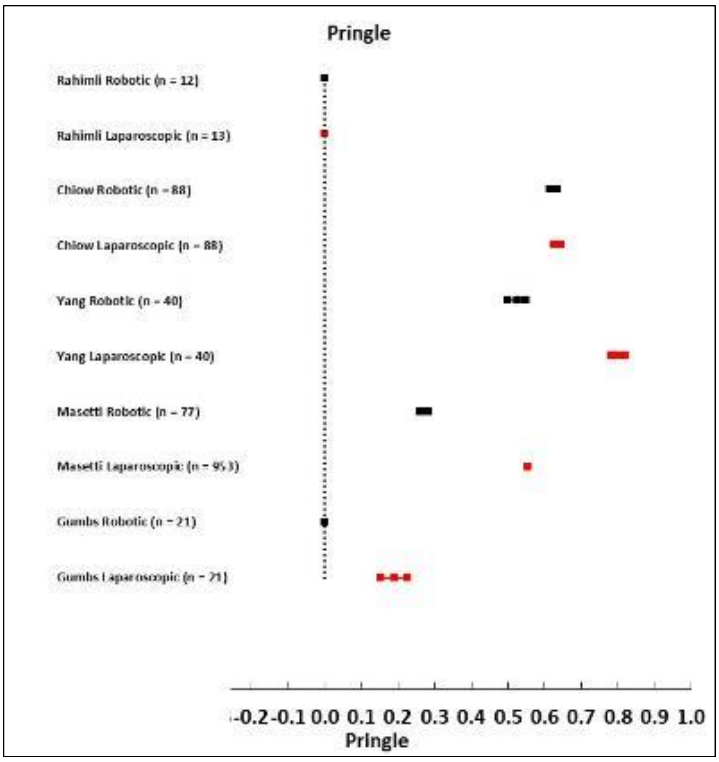


Figure 4 Forest plot for Pringle use

Forest plot for Pringle proportion used in the robotic method (black) and the laparoscopic method (red). The vertical dotted line is drawn at zero.

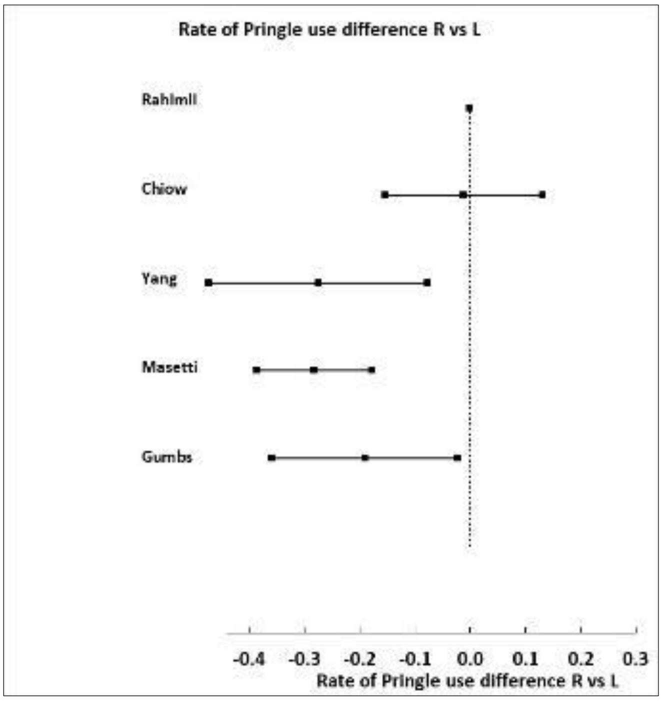


Figure 5 Forest plot for difference in Pringle use

Note: because one author reported zero use of Pringle, an overall difference could not be calculated.

Negative values mean less use of Pringle in the Robotic method.

3.3.5 Conversion rate

The conversion rate ranged from 0% to 17.4%.

Beard *et al*. had significantly less conversions in the robotic group compared to the laparoscopic one, but this was before PSM, no value was given after PSM. Chiow *et al* had a significantly lower conversion rate in their robotic group after PSM: R 2/88 (2.3%) vs. L 10/88 (11.4%) (p=0.016). Other cohort studies found no differences.

Meta-analysis of the data of conversion rate

Meta-analysis of the robotic data

Table 8: Meta-analysis of the data of conversion rate: study inclusion, robotic

Study	**x**	**n**	**Prop**
Beard	6	115	0.052174
Chiow	2	88	0.022727
Yang	2	40	0.05
Masetti	9	77	0.116883
Gumbs	1	21	0.047619

Table 9: Meta-analysis of the data of conversion rate: effect analysis, robotic

Fixed effects		**Random effects**	
ES	0.0435	ES	0.0491
var	0.0001	var	0.0002
LL	0.0220	LL	0.0202
UL	0.0650	UL	0.0780
df	4	error	0.0289
Q	5.9		
I^2	0.327		
tau^2	0.0003		
C	5630.1		

The effect size (ES) is a weighted measure of the effect, here defined as rate of conversion. 'var' is the variance of the data. LL and UL are the lower and upper limit of the 95% confidence interval. Df is the degrees of freedom. Q is Cochran's Q: a value used to calculate the heterogeneity index I^2. I^2 is a measure of heterogeneity and varies between 0 and 100%. Tau^2 is the random effect, which is used in the random effects estimation of the effect size.

The Robotic method shows an overall effect size (rate of conversion) of 4.9% with 95%CI [2.0; 7.8]. The heterogeneity is modest (only 33%). Fixed effect size and random effects effect size are very similar.

It is important to assess the dispersion of effect sizes from study to study, and then taking this into account when interpreting the data. If the effect size is consistent, then we will usually focus on the summary effect, and note that this effect is robust across the domain of studies included in the analysis. If the effect size varies modestly, then we might still report the summary effect but note that the true effect in any given study could be somewhat lower or higher than this value. If the effect varies substantially from one study to the next, our attention will shift from the summary effect to the dispersion itself.

Under the fixed-effect model we assume that there is one true effect size (hence the term fixed effect) which underlies all the studies in the analysis, and that all differences in observed effects are due to sampling error. While we follow the practice of calling this a fixed-effect model, a more descriptive term would be a common-effect model. In either case, we use the singular (effect) since there is only one true effect. By contrast, under the random-effects model we allow that the true effect could vary from study to study. For example, the effect size might be higher (or lower) in studies where the participants are older, or more educated, or healthier than in others, or when a more intensive variant of an intervention is used, and so on. Because studies will differ in the different populations and in the implementations of interventions, among other reasons, there may be different effect sizes underlying different studies. If it were possible to perform an infinite number of studies (based on the inclusion criteria for our analysis), the true effect sizes for these studies would be distributed round some mean effect. The effect sizes in the studies that actually were performed are assumed to represent a random sample of these effect sizes (hence the term random effects). Here, we use the plural (effects) since there is an array of true effects.

Meta-analysis of the laparoscopic data

Table 10: Meta-analysis of the data of conversion rate: study inclusion, laparoscopic

Study	**x**	**n**	**Prop**
Beard	62	514	0.120623
Chiow	10	88	0.113636
Yang	2	40	0.05
Masetti	50	953	0.052466
Gumbs	4	21	0.190476

Table 11: Meta-analysis of the data of conversion rate: effect analysis, laparoscopic

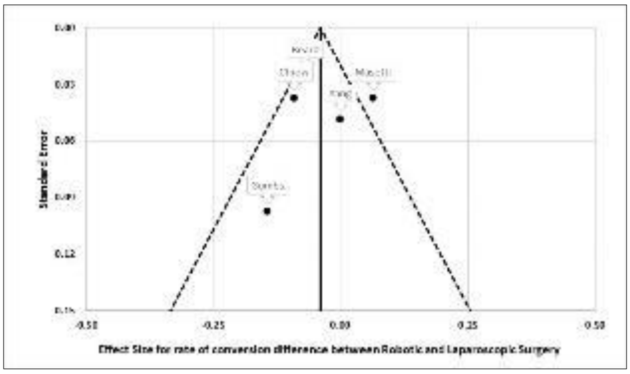
Fixed effect		**Random effects**	
ES	0.0679	ES	0.0838
var	0.0000	var	0.0002
LL	0.0558	LL	0.0580
UL	0.0801	UL	0.1095
df	4	error	0.0258
Q	22.2		
I^2	0.820		
tau^2	0.0017		
C	10695.9		

The overall effect size (rate of conversion) is 8.4% with 95%CI [5.80; 11.0%]. There is quite some heterogeneity (I^2 = 82%) and the fixed effect size (6.8%) is more different from the random effects ES as compared to the Robotic method.

Rate of conversion difference between robotic and laparoscopic:

The meta-analysis for the risk difference (difference between proportions) results in an overall effect size of -4.0% with 95%CI [-7.3%; -0.7%] not including zero, meaning that this overall effect size is significantly different from zero. This means that the rate of conversion is significantly lower in robotic than in laparoscopic surgery.

Figure 6: Funnel plot for conversion rate



Funnel plot for the rate of conversion (overall effect size of -0.04 (-4.0%)).

3.3.6 *Complication rate*

Complication rates ranged from 3.28% to 25%: It seems the more extensive surgery came with higher complications rates compared to the other studies: e.g. Guilianotti *et al*. (25%), Croner *et al*. (11%), Guerra *et al*. (27% of which 5% CD≥3), Yang *et al*. (5.0% CD≥3, both groups).

Complication rates scoring a Clavien-Dindo ≥3, ranged in between 0% and 10% for the different robotic groups.

None of the cohort studies had a significant difference. The RCT of Li *et al*. however did: here the robotic group had significantly less complications: R 3,28% vs. L 13,11% (p=0.048).

Due to the data being reported so heterogeneously no pooling of data was possible.

3.3.7 *R0 rate, margin*

R0 rate ranged from 74% to 100%. Many of the case series showed a 100% R0 rate, this could be related to a selection bias. The studies with larger sample sizes had comparable rates in their robotic groups: Beard *et al.* (74%), Chiow *et al.* (86%), Yang *et al.* (84%).

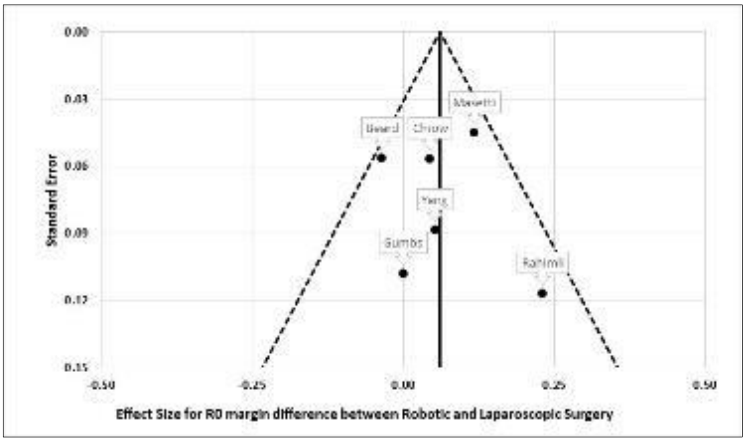
Masetti *et al*. showed significantly less R1 resections in the robotic group compared with laparoscopic: 16.9% versus 28.8 (p = 0.025). Also the robotic group had a wider mean margin: 0.8 cm (0.1–1) versus 0.3 cm (0–0.10) (p < 0.001). As further experiment they compared R1 and R0 resection groups in an univariable and multivariable analysis: both times surgical technique was a significant variable (p=0.025, p=0.046). No other statistical difference were reported in the other studies.

Meta-analysis of the data of R0 rate

Table 12: Meta-analysis of the data of R0 rate: study inclusion and effect size

	Robotic				**Laparoscopic**						
Study	x	n	Prop	SD	x	n	Prop	SD	Pooled SD	Risk diff	SE
Beard	85	115	0.73913	0.040947	89	115	0.773913	0.039006	0.04	-0.03	0.057
Chiow	70	81	0.864198	0.038064	68	83	0.819277	0.042236	0.04	0.04	0.057
Yang	32	38	0.842105	0.059153	32	38	0.789474	0.066135	0.06	0.05	0.089
Masetti	64	77	0.831169	0.04269	679	953	0.712487	0.014661	0.02	0.12	0.045
Gumbs	18	21	0.857143	0.07636	18	21	0.857143	0.07636	0.08	0.00	0.108
Rahimli	12	12	1	0	10	13	0.769231	0.116855	0.08	0.23	0.117

Figure 7: Funnel plot for R0 rate



Funnel plot for R0 rate difference between robotic and laparoscopic surgery

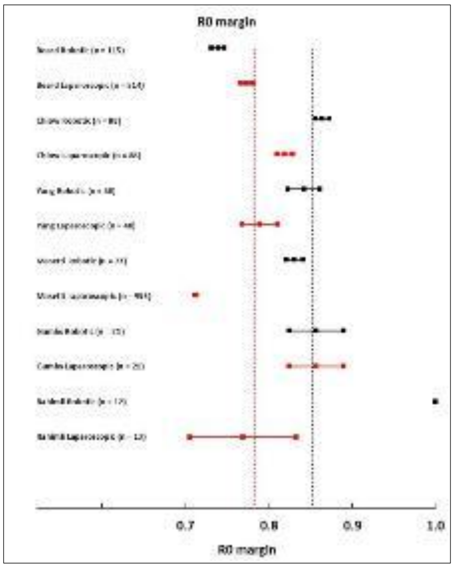
Table 13: Meta-analysis of the data of R0 rate: effect analysis, robotic and laparoscopic

Robotic				**Laparoscopic**			
Fixed effect		Random effects		Fixed effect		Random effects	
ES	0.8433	ES	0.8515	ES	0.7385	ES	0.7827
var	0.0004	var	0.0012	var	0.0002	var	0.0009
LL	0.8050	LL	0.7827	LL	0.7140	LL	0.7238
UL	0.8815	UL	0.9204	UL	0.7630	UL	0.8416
df	5	error	0.0688	df	5	error	0.0589
Q	15.1			Q	13.2		
I^2	0.668			I^2	0.621		
tau^2	0.0048			tau^2	0.0028		
C	2109.8			C	2884.3		

Random effects ES is 85.2% [78.3; 92.0] for robotic surgery and 78.3% [72.4; 84.2] for laparoscopic surgery.

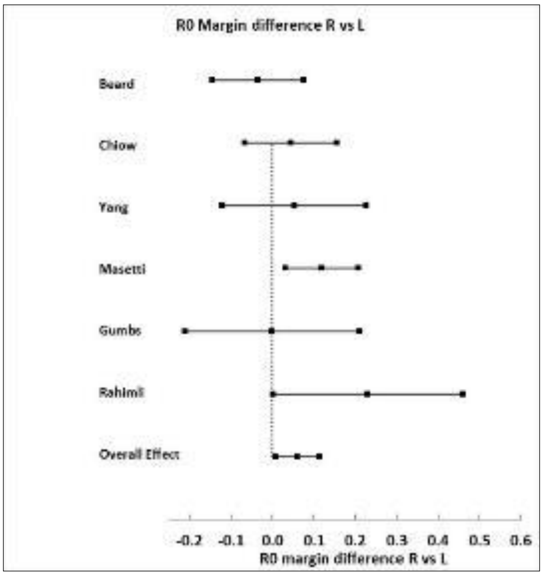
The proportion difference between robotic and laparoscopic R0 rate is 6.07% with 95% CI [0.8%; 11.3%], showing a CI that does not contain zero, indicating a significant difference in R0 rate between both methods.

Figure 8: Forest plot for R0 rate



Forest plot for R0 rate for the Robotic and Laparoscopic surgery method. The vertical dotted lines give the overall R0 rate for Robotic (black) and Laparoscopic (red) Surgery method.

Figure 9: Forest plot for difference between robotic and laparoscopic



Forest plot for the R0 rate difference between robotic and laparoscopic Surgery. The overall effect is 6.07% with 95% CI [0.83; 11.30], meaning that zero is not contained in the 95% CI, indicating a statistical significant difference between both methods for R0 rate (Robotic has higher R0 rate than laparoscopic).

3.3.8 Mean estimated blood loss and transfusion need

The mean estimated blood loss (EBL) ranged from 100 mL to 550 mL.

There is a clear trend showing smaller blood loss in the studies with a lower major resection rate (Sucandy *et al;* Masetti *et al;* Shapera *et al…*) and more blood loss vice versa (Guilianotti *et al;* Rahimli *et al;* Birgin *et al.*)

Multiple cohort studies found significant results: Chiow *et al*. reported significantly less median EBL in the robotic group after PSM: R 200 mL (100–400) vs. L 450 mL (200–900) (p=< 0.001). The lower EBL was tied to a significantly lower rate of intraoperative transfusion: R 10.2% vs. L 23.9% (p=0,014). Yang *et al*. had similar findings: R 200 mL (100–500) vs. L 350 mL (200–725) (p=0,019). Both groups studied complex liver resections (right posterior sectionectomy and right anterior sectionectomy / central hepatectomy respectively). It could be that in these complex and hard to reach liver segments the advantages of robotic technique are more noticeable compared to the laparoscopic technique. This could be the reason blood loss in these studies was lower. To add to this also Succandy *et al*. had significantly less EBL robotic versus open: R 200 mL(239 ± 183.6) vs. O 300 mL(491 ± 577.1) (p = 0.01) and Gumbs *et al*. had significantly less EBL comparing robotic to laparoscopic techniques: R 223.7 ± 255.7 vs. L 777.7 ± 827.1 (p= 0,04)

The RCT of Li *et al*. revealed significantly less EBL (R 203,11 mL vs. L 356,0 mLv(p=<0,001)) and the need for less average volume of intraoperative transfusion (R 608,31 mL ± 117,08 vs. L 656,21 mL ± 103,75 (p=0.018).

Meta-analysis of the data of blood loss

We found 5 studies with the required data (n, mean, stdev). We performed a fixed and random effects meta-analysis.

Table 14 Meta-analysis of the data of blood loss, study inclusion and effect size

	Robotic			**Laparoscopic**					
Study	n	Mean	SD	n	Mean	SD	Pooled SD	ES	SE
Sucandy	42	239	183.6	42	491	577.1	428.23	-0.59	0.21
Gumbs	36	223.7	255.7	462	777.7	827.1	800.27	-0.69	0.17
Chiow	96	200	224	244	450	519	455.39	-0.55	0.12
Yang	48	200	299	185	350	392	374.70	-0.40	0.16
Shapera	42	265	303.8	14	372	629.1	406.64	-0.26	0.30

Meta-analysis of the robotic data:

Table 15 Meta-analysis of the data of blood loss: effect analysis, robotic

Fixed effect	**Random effects**
Overall Mean = 219.4 (SE = 14.6) 95% CI[190.81, 247.96] z-score = 15.05 (p = 0.0000) Homogeneity analysis Q = 2.36 df = 4 p = 0.6701 I^2 = 0% (Low heterogeneity)	Random Effect = -479.1 Overall Mean = 206.2 (SE = 5.9) 95% CI[194.57, 217.84] z-score = 34.74 (p = 0.0000)

Meta-analysis of the laparoscopic data:

Table 16 Meta-analysis of the data of blood loss: effect analysis, laparoscopic

Fixed effect	**Random effects**
Overall Mean = 485.0 (SE = 18.4) 95% CI[448.90, 521.08] z-score = 26.34 (p = 0.0000) Homogeneity analysis Q = 81.39 df = 4 p = 0.0000 I^2 = 95.1% (High heterogeneity)	Random Effect = 38361.5 Overall Mean = 497.9 (SE = 94.3) 95% CI[313.13, 682.61] z-score = 5.28 (p = 0.0000)

Comparing the two groups:

Table 17 Meta-analysis of the data of blood loss: effect analysis, comparing laparoscopic and robotic

Fixed effect	Random effects
Overall Mean = -0.53 (SE = 0.07) 95% CI[-0.678, -0.385] z-score = 7.13 (p = 0.0000) Homogeneity analysis Q = 2.43 df = 5 p = 0.6567 I^2 = -64.4% (Low heterogeneity)	Random Effect = -0.01 Overall Mean = -0.54 (SE = 0.04) 95% CI[-0.61, -0.47] z-score = 14.60 (p = 0.0000)

3.3.9 Conclusion

There is a significant difference in blood loss between robotic and laparoscopic surgery (standardized mean difference is -0.54 [-0.61; -0.47], p < 0.0001), with significantly less blood loss in the robotic group (overall random effect mean = 206.2 [194.6; 207.8] mL) vs. the laparoscopic group (overall random effect mean = 497.9 [313.1; 682.6] mL). There is large heterogeneity in the laparoscopic group, but not in the robotic group.

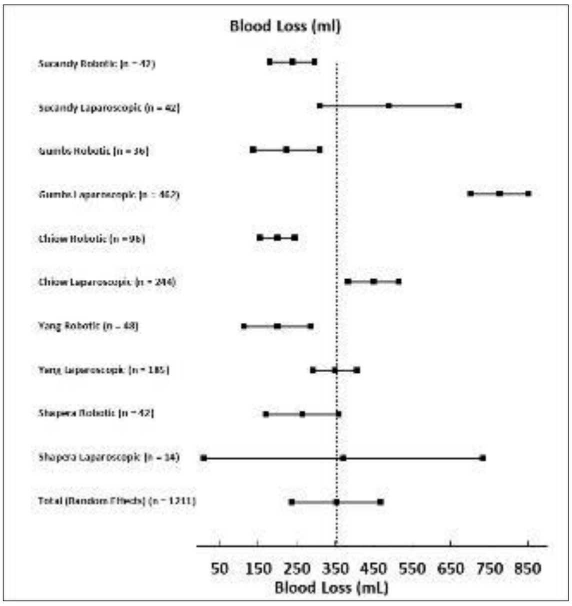


Figure 10 Forest plot for blood loss

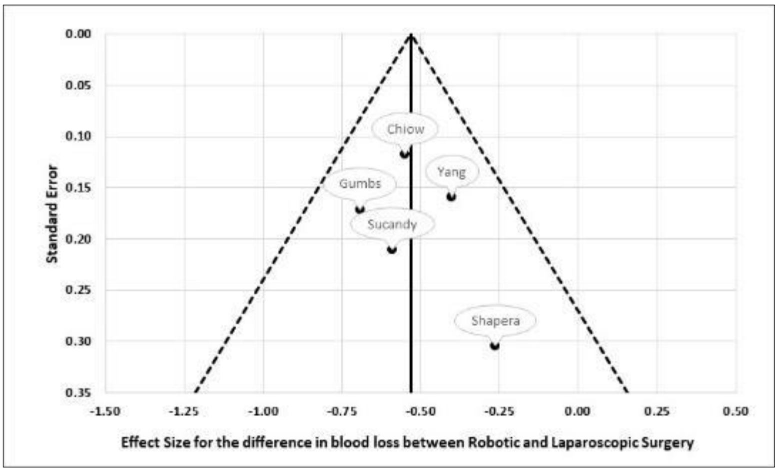


Figure 11 Funnel plot for blood loss

Although the overall fixed effect mean value is shifted away from zero (indicating significantly less blood loss in robotic surgery) all studies are within the funnel indicating no publication bias.

3.4 Hospitalisation characteristics

Supplemental Table 4 shows hospitalisation data.

Mean length of hospital stay (LOS) ranged between 4 to 9 days. Studies at the high end of the range all had a higher major resection rate.

Only 2 studies showed significant results: Shapera *et al*. and Succandy *et al.* showed significantly shorter hospital and ICU durations (comparing open vs. robotic surgery). Few other studies reported ICU stay: typically between 0-2 days.

3.5 Mortality

Supplemental Table 5 shows mortality figures.

Intraoperative mortality (if disclosed) was 0% in all studies.

There was great variability in the manner in which survival was reported.

In hospital mortality was very low in all studies: ranging between 0-3%. The 30 day mortality and 90-day mortality were also very low in all studies: ranging between 0-2.5% and 0-5%, respectively.

Mean overall survival (OS) was reported in a couple of studies: Rahimli *et al*. (R 29 months versus, L 47 months (p = 0.733)), Shapera *et al.* (R 65,8 months vs. O 42,1 months).

Few studies published long-term results: e.g. Guerra *et al*. (1 year overall survival (OS): 90.4% and 3 year OS: 66.1%), Rahimli *et al*. (1 year OS: R 100% vs. L 70% and 3 year OS: R 44,4% vs. L 60%).

Li *et al*. reported 1, 2 and 3 year mortality: R 85,25% vs. L 78,69%, R 70,49% vs. L 65,57%, and R 50,82% vs. L 42,62%, respectively.

5 year OS ranged in between 60 -75%: reported by Beard *et al*.: R 61% versus L 60% and Gumbs *et al.* R 75% versus L 68%.

None of the cohort studies or the RCT reported statistical differences between techniques.

3.6 Recurrence

Supplemental Table 6 shows recurrence figures.

There was great variability in the manner in which survival was reported.

Few studies presented 1 year recurrence free survival (RFS): on average this seemed about 80-90% (e.g. Guerra *et al*. (83,5%), Guadagni *et al*. (89.5%), Rahimli *et al*. (R 44,4% vs. L 54,9%)). Rahimli *et al.* had much lower rates, no explanation was found, only that they had a relatively low population size (R 12 versus L 13) and they had a 41% major resection rate.

Reported 3 year RFS seemed around 30%, remaining stable until a 5 year RFS of also around 30%.

None of the cohort studies reported significant differences.

4 Discussion

This literature review shows that robotic surgery for CRLM significantly decreases the need for Pringle manoeuvre (no difference in duration of clamping is found). There seems to be a lower rate of conversion to open surgery. Furthermore the complication rate is decreased statistically.

The effect on operating times is disputed. There seems to be an increase in the rate of R0 resections, and an increase the resection margin. Multiple cohort studies found significant lower blood loss and lower need for transfusion. The data show a no discrepancies in the data when comparing mortality and recurrence data in laparoscopic versus robotic liver resections, but no actual meta-analysis was possible due to the heterogeneity of reporting of the data.

Other review papers have come to similar conclusions: Kamarajah *et al*. compared robotic and laparoscopic liver resections and found significantly less blood loss, but longer operation times.[11] Garritano *et al*. also came across data that was too heterogeneous to calculate a meta-analysis.[12] Rocca *et al*. researched robotic surgery specifically for CRLM: overall they found a mean EBL of 309.4mL, operative time of 250 min, mean LOS of 7.89 days, overall postoperative mortality of 0.4%, complication rate of 37% (8% serious complications, Clavien-Dindo grade III-IV), 3 year OS of 55.25% and 3 year RFS of 37%.[13] These data align with ours.

The RCT of Li *et al*. tried to explain why robotic surgery can give even better results over laparoscopic surgery: they measured stress responses of the body 3 days after robotic or laparoscopic liver resections. The robotic group showed significantly less cortisol, norepinephrine and glucose, showed significantly less Resting Energy Expenditure (REE), showed a significantly smaller dip in serum CD3+ and CD4+ levels. This might indicate that robotic surgery induces less of a stress response, a smaller metabolic jump and less immunologic impairment.[14]

We found a study of Shapera *et al*. that showed that the use of robotic surgery improved the resection margin, they also grouped the cases by margin and found better survival with wider margins.[15]A systematic review and meta-analysis of Rahimli *et al*. studying all kinds of liver pathology found that there were no significant differences between R1 resections comparing robotic and laparoscopic surgery (5.3% versus 8.6%, p=0.18).[16]

We found no mention of cost in the studies we found. There are worries in the literature whether the cost of robotic surgery is higher than standard of care. Sham *et al*. studied this and found that the perioperative cost was higher, but the postoperative costs were lower resulting in lower total hospital cost after robotic versus laparoscopic hepatectomy ($14,754 vs. $18,998; p = 0.001)[17] It is to be expected that cost will drop after the patent of the robots expires and more brands enter the marketplace.

This study has multiple limitations: all the steps of the search and gathering of data were performed by 1 researcher. There was a plethora of heterogeneity in the available data: different patient populations, different interventions, different ways of recording data (e.g. mortality and recurrence data), because of this no meta-analysis of the data was possible for some of the studied subjects. Most of the studies found are retrospective, most of them case-series of cohort studies. These all had propensity matched analyses performed on them to unify the groups and therefore reduce bias. We could only find 1 RCT at the current time. Given that robotic surgery is a new field of surgery, 2 problems occur. There is very little long-term follow-up concerning the use of robotic surgery. Furthermore during the expansion of this technique experience with surgeons will grow, this learning curve will cloud the initial data.

5 Conclusion

In this systematic review with meta-analysis of the data we compare laparoscopic versus robotic surgery for the resection of colorectal liver metastases. Our literature search yielded 16 studies. We compiled the data and performed an meta-analysis where possible: this showed a large heterogeneity in the operation times, without a significant difference. De meta-analysis shows significantly lower conversion rate with robotic surgery compared to laparoscopic. Also there was a significantly higher R0 resection in the robotic group. There was significantly less blood loss in the robotic group. A lot of the data was to heterogeneous to compile. There was significantly less usage of the Pringle manoeuvre in one individual study, but no meta-analysis was possible. Also the data on complication rate, length of stay, mortality, and recurrence couldn't be compiled.

We conclude that robotic surgery is promising in the therapy of CRLM. In the future there is need for RCT to compare robotic versus laparoscopic liver surgery for CRLM. Furthermore a longer follow-up is needed.

Abbreviations

ALPPS	Associating Liver Partition and Portal vein Ligation for Staged hepatectomy
APR	abdominal perineal resections
AR	anterior resection

CD	Clavien-Dindo
CH	central hepatectomy
CI	confidence interval
CRC	colorectal cancer
CRLM	colorectal liver metastases
df	degrees of freedom
EBL	estimated blood loss
ES	effect size
HCC	hepatocellular carcinoma
I^2	measure of heterogeneity
IC	intensive care
L	laparoscopic
LAR	low-anterior resection
LHC	left hemicolectomy
LLR	laparoscopic liver resection
MeSH	medical subject headings
MILS	minimally invasive liver surgery
mo	months
Mort	Mortality
OS	Overall survival
OS	overall survival
PSM	propensity score matching
Q	Cochran's heterogeneity statistic
R	robotic
RAS	right anterior sectionectomy
RCT	randomized controlled trial
RFA	radiofrequency ablation
RFS	recurrence free survival
RHC	right hemicolectomy
RLR	robotic liver resection
RPS	right posterior sectionectomy
SCLR	robotic simultaneous colorectal and liver resection
SE	standard error
SSI	surgical site infection

Compliance with ethical standards

Disclosure of conflict of interest

None of the authors have any financial or non-financial support to disclose. None of the authors have any conflicting interests to disclose.

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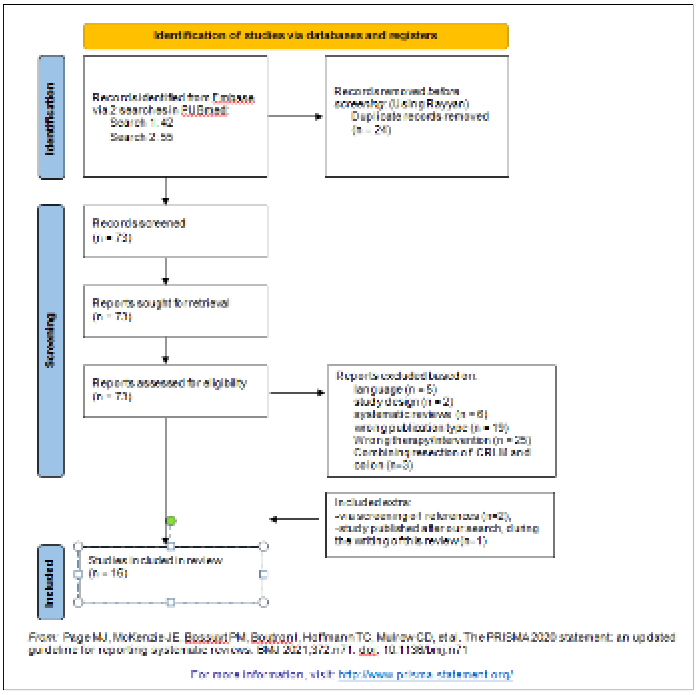
Supplemental figures and tables



Supplemental Figure 1 Flow chart of the search, inclusion and exclusion

Supplemental Table 1 Overview of included studies

study (author)	year	study type	number of included patients
Guilianotti[18]	2011	multicenter case series	24 right hepatectomies: 11 CRLM, *4 nonCRLM, (4 hemangioma, 2 adenoma, 1 hepatocellular carcinoma 1 hepatoblastoma, 1 biliary hamartoma)*
Croner[19]	2015	single center case series	9; 4 CRLM *1 intrahepatic cholangiocellular carcinoma, 4 hepatocellular carcinoma,*
Guerra[20]	2019	case series	59 patients undergoing 82 resections
Beard[21]	2020	retrospective propensity matched cohort	RLR 115, LLR 514, matching cohorts of 115 each
Guadagni[22]	2020	single center case series	20
Araujo[23]	2020	single center case series	5; robotic resection of posterosuperior (PS) segments
Rahimli[24]	2020	retrospective cohort	25; 13 LLS vs 12RLS
Chiow[25]	2021	multicenter retrospective cohort analysis + propensity score matching	340 right posterior sectionectomy (RPS), -96 robotic PRS, -244 laparoscopic RPS,

			after PSM: 88 R-RPS vs 88 L-RPS, *(RLM: 21/88 (23.9%) each)*
Yang[26]	2022	multicenter retrospective analysis + propensity scorematching	233;right anterior sectionectomy (RAS) and central hepatectomy (CH), -48 robotic -185 laparoscopic, -after PSM: 2 groups of 40; *(CRLM 7/40 (R) and 6/40 (L))*
Shapera[27]	2022	single center prospective cohort	56; -Robot 42, -Open 14
Sucandy[28]	2022	prospectieve cohort + propensity score matching	48; -42 robot -42 open major hepatectomy, *(CRLM both 6/42)*
Masetti[29]	2022	multicenter retrospective cohort	1030; -77 R-MILS -953 L-MILS
Brigin[30]	2022	case series	10; mesohepatectomy: -2 robotic -8 laparoscopic *(3 CRLM; -5 HCC, 1 cholangioCa, 1 hydatid cyst)*
Li[14]	2022	RCT	122, -61 robotic -61 laparoscopic
Gumbs[31]	2022	multicenter retrospective cohort + propensity matching between open and laparoscopic, and robotic surgery	1064; -open 566, -lap 462 -robot 36 after matching lap vs robot: 21 vs 21
Gumbs[10]	2022	multicenter retrospective cohort + propensity matching between open and laparoscopic, and robotic surgery	1064; -open 566, -lap 462 -robot 36 after matching lap vs robot: 21 vs 21

CH: central hepatectomy, CRLM: colorectal liver metastasis, LLR: laparoscopic liver resection, MILS: minimally invasive liver surgery, PSM: propensity score matching, RAS: right anterior sectionectomy, RCT: randomized controlled trial, RLR: robotic liver resection, RPS: right posterior sectionectomy, SCLR: robotic simultaneous colorectal and liver resection

Supplemental Table 2 Patient and tumor characteristics -only general tumor size was given, not specific for CRLM

study (author)	sex (% male)	Age (years)	tumor size (mm)
Guilianotti[18]	10/24 (41%) (overall)*	median 55 (range, 21-84) (overall)*	-
Croner[19]		mean 63 (range 45–71) (overall)*	-
Guerra[20]	37%	median age 64 (range 43–84)	27 mm (range 4–130)

Beard[21]	R 66,1% vs L 65,2% (after PSM)	R 61 vs L 61 (after PSM)	Before PSM: R 25 vs L 24
Guadagni[22]	13/20 (65%)	66 ± 12 years	mean nodule size 30 mm ± 18 mm
Araujo[23]	0/5 (0%)	median 59 (range 33 - 68)	mean size of the lesions was 23 mm (±10 mm)
Rahimli[24]	R 2/12 (50%) vs L 10/13(76,9%) (p=0,226)	R 63,5 (SD 11,3) vs L 62,1 (SD 126), (p=0,770)	R 42mm (SD1,6) vs L 28 (SD 1,9)
Chiow[25]	after PSM: R 59/88 (67.0%) vs L 61 (54–69) (p=0,413) (overall)*	after PSM: R 60 (51–69) vs L 61 (54–69) (p=0,410) (overall)*	-
Yang[26]	after PSM: R 32 of 40 (80.0) vs L 33 of 40 (82.5) (p=0.901) (overall)*	after PSM: R 62 (55–68) vs L 62 (54–72) (p=0.630) (overall)*	-
Shapera[27]	R 26/42 (62%), O 6/14 (43%) (p=0,23)	R 63 (61 ± 13.5) vs O 72 (69 ± 12.3) (p=0,06)	R 20 mm (30 ± 19) vs O 30 mm (44 ± 21) (p=0,10)
Sucandy[28]	R 19 M/23 W vs O 19 M/23 W (overall)*	R 61(61 ± 12.5) vs O 64(64 ± 12.1) (overall)*	-
Masetti[29]	L-MILS 62,7% vs R-MILS 64,9%	L-MILS 65,6 vs R-MILS 65,0	main lesion >50mm L-MILS 111/953 (11.6%) vs R-MILS 8/77(10,4%)
Brigin[30]	M:F 9:1 (overall)*	66 (overall)*	-
Li[14]	R72,13% vs L 62,30%	R 57,13 vs L 57,51	R 29 vs L 27
Gumbs[31]+ Gumbs[10]	after PSM: R 8 (38.1) vs L 10 (47.6)	after PSM: R 60.6 ± 10.9 vs L 62.4 ± 10.6	After PSM: R 26 ± 12 vs L 28 ± 13

*if only overall data was given, not specified by indivuduals groups

Supplemental Table 3 Operation characteristic

study (author)	major resection	Mean operation time (OT) (min)	Pringle / time	rate of conversion	Complications *	R0, margin	blood loss ** (mL)	Transfusion need
Guilianotti[18]	100%, right hemihepatectomy	337 ± 65 min (range, 240-480 min)	0%	1/24 (4,2%), because adhesion of de CRLM to the vena cava	6 patients (25%): 2 cases of transitory liver failure, 1 pleural effusion, 1 bile leak -> percutaneous drainage, 1 fluid collection, 1 deep vein thrombosis	-	mean (SD) EBL was 457 ±401 mL (range, 100-2000 mL)	3/24 (12,5%)
Croner[19]	0%, 6 left lateral liver resection, 2 single segment resection, 1 liver ablation	312 min (range 115–458 min)	-	0%	1/9 (11%), Small bowel fistula -> conservative treatment	100%, mean margin 0,6 cm (range 0.1–1.5 cm)	mean EBL 251 mL (range 10–650 ml)	no transfusion
Guerra[20]	4/59, (6,7%): 82 liver resections 35 wedge resections, 26 segmentectomies/ subsegmentectomies, 17 bisegmentectomies, 1 left hepatectomy, 3 right hepatectomy.	median OT was 210 min (range 50–600)	18/59 (30%)	7/59 (12%)	16/59 (27%), 13 (22%) class I-II, 3 (5%) class III-IV: 1 case of postoperative bile leak -> radiological and endoscopic treatment, 2 cases of heart failure, -> IC management	92%	Median EBL 200 mL (0–1500)	-
Beard[21]	After PSM: R 15,7 % vs L 18,3%	Before PSM: R 272 ± 115 vs L 253 ± 118 (p=0,12),	-	Before PSM: R 5,2 % vs L 12,1% (p=0,03)	R 31,3 % vs L 27,8 % (p=0,66), CD> 3: R 10,4 % vs L 14,8 % (p=0,3)	R0 R 73,7% L 77,4 %, (p=0,18)	-	before PSM: R 11/115 (9,6%) vs L 166/514 (32,5%) (p=0.001)
Guadagni[22]	0%; all cases were wedge resections	198.5 ± 98.0 min	-	0%	25%, 1 CD I, 4 CD II	100%	mean EBL 250 mL	2/20 (10%) patients needed 2 units of blood

							(range: 200–300 ml);	
Araujo[23]	0%, all nonanatomical segmentectomy	294 ± 69 min	0%	-	1/5 (20%): pulmonary embolism		mean EBL 160 mL (±89 mL)	no transfusion
Rahimli[24]	R 5/12 (41,7%) vs L 3/13(23.1%) (p=0,411)	R 342,0 (± 101,4) vs L 200,0 (± 116,8) (p=0,004)	0% both groups	-	R 3/12 (25%) vs L 2/13(15,4%) (p=0,645); robot: 1 conservatively enterocutaneous fistula from the small intestine, 1 conservatively lymphocele, 1 postoperative bile leak after right hemihepatectomy -> drainage. lap: 2 SSI	R 12/12 (100%) vs L 10/13 (76,9%) (p=0,220)	R 450 ± 278,0 vs L 412,3 ± 529,1 (p=0,225)	R 2/12 (16,7%) vs L 2/13(15,4) (p=1,000)
Chiow[25]	0% all right posterior sectionectomy (RPS)	after PSM: R 272 (range 196–397) vs L 310 (range 243–405) (p=0,132)	after PSM: R 55/88 (62.5%) vs L 56/88 (63.6%) (p=0.882)	after PSM: R 2/88 (2.3%) vs L 10/88 (11.4%) (p=0.016)	after PSM: R 22/88 (25.0%) vs L 18/88 (20.5%) (p=0.451); CD>II: R 2/88 (2.3%) vs L 7/88 (8.0%) (p=0,158)	after PSM: Close/involved margins (<=1mm): R 11/81 (13.6%) vs L 15/83 (18.1%) (p=0.655)	after PSM: median EBL: R 200 (100–400) vs L 450 (200–900) (p=< 0.001)	intra-operative transfusion: R 9/88 (10.2%) vs L 21/88 (23.9%) (p=0,014)
Yang[26]	after PSM: central hepatectomy: R 10/40 (25.0%) vs L 8/40 (20.0%) (p=0.800)	after PSM: R 339 (228–505) vs L 298 (210–358) (p=0.133)	after PSM: R 21/40 (52.5%) vs L 32/40 (80.0%) (p=0.131); time R 61 min (50–84) vs L 63 (53–	after PSM: R 2/40 (5.0%) vs L 2/40 (5.0%) (p=1,0)	after PSM: R 8/40 (20.0%) vs L 14/40 (35.0%) (p=0.201); CD >II: R 2/40 (5.0%) vs L 2/40 (5.0%) (p=1,0)	after PSM: Close/involved margins (<=1mm): R 6/38 (15.8%) vs L 8/38 (21.1%) (p=0,791)	after PSM: R 200 (100–500) vs L 350 (200–725) (p=0,019)	-

			98) (p=0.853)					
Shapera[27]	R 26%, Formal right 14%, Formal left 12%, Non-anatomic 74%, vs O 21% Formal right 21% Formal left 0% Non-anatomic 79% (p=0,72)	R 375 min (358 ± 130.5) vs O 269 min (279 ± 113.3) (p=0,05)	-	0%	R 5/42 (11%) CD II(4), CD IVa(1); (2 Ileus, 1 pneumonia, 1 acute kidney injury, 1 metabolic acidosis) vs O 3/14 (21%) CDII(1), CD IIIa(1), CD V(1); (1 Multisystem organ failure (death), 1 clostridium difficile infection, 1 pleural effusion) (p=0,15)	100%	R 200 (265 ± 303.8) vs O 200 (372 ± 629.1) (p=0,4)	-
Sucandy[28]	100% both groups	R 293 (302 ± 131.5) vs O 280 (300 ± 115.6), (p=0,7)	-	-	R: 2/42 (4.7%) 2 Ileus vs O: 7/42 (16.7%) 2 UTI, 1 Anastomotic leak, 1 Sepsis,2 Respiratory failure, 1 systemic Inflammatory response syndrome (p = 0.26)	(R0/R1/R2) R 33/6/0 vs O 38/3/0, (p = 0.43), margin (cm) R 1(1 ± 1.3) vs O 1(1 ± 0.9) (p = 0.30)	R 200 (239 ± 183.6) vs O 300 (491 ± 577.1) (p = 0.01)	-
Masetti[29]	L-MILS 8,5% vs R-MILS 11,7%, (p=0.341)	L-MILS 270min vs R-MILS 270min; (p=0,708)	Overall: L-MILS 55.5% vs R-MILS 27.3%, (p < 0.001) inter-mitten:	L-MILS 11,1% vs R-MILS 5,2%, (p= 0,100)	L-MILS 20% vs R-MILS 19.5%,(p=0,906)	R1 rate L-MILS 28.8% vs R-MLS 16.9%, (p = 0.025), margin L-MILS 0.3 cm (0–0.10), vs R-MILS 0.8 cm (0.1–1) (p < 0.001)	L-MILS 150mL (50–300)vs R-MILS 100mL (85–200); (p= 0,399)	L-MILS 4% vs R-MILS 6.5% (p= 0.213)

			L-MILS 54.5% vs R-MILS 27.3%, (p = 0.001)					
Brigin[30]	100%	428 min (range 293–512 min)	60%; 61 min (range 91–120 min)	10%	20% post-op liver failure; 10% post-op haemorrhage; 10%, intra-abdominal fluid collection -> antibiotics; 10% perforation of transverse colon after extensive lysis of adhesions	100%, -	550 mL (range 413–850 mL)	-
Li[14]	-	R 156,34 vs L 184,18 (p=<0,001)	Time: R 39,39 min vs L 40,52 min (p=0,210)	R 0% vs L 0%	R 3,28% vs L 13,11%, (p=0.048) R 1 pleural effsion 1 ileus L 1 incision infection, 1 abdominal hemorrage, 2 pleural infusion, 2 bile leakage, 2 ileus	-	R 203,11mL vs L 356,0 mL (p=<0,001)	Average intraoperative blood transfusion (ml): R 608,31 ± 117,08 vs L 656,21 ± 103,75 (p=0.018)
Gumbs[31]	After PSM: R 3 (14.3%) vs L 5 (23.8) (p= 0.7)	After PSM: R 271.5 ± 106.3 vs L 209.7 ± 116.0 (p=0,1)	After PSM: R 0(0%) vs L 4(19%) (p=0,1)	After PSM: R 1 (4.3%) vs L 4 (17.4%) (p=0,3)	After PSM: CD ≥ grade 3: R 0 vs L 1 (4,8%), (p=1)	After PSM: R 18 (85,7%) vs L 18 (85,7%) (p=1)	After PSM: R 223.7 ± 255.7 vs L 777.7 ± 827.1 (p= 0,04)	-

*: classes mentioned regard Clavien-Dindo scores; **: EBL: estimated blood loss; Abbreviations: ALPPS: Associating Liver Partition and Portal vein Ligation for Staged hepatectomy, APR: abdominal perineal resections, AR: anterior resection, CD: Clavien-Dindo , L: laparoscopic, LAR: low-anterior resection, LHC: left hemicolectomy, IC: intensive care, PSM: propensity score matching, R: robotic, RHC: right hemicolectomy, SSI: surgical site infection

Supplemental Table 4 Length of hospital and ICU stay

study (author)	Length of ICU stay (days)	Length of hospital stay (days)
Guilianotti[18]	-	overall mean (SD) hospital length of stay was 9.0 (3.0) days (range, 3-23 days)
Croner[19]	-	mean hospital stay of the patients was 6 days (range 3–10 days)
Guerra[20]	-	median postoperative hospital stay was 6.7 ± 6.2 days
Beard[21]	IC need % (not days), R 14,8% vs L 18,3% (p=0.59)	-
Guadagni[22]	-	mean 4.7 ± 1.8 days
Araujo[23]	median time 2 (range 1-4) days, with only one case spending more than 2 days at the ICU	median hospitalization time 4 days (range 3-7 days)
Rahimli[24]	-	R9,3 (SD 4,2) vs L 8,5 (3,4) (p=0,852)
Chiow[25]	-	after PSM: R 6 (5–8) vs L 6 (5–9) (p=0.845)
Yang[26]	-	after PSM: R 7days (6–11) vs L 8 (5–10) (p=0.853)
Shapera[27]	R 0 (0 ± 0.8) vs O 0 (1 ± 2.0) (p= 0,01)	R 4 days (5 ± 2.6) vs O 7 (7 ± 4.0) (p=0.04)
Sucandy[28]	R 1(1 ± 0) vs O 2(3 ± 2.0) (p = 0.0001)	R 4(4 ± 3.3) vs O 6(6 ± 2.7), (p = 0.003)
Masetti[29]	-	5 vs 5, (p=0,654)
Brigin[30]	-	7 days (5-12)
Li[14]	-	-
Gumbs[31]	-	After PSM: R 5.1 ± 3.3 vs L 4.7 ± 3.1 (p=0,7)
Gumbs[10]	-	-

Supplemental Table 5 Mortality

study (author)	intraoperative mort.	General mortality	1year mort.	2year mort.	3year mort.	4year mort.	5 year mort.
Guilianotti[18]	0%	over a mean follow-up of 36 mo (range: 1-57 mo): 2/11 (18%) mortality	-	-	-	-	-
Croner[19]	0%	over a mean follow up of 12 mo (range: 1–21 mo): no mortality	-	-	-	-	-
Dwyer[32]	0%	30 day: 0%, At a mean follow-	-	-	-	-	-

		up of 19 mo, 1/6 (16%) cancer related death at 26 mo					
Guerra[20]	0%	over a mean follow-up of 19.5 ± 15 mo: 9 deaths (15%)	1y OS: 90,4%	-	3y OS 66,1%	-	-
Navarro[33]	0%	30 day mortality 0%; mean OS 75,2 months	-	-	-	-	-
Beard[21]	-	-	-	-	-	-	5y OS R 61% L 60% (p = 0.78)
Guadagni[22]	0%	over a mean follow-up of 22.5 ± 19.5 mo: no mortality	-	-	-	-	-
Araujo[23]	-	-	-	-	-	-	-
Rahimli[24]	-	median OS: R 29 mo (SE 9.0, 95% CI 11.4–46.6) vs L 47 mo (SE 18.7, 95% CI 10.4–83.6) (p = 0.733)	1 y OS: R 100% vs L 70% (no p)		3year OS: R 44,4% vs L 60% (no p)	-	-
Ceccarelli[34]	0%	median OS is 27.5 mo, end of study 7/28 died (25%)	-	-	-	-	-
Chiow[25]	0%	After PSM: 30-days: 0% both groups; 90-days R 0/88 vs L 1/88 (1,1%) (p=0,316)	-	-	-	-	-
Yang[26]	-	After PSM in hospital mort: R 1/40 (2.5%) vs L 0/40 (0%) (p=0.317) 30 days: R 1/40 (2.5%) vs L 0/40 (0%) (p=0.317); 90-days R 2/40 (5.0%) vs L 1/40 (2.5%) (p=0,157)	-	-	-	-	-

Shapera[27]	0%	in hospital mort: R 0 vs O 1/56 (1.7%) (p=1,0); 30-day: R 1/56 (1.7%) vs O 1/56 (1.7%) (p=0,44); 60-day: R 2/56 (3.6%) vs O 1/56 (1.7%) (p=1,0), 90-day: R 2/56 (3.6%) vs O 1/56 (1.7%) (p=1,0); estimated mean OS: R 65,8 mo vs O 42,1 mo, (p=0,4)	-	-	-	-	-
Sucandy[28]	-	after PSM: In-hospital mort: R 1/42 (2.3%) vs O 3/42 (7.1%) (p = 0.30), Kaplan Meier OS: no statistical difference (p=0,74)	-	-	-	-	-
Masetti[29]	L 0% vs R 0%	L 0,3% vs R 0% (p=0,972)	-	-	-	-	-
Brigin[30]	0%	30 day: 0%; 90 day: 0%	-	-	-	-	-
Li[14]	0% vs 0%	-	R 52/61 (85,25%) vs L 48/61 (78,69%) (p=0.347)	R 43/61 (70,49%) vs L 40/61 (65,57%) (p=0.493)	R 31/61 (50,82%) vs L 26/61 (42,62%) (p=0.327)	-	-
Gumbs[31]	-	After PSM: 30 day: no mortality in both groups 90 day: no mortality in both groups	-	-	-	-	-
Gumbs[10]	-	Median survival: RLR 46mo vs LLR 53mo (p = 0.908)	RLR 100% vs LLR 9,4%	-	RLR 75% vs LLR 68,1%	-	RLR 75% vs LLR 68,1%

Abbreviations: OS: Overall survival, mo: months, Mort. Mortality

Supplemental Table 6 Recurrence

study (author)	Overall recurrence free survival	1year recurrence free survival	3year recurrence free survival	5year recurrence free survival
Guilianotti[18]	mean follow-up of 36 months (range/ 1-57 months): 2/11 recurrence: 1 repeat CRLM, 1 bilateral pulmonary metastases	-	-	-
Croner[19]	mean follow up of 12months (range/ 1-21months): 2 recurrence: 1 case of cholangiocellular carcinoma, 1 case of CRLM	-	-	-
Guerra[20]	mean follow-up of 19.5 ± 15months: 16 recurrences (27%): 10 liver, 8 lung and 3 peritoneum recurrence;	83,5%	41,9%	-
Beard[21]	-	-	-	R 38% vs L 44% (p = 0.62)
Guadagni[22]	-	89.5%	35.8%	
Araujo[23]	-	-		
Rahimli[24]	medial overall RFS: R 11 months (SE 8.9, 95% CI 0–28.5) vs L 24 months (SE 12.2, 95 % CI 0.2–47.8) (p = 0.646);	R 44,4% vs L 54,9%	R 33,3% vs L 41,1%	-
Chiow[25]	-	-	-	-
Yang[26]	-	-	-	-
Shapera[27]	-	-		
Sucandy[28]	-	-	-	-
Masetti[29]	-	-	-	-
Brigin[30]	5months FU: no recurrence of CRLM specifically	-	-	-
Li[14]	-	-	-	-
Gumbs[31]	-	-	-	-
Gumbs[10]	-	RLR 80,8% vs LLR 73,5% (p=0,606)	RLR 34,6% vs LLR 45,3% (p=0,606)	RLR 34,6% vs LLR 22,7% (p=0,606)

Abbreviations: RFS: recurrence free survival