Long-term survival outcome of laparoscopic liver resection for hepatocellular carcinoma

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Abstract

Long-term survival is the most important outcome measurement of a curative oncological treatment. For hepatocellular carcinoma (HCC), the long-term disease-free and overall survival of laparoscopic liver resection (LLR) is shown to be non-inferior to the current standard of open liver resection (OLR). Some studies have reported a superior long-term oncological outcome in LLR when compared to OLR. It has been argued that improvement of visualization and instrumentation and reduced operative blood loss and perioperative blood transfusion may contribute to reduced risk of postoperative tumor recurrence. On the other hand, since most of the comparative studies of the oncological outcomes of LLR and OLR for HCC are non-randomized, it remained inconclusive as to whether LLR confers additional survival benefit compared to OLR. Despite the paucity of level 1 evidence, the practice of LLR for HCC has gained wide-spread acceptance due to the reproducible improvements in the perioperative outcomes and non-inferior oncological outcomes demonstrated by large-scaled, matched comparative studies. Meta-analyses of the outcomes of these studies by multiple systematic reviews have also returned noncontradictory conclusions. On the basis of a theoretical advantage of LLR over OLR in preventing tumor recurrence, the current review aims to dissect from the current meta-analyses and comparative studies any evidence of such superiority.

Key Words: Hepatocellular carcinoma; Laparoscopic hepatectomy; Liver resection; Long-term outcome; Overall survival; Disease-free survival

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Core Tip: Laparoscopic liver resection (LLR) resulted in better perioperative outcomes when compared with open liver resection. However, for long-term outcomes, the
Interestingly, such difference is less frequently observed in the more recent reports, consideration that is difficult to quantify for the performance of matching. The distance of tumor from the vital vasculature for LLR—an important preoperative predictor—has been published.

For HCC, predictors of long-term survival after resection of HCC include factors relating to tumor extent (size, number, macrovascular invasion), tumor biology (microvascular invasion, differentiation grading, serum alpha-fetoprotein level, etc.), ongoing liver damage and technical success of surgery (resection margin, perioperative transfusion, anatomical resection[4]). With accumulation of worldwide experience in LLR, reports to address such factors in the practice of LLR have also been published.

Prior to 2018, all studies comparing outcomes of LLR and OLR were non-randomized[5–14]. Selection bias has been a significant concern, especially in the earlier cohorts, in which patients included for LLR tended to have more favorable disease for oncologically adequate resections (tumor size, location, width of tumor-free margin)[5]. Later studies have attempted to ameliorate the impact of selection bias by matching of baseline patient characteristics such as demographic features, tumor status, degree of cirrhosis, American Society of Anesthesiologists (ASA) class, procedure types etc. in the LLR and OLR group. Nevertheless, a wider resection margin is often observed in the resected specimens from the LLR group. As acknowledged by Belli et al[5], this could be due to the selection of tumors with greater distance of tumor from the vital vasculature for LLR—an important preoperative consideration that is difficult to quantify for the performance of matching. Interestingly, such difference is less frequently observed in the more recent reports,

**COMPARATIVE STUDIES**

It appears to be true that LLR has a non-inferior oncological outcome compared to OLR for HCC—a finding supported by multiple comparative studies, despite the presence of heterogeneity of treatment effect among the studies.

In general terms, the survival outcome of a cancer treatment program is a function of the disease spectrum of patients included and the adequacy of treatment delivery. For HCC, predictors of long-term survival after resection of HCC include factors relating to tumor extent (size, number, macrovascular invasion), tumor biology (microvascular invasion, differentiation grading, serum alpha-fetoprotein level, etc.), ongoing liver damage and technical success of surgery (resection margin, perioperative transfusion, anatomical resection[4]). With accumulation of worldwide experience in LLR, reports to address such factors in the practice of LLR have also been published.

Prior to 2018, all studies comparing outcomes of LLR and OLR were non-randomized[5–14]. Selection bias has been a significant concern, especially in the earlier cohorts, in which patients included for LLR tended to have more favorable disease for oncologically adequate resections (tumor size, location, width of tumor-free margin)[5]. Later studies have attempted to ameliorate the impact of selection bias by matching of baseline patient characteristics such as demographic features, tumor status, degree of cirrhosis, American Society of Anesthesiologists (ASA) class, procedure types etc. in the LLR and OLR group. Nevertheless, a wider resection margin is often observed in the resected specimens from the LLR group. As acknowledged by Belli et al[5], this could be due to the selection of tumors with greater distance of tumor from the vital vasculature for LLR—an important preoperative consideration that is difficult to quantify for the performance of matching. Interestingly, such difference is less frequently observed in the more recent reports,
probably due to the more liberal inclusion of patients for LLR with accumulation of technical experience (Tables 1 and 2).

After 2018, 21 comparative studies of LLR vs OLR for HCC can be identified[15-35] (Tables 1-4). Only one was a randomized controlled trial[18], while the rest were non-randomized. Studies with special focus of patient population included major hepatectomy in six, minor hepatectomy in one, cirrhosis in four, small tumors in two, multiple tumors in one and elderly patients in one. All but three of the non-randomized studies adopt propensity score-matching (Table 3). Sporadic differences between the LLR and OLR group were still identifiable in some reports, including: Tumor size in the studies by Li et al[25] and Tsai et al[23]; prevalence of cirrhosis in the study by Guro et al[17]; ASA class in the study by Yoon et al[29] and procedure magnitude in the study by Tsai et al[23].

The only randomized controlled trial was performed in Egypt[18]. They included patients with Child’s A solitary HCC equal to or less than 5 cm, located in the peripheral segments of the liver II-VI, at a distance from the line of transection, hepatic hilum, and the vena cava and treatable by limited resection (< 3 segments). Exclusion criteria were tumors close to the portal pedicle or hepatic veins, located in segments I, VII and VIII, an ASA score exceeding 3, a decompensated cirrhosis (Child B or C), esophageal varices grade > 2, and a platelet count < 80 × 10^3/L, and patients with previous upper abdominal surgeries. On sample size calculation, a total of 42 patients was required in the study to detect a change of mean hospital stay duration from 8.5 d among patients subjected to OLR to 4.0 d among patients subjected to LRR. The estimated sample size was made assuming 95% confidence interval (CI) and 80% power of study. Eventually, they recruited a total of 50 patients with 25 patients in each group. The LLR group achieved similar disease-free survival compared to the OLR group (P = 0.849). The 1- and 3-year disease-free survival was 88% and 59%, and 84% and 54% for the LLR and OLR groups, respectively. However, survival outcomes were secondary endpoints, with such a small sample size, these survival outcomes were subject to type II error.

 META-ANALYSES

Due to the paucity of randomized controlled trial, meta-analyses of non-randomized comparative studies with low risk of bias represented the highest level of evidence until recently. The majority of meta-analyses were published after the Morioka consensus, although evidence of four meta-analyses have been adopted by the consensus[2]. A summary of the findings of these four meta-analyses is provided in the systematic review of Morise et al[36] – there is no difference in disease-free and overall survival with LLR or OLR for HCC, a result with low impact of statistical heterogeneity. This is probably because the studies included four meta-analysis of oncological outcome published between the release of Louisville and Morioka consensus statements, when LLRs were mainly performed for resection of lesions in the antero-lateral segments[37-41].

Following the Morioka consensus meeting in 2014, there was a bloom of publications reporting experience worldwide on the practice of LLR for the treatment of
While level 1 evidence was lacking at that time, strong recommendations were made regarding the non-inferiority of both minor and major LLR in short-term postoperative and long-term outcomes, as the relative benefits of LLR over OLR had appeared to be reproducible in the larger-scaled, propensity score-matched non-randomized comparative studies conducted worldwide[2]. Yet in 2018, the very “concern of selection bias” that is inherent to non-randomized studies was then resolved with the publication of the OSLO-COMET trial, which convincingly showed that LLR has superior perioperative outcomes, non-inferior oncological safety, similar cost and better gain of life quality to OLR for the treatment of colorectal cancer liver metastases[42].

### Table 1 Summary of comparative studies: Operative outcomes

| Ref. | Blood loss in mL /transfused % | Resection margin in mm | R0 resection rate % |
|------|-------------------------------|------------------------|---------------------|
|      | LLR | OLR | P      | LLR | OLR | P | LLR | OLR | P |
| Belli et al[5] | 297 | 580 | < 0.001 | 100 | 93.6 | 0.057 |
| Tranchart et al[6] | 364.3 | 723.7 | < 0.0001 | 10.4 | 10.6 | NS |
| Lee et al[7] | 150 | 240 | NS | 1.8 | 1.05 | 0.016 |
| Ahn et al[8] | 350 | 355 | NS | 17 | 13 | NS |
| Memeo et al[9] | 200 | 200 | NS | 10 | 6 | 0.02 |
| Lee et al[10] | 300 | 700 | 0.004 | 13 | 10 | 0.25 |
| Yoon et al[11] | 3.4% | 7.5% | 0.04 | 2.03 | 1.12 | 0.01 |
| Xiao et al[12] | 272 | 450 | 0.001 | 100 | 98 | NS |
| Sposito et al[13] | NS | 6 | 5 | NS | 98 | 98 | NS |
| Cheung et al[14] | 100 | 300 | < 0.001 | 100 | 93.1 | NS |
| Ryu et al[15] | 95 | 83 | NS |
| Rhu et al[16] | 13% | 2% | NS | 13 | 12 | NS |
| Guro et al[17] | 1543 | 1248 | 97.6 | 94.6 | NS |
| El-Gendi et al[18] | 230 | 250 | NS | 100 | 100 | NS |
| Inose et al[19] | 100 | 380 | < 0.0001 | 7 | 5 | NS |
| Kim et al[20] | 300 | 250 | NS | 13 | 15 | NS |
| Deng et al[21] | 150 | 380 | < 0.001 | 98 | 90 | NS |
| Wu et al[22] | 150 | 250 | NS |
| Tsai et al[23] | 363 | 839 | < 0.001 | 5 | 5.2 | NS |
| Di Sandro et al[24] | 150 | 200 | 0.007 | 5 | 5 | NS |
| Li et al[25] | 328 | 396 | NS |
| Kim et al[26] | 152 | 245 | 8.5 | 8.4 | NS |
| Chen et al[27] | 300 | 500 | < 0.1 | 97 | 100 | NS |
| Untereiner et al[28] | 150 | 250 | NS | 91 | 85 | NS |
| Yoon et al[29] | 226 | 251 | 98 | 98 |
| Peng et al[30] | 200 | 300 | NS | 100 | 100 | NS |
| Yamamoto et al[31] | 87 | 223 | 3 | 3 | NS |
| Lee et al[32] | 19% | 28% | 9 | 16.5 | NS |
| Navarro et al[33] | 234 | 454 | 0.021 | 100 | 100 | NS |
| Delvecchio et al[34] | 13% | 25% | NS | 95 | 87 | NS |
| Ho et al[35] | 500 | 725 | NS | 5 | 3 | 0.043 |

LLR: Laparoscopic liver resection; NS: Statistically not significant; OLR: Open liver resection.
| Ref.            | Difference between study groups                                               | ICG, % | Child A/B/C, % | Tumor size in cm | Microvascular invasion, % |
|----------------|------------------------------------------------------------------------------|--------|----------------|------------------|---------------------------|
|                |                                                                               | LLR    | OLR            | LLR +/- SD/95%CI  | OLR +/- SD/95%CI           | LLR     | OLR     |
| Belli et al[5] | Tumor size, AFP level, margin width                                          | 91/9/0 | 93.6/6.4/0     | 3.8 +/-1.3       | 6 +/- 2.3                 | 37      | 39.2    |
| Tranchart et al [6] |                                                  |        |                |                  |                           |         |         |
| Lee et al[7]   | Cirrhosis, previous abdominal surgery, margin width                           |        |                |                  |                           |         |         |
| Ahn et al[8]   |                                                                               | 14.5   | 13.1           | 2.6 +/-1.5       | 2.8 +/- 1.2               | 15.7    | 19.6    |
| Memeo et al[9] | Margin width                                                                  | 98/2/0 | 96/4/0         | 3.2 +/- 1.1      | 3.7 +/- 0.1               | 0.1-15  | 56.6    |
| Lee et al[10]  | Margin width                                                                  | 97.6/2.4/0 | 97.6/2.4/0 | 5.4 +/- 1.16    | 4.4 +/- 2.14             | 52.5    | 43.5    |
| Yoon et al[11] | Margin width                                                                  | 12.1   | 12.4           | 2.87 +/- 0.749   | 3.04 +/- 0.249           | 0.2-4.9 |         |
| Xiao et al[12] |                                                                               | 95/5/0 | 96.5/3.5/0     | 4.22 +/- 2.05    | 4.3 +/- 1.49             |         |         |
| Sposito et al[13] |                                                   | 15     | 15             | 98/2/0           | 95/5/0                   | 56      | 37      |
| Cheung et al[14] |                                                   |        |                |                  |                           |         |         |
| Ryu et al[15]  |                                                                               | 11.9   | 14             | 3.9 +/- 1.17     | 4.9 +/- 1.145            | 30      | 40      |
| Rhu et al[16]  |                                                                               | 37.7/0 | 37.1/0/0       | 3.1 +/- 5.7      | 3.1 +/- 1.7              | 56.6    | 58.8    |
| Guro et al[17] | Cirrhosis, tumor size                                                          | 95/2.4/2.4 | 88/9.9/7.2 | 4.1 +/- 2.4      | 6.3 +/- 3.8              |         |         |
| El-Gendi et al [18] |                                               | 100/0/0 | 100/0/0       | 3.3 +/- 0.57    | 3.4 +/- 0.59            | 60      | 68      |
| Inoue et al[19] |                                                                               | 89/11/0 | 100/0/0       | 2.5              | 2.6                       | 12      | 13      |
| Kim et al[20]  |                                                                               | 9.3    | 8              | 2.8              | 2.8                       | 25      | 23      |
| Deng et al[21] | Procedure type                                                                | 100/0/0 | 100/0/0       | 2.5              | 2.8                       | 10.2    | 16.6    |
| Wu et al[22]   |                                                                               | 3.5    | 3.5            | 0.9-12.5         | 3.5                       | 38.4    | 41.9    |
| Tsai et al[23] | Procedure magnitude, tumor size                                               | 93/7/0 | 98/2/0        | 3.9 +/- 2.6      | 7.2 +/- 5.3              |         |         |
| Di Sandro et al[24] |                                             | 87/13/0 | 84/16/0       | 2.5              | 2.3                      | 2.5     | 3.3     |
| Li et al[25]   | Tumor size                                                                    | 4      | 4              | +/- 2           | 5.7                       | 17      | 30      |
| Kim et al[26]  |                                                                               | 10.4   | 12.8           | 3 +/-2.1         | 3.2 +/- 3.14             | 22.2    | 27.8    |
| Chen et al[27] |                                                                               | 6.9    | 6.9           | 7.3 +/-3.4       | 7.6 +/- 4.2              | 37      | 32      |
| Untereiner et al[28] |                                         | 64/0/0 | 73/0/3        | 3                | 2.1-4.9                  | 3       | 2.3-5   |
| Yoon et al[29] | ASA class, medical disease                                                     | 13.6   | 14            | 66.8/0.0/0      | 65.4/0.0/0               | 14.3    | 15.7    |
| Peng et al[30] |                                                                               | 94/6/0 | 91/9/0        | 4.8              | 2.8-5                     | 30      | 30      |
| Yarnamoto et al[31] |                                           | 88/22/0 | 84/16/0   | 1.7              | 1.2-4.2                  | 2       | 0.7-9.9 |
| Lee et al[32]  |                                                                               | 90/10/0 | 91/9/0        | 2.5              | 7.1-4.5                  | 2.6     | 1.1-14.5 |
| Navarro et al [33] |                                                   | 3.5    | 3.5           | 8.5              | 3.3                       | 8.1     | 51.2    |
| Delvecchio et al[34] |                                             | 97/3/0 | 98/2/0        | 4                | 3.0-16                   | 7       | 1.5-14  |
| Ho et al[35]   | Hepatitis C carrier status                                                     | 100/0/0 | 92/8/0       | 3.5              | 2.5                       | 4       | 3-5     |

Table 2 Summary of comparative studies: Baseline clinical-pathological features of both treatment groups
DISCUSSION

The question is now left with HCC though, as obvious difference exists between patients with HCC and colorectal liver metastases. As a majority of HCC patients have underlying cirrhosis, liver decompensation and oncological outcomes are HCC-specific outcomes to consider for LLR. Since the first published meta-analysis on the long-term outcomes of LLR for HCC in 2011[43], there have been about 20 meta-analyses on the topic published, 15 of which were published after 2017. Ciria et al.[44] published a meta-analysis in 2018 that included 28 non-randomized comparative studies with low risk of bias. In contrast to those included by meta-analyses in the “pre-Morioka era”, the studies reviewed by Ciria et al.[44] encompassed a much wider spectrum of disease in clinical practice: Three were on major liver resection, twenty-two on minor liver resection, five on Child-Pugh class A cirrhosis, sixteen on solitary tumors and three on unstratified operable patients. For the disease-free and overall survival, meta-analyses could only be performed for studies featuring cirrhotic patients, minor hepatectomy and solitary tumors but not for major hepatectomy. The pooled relative effect of LLR to OLR showed an odds ratio (OR) in favor of LLR for 1-year disease-free survival in patients with minor hepatectomy ($I^2 = 66\%$; OR = 0.133; 95\%CI: 0.001–0.265; $P < 0.048$). For patients with Child’s A cirrhosis and solitary tumor, no significant relative benefit or harm were found for the 1-, 3- and 5-year disease-free and overall survivals. For patients with major hepatectomy, meta-analysis was not performed due to lack of data. Moderate to high heterogeneity ($I^2 = 17\%–66\%$) was noted among the studies of laparoscopic minor hepatectomy. The highest heterogeneity is among the five studies for compilation of 1-year disease-free survival ($I^2 = 66\%$), and the biggest discrepancy of mean relative effect lies between the study by Cheung et al.[14] and Kobayashi et al.[45]. This is probably related to the inclusion of recurrent HCC and hybrid or hand-assisted laparoscopic procedures in the study population in the study by Kobayashi et al.[45]. Moreover, two studies with the greatest tendency to favor LLR came from the same center[14,46] with overlapping study period and study population (left lateral sectionectomy in 25% and 100% of studied population), giving rise to the concern of overestimation of the relative benefit of LLR.

The lack of long-term survival data specifically for laparoscopic major hepatectomies in the above meta-analysis was addressed by a recent meta-analysis by Wang et al.[47] that included nine studies of the patient population. Interestingly, a favorable result for LLR was again noted in 1-year disease-free survival ($I^2 = 0\%$; OR = 1.55; 95\%CI: 1.04–2.31; $P = 0.03$), but not in disease-free or overall survival in another analyzed timespan. Again, one of the constituent studies for the pooled analysis of 1-year disease-free survival is notably out-standing with regard to the tumor recurrence rate in the OLR group, and an apparent reason that is also acknowledged by the author was the significantly bigger tumor size (6.3 ± 3.8 vs. 4.1 ± 2.4 cm; $P = 0.000$) included in the OLR arm[17].

In contrast to most of the meta-analyses showing non-significant difference in overall survival, Jiang et al.[48] meta-analyzed studies of cirrhotic patients and found significant relative benefit of LLR in 1-, 3- and 5-year overall survival and 1-year disease-free survival, with only moderate issue of heterogeneity ($I^2 = 36\%–39\%$). The apparent reason for the discrepancy between that study and Ciria et al.[44]’s sub-group analyses for cirrhotic patients is that the two reviews included different sets of studies for analyses. The rationale behind study selection is difficult to judge, but Jiang et al.[48] excluded the study because the data were not retrievable, which could potentially lead to bias. On the other hand, Ciria et al.[44] only included three studies for the analyses of long-term outcome of cirrhotic patients, which may not be powerful enough to detect small effects.
| Ref.            | Year | Number of patients | Matching | Study population     | Procedure               |
|----------------|------|--------------------|----------|----------------------|-------------------------|
|                | LLR  | OLR                |          |                      |                         |
| Belli et al[5] | 2009 | 54                 | 125      | No                   | < 5 cm, anterolaterally located |
| Tranchart et al[6] | 2010 | 42                 | 42       | Yes                  |                         |
| Lee et al[7]   | 2011 | 33                 | 50       | Yes                  | Minor resection         |
| Ahn et al[8]   | 2014 | 51                 | 51       | Yes                  | Solitary                |
| Memeo et al[9] | 2014 | 45                 | 45       | Yes                  | Cirrhosis               |
| Lee et al[10]  | 2015 | 43                 | 86       | Yes                  |                         |
| Yoon et al[11] | 2015 | 58                 | 174      | Yes                  | < 5 cm                  |
| Xiao et al[12] | 2015 | 41                 | 86       | No                   | Posterolateral          |
| Sposito et al[13] | 2016 | 43                 | 43       | Yes                  | Cirrhosis               |
| Cheung et al[14] | 2016 | 24                 | 29       | Yes                  | Left lateral sectionectomy |
| Ryu et al[15]  | 2018 | 40                 | 30       | No                   | Anatomical resection    |
| Rhu et al[16]  | 2018 | 58                 | 133      | Yes                  | Right posterior sectionectomy |
| Garro et al[17] | 2018 | 67                 | 110      | No                   | Major hepatectomy       |
| El-Gendi et al[18] | 2018 | 25                 | 25       | Randomized           | < 5 cm                  |
| Inoue et al[19] | 2018 | 61                 | 175      | Yes                  | Child A                 |
| Kim et al[20]  | 2018 | 37                 | 37       | Yes                  | Left hepatectomy        |
| Deng et al[21] | 2018 | 157                | 157      | Yes                  |                         |
| Wu et al[22]   | 2019 | 86                 | 86       | Yes                  | Cirrhosis               |
| Tsai et al[23] | 2019 | 153                | 160      | Yes                  |                         |
| Di Sandro et al[24] | 2018 | 75                 | 75       | Yes                  | Cirrhosis               |
| Li et al[25]   | 2019 | 41                 | 307      | Yes                  | Mesohepatectomy         |
| Kim et al[26]  | 2018 | 18                 | 36       | Yes                  | Central                 |
| Chen et al[27] | 2019 | 38                 | 38       | Yes                  | Right hepatectomy       |
| Untereiner et al[28] | 2019 | 33                 | 33       | Yes                  |                         |
| Yoon et al[29] | 2020 | 217                | 434      | Yes                  |                         |
| Peng et al[30] | 2019 | 33                 | 33       | Yes                  | Multiple                |
| Yamamoto et al[31] | 2020 | 58                 | 197      | Yes                  | Cirrhosis               |
| Lee et al[32]  | 2021 | 58                 | 110      | Yes                  |                         |
| Navarro et al[33] | 2021 | 106                | 299      | Yes                  | Major hepatectomy       |
| Delvecchio et al[34] | 2021 | 38                 | 84       | Yes                  | Elderly                 |
| Ho et al[35]   | 2021 | 45                 | 90       | Yes                  |                         |

LLR: Laparoscopic liver resection; OLR: Open liver resection.

Operative stratification, diverting away of selected patient population to liver transplantation, improved surgical techniques to minimize blood transfusion requirement even in the OLR group, a better medical control of background liver disease activity, etc., might all be possible to ameliorate any marginal survival advantage of LLR over OLR.
| Ref.          | 1-year OS, % | 3-year OS, % | 5-year OS, % | 1-year DFS, % | 3-year DFS, % | 5-year DFS, % |
|--------------|-------------|-------------|-------------|-------------|-------------|-------------|
|              | LLR | OLR | P | LLR | OLR | P | LLR | OLR | P | LLR | OLR | P | LLR | OLR | P |
| Belli et al[5] | 94 | 85 | NS | 67 | 73 | NS | 78 | 79 | NS | 52 | 52 | NS |
| Tranchart et al[6] | 93.1 | 81.8 | NS | 74.4 | 73 | NS | 81.6 | 70.2 | NS | 60.9 | 54.3 | NS | 45.6 | 37.2 | NS |
| Lee et al[7] | 86.9 | 98 | NS | 81.8 | 80.6 | NS | 78.8 | 76.1 | NS | 51 | 55.9 | NS | 45.3 | 55.9 | NS |
| Ahn et al[8] | 80.1 | 85.7 | NS | 59 | 44 | NS | 60 | 88 | NS | 63 | 62 | NS | 60.9 | 54.3 | NS |
| Memeo et al[9] | 88 | 63 | NS | 59 | 44 | NS | 60 | 88 | NS | 63 | 62 | NS | 60.9 | 54.3 | NS |
| Lee et al[10] | 95.3 | 93.9 | NS | 89.7 | 89.5 | NS | 60.5 | 81.5 | NS | 60.3 | 66.7 | NS | 60.3 | 58.6 | NS |
| Yoon et al[11] | 95 | 98 | NS | 86 | 84 | NS | 82 | 88 | NS | 63 | 62 | NS | 60.9 | 54.3 | NS |
| Xiao et al[12] | 95.1 | 89.5 | NS | 78 | 76.7 | NS | 87.8 | 82.6 | NS | 70.7 | 68.6 | NS | 60.9 | 54.3 | NS |
| Sposito et al[13] | 75 | 79 | NS | 38 | 46 | NS | 41 | 44 | NS | 25 | 11 | NS | 60.9 | 54.3 | NS |
| Cheung et al[14] | 100 | 93 | NS | 85.6 | 84.1 | NS | 69.1 | 77.6 | NS | 95 | 69.2 | NS | 72.8 | 61.5 | NS |
| Ryu et al[15] | 89.9 | 89.9 | NS | 84.7 | 68 | NS | 70.9 | 63.1 | NS | 79.5 | 72.4 | NS | 58 | 56.1 | NS |
| Rhu et al[16] | 96.8 | 96.8 | NS | 94.5 | 94.5 | NS | 94.5 | 94.5 | NS | 77.8 | 77.8 | NS | 68.3 | 68.3 | NS |
| Guro et al[17] | 77.3 | 60.2 | NS | 75 | 79 | NS | 38 | 46 | NS | 41 | 44 | NS | 25 | 11 | NS |
| El-Gendi et al[18] | 88 | 84 | NS | 58.7 | 54 | NS |
| Inoue et al[19] | 97.8 | 87.9 | NS | 78.8 | 70.6 | NS | 83.8 | 75 | NS | 57.5 | 54.8 | NS | 79.6 | 91.1 | NS |
| Kim et al[20] | 93.9 | 93.8 | NS | 72.6 | 73.4 | NS | 77 | 79.6 | 91.1 | NS | 79.6 | 91.1 | NS |
| Deng et al[21] | 96.2 | 96.8 | NS | 81.4 | 73.5 | NS | 69.8 | 62.8 | NS | 75.6 | 69.8 | NS | 60.5 | 53.5 | NS |
| Wu et al[22] | 93 | 81.4 | NS | 81.4 | 73.5 | NS | 69.8 | 62.8 | NS | 75.6 | 69.8 | NS | 60.5 | 53.5 | NS |
| Tsai et al[23] | 90.3 | 85 | 0.002 | 82.9 | 63.6 | 0.002 | 78.1 | 57.6 | 0.002 | 72.9 | 60.8 | NS | 49.2 | 43 | NS |
| Di Sandro et al[24] | 68 | 76 | NS | 38 | 46 | NS | 41 | 44 | NS | 25 | 11 | NS |
| Li et al[25] | 96.3 | 95.3 | NS | 68.4 | 90.5 | NS | 84 | 87.2 | NS | 36 | 59.7 | NS |
| Kim et al[26] | 94.4 | 100 | NS | 94.4 | 92.9 | NS | 93.8 | 76.5 | NS | 56.3 | 41.3 | NS |
| Chen et al[27] | 69.8 | 74 | NS | 51.6 | 57.8 | NS |
| Untereiner et al[28] | 78 | 79 | NS | 72 | 58.6 | NS |
| Yoon et al[29] | 98.1 | 93.8 | NS | 87 | 90.8 | NS | 81 | 85.3 | NS | 62 | 64.7 | NS | 49.1 | 56.2 | NS |
Two observations were made from the current review of meta-analyses and recent comparative studies. Firstly, the non-inferiority in long-term oncological outcome of LLR vs OLR has been repeatedly shown by pooling of various combinations of studies, patient populations and LLR procedures. This should partially address the concern of selection bias, as such outcomes are now widely reproducible worldwide. Secondly, while the studies on LLR for HCC are increasingly heterogenous in terms of disease spectrum included and type of procedure performed, the study methodologies adopted are more and more standardized. Thus, future publications are likely to reflect the advanced practice of difficult procedures of high-volume centers, while the diffusion of the technique among lower-volume centers may be underrepresented in the medical literature. This echoes the need of a broad-based prospectively collected registry database for the purpose of ongoing consolidation of evidence and monitoring of the development of LLR.

**CONCLUSION**

The current review has updated the findings on long-term oncological outcomes of LLR for HCC. Depicted is also a phenomenal development of LLR, in which there is a widespread adoption of an innovative invasive technique long before the availability of level 1 evidence. Complicated surgical procedures, heterogenous diseases presentation and a long learning curve are the main hurdles of conducting a widely generalizable randomized controlled trial. Given the heterogeneity of the data and the lack of randomized controlled trial, it may still be too bold to prioritize LLR in long-term survival, its advantage being more evident in the perioperative period. A broad-based prospective LLR registry keeping safety and oncological outcomes in check may be a better solution to the need of stronger evidence in the field.
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