Accepted Manuscript

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PII: S0090-4295(17)30989-5
DOI: https://doi.org/doi:10.1016/j.urology.2017.09.008
Reference: URL 20666

To appear in: *Urology*

Received date: 30-7-2017
Accepted date: 14-9-2017

Please cite this article as: Bhavan Prasad Rai, Patrick Jones, Campbell Tait, Ramachandran Amitharaj, Raj Gowda, Aftab Bhatti, Jim Adshead, Bhaskar Somani, Is Cryotherapy a Genuine Rival to Robotic Assisted Partial Nephrectomy in the Management of Suspected Renal Malignancy? a Systematic Review and Meta-Analysis, *Urology* (2017), https://doi.org/doi:10.1016/j.urology.2017.09.008.

Title Page

Is Cryotherapy a genuine rival to Robotic Assisted Partial Nephrectomy in the management of suspected renal malignancy? A Systematic Review and Meta-Analysis

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Keywords:
Robotic Assisted Partial Nephrectomy; Cryotherapy; Recurrence Rates; Ablation; RFA

Acknowledgements: Nil

Conflicts of interest: None

Support/ Financial Disclosures: None

Abstract word count: 99

Main Manuscript Word Count: 2712

Abstract

We systematically reviewed world literature and compare oncological outcomes, morbidity, renal function and peri-operative outcome between cryotherapy (CA) and robotic assisted partial nephrectomy (RAPN) for suspected renal malignancy. There was a statistically significant difference for “recurrence rates” between the 2 techniques, favouring the RAPN cohort. There was no statistically significant difference in overall and ≥Clavien 3a complication rates between the 2 techniques. The quality of evidence for recurrence rates, overall complication and ≥Clavien 3a were ‘moderate’, ‘low’ and ‘very low’ respectively on GRADE approach. If a nephron sparing approach is indicated, RAPN should be the approach of choice.

Main Manuscript

Introduction:

A plethora of options are available in the management of renal masses suspected to be a malignancy. The eventual option opted for by a clinician is influenced by factors such as tumour complexity, patient factors and expertise. An ideal technique would ensure preservation of renal function and minimal morbidly without oncological compromise in a patient’s lifetime. Ablative treatment options and partial nephrectomy (PN) offer definitive treatment with an ability to retain nephrons. In contemporary literature, the most commonly described ablative options for renal masses are radiofrequency ablation (RFA) and cryotherapy (CA)(1). The reported complications between these two approaches are similar (1). However, incomplete

ablation rates are significantly lower in CA compared to RFA (1). In a recent survey, laparoscopic cryotherapy (LCA) and percutaneous cryotherapy (PCA) were reported to be the most common ablative procedures offered by academic institutions in the USA (2). It has generally been perceived that ablative options such as CA carry a superior safety profile compared with PN. However, with the advent of robotic technology and improved renorraphy techniques, the morbidity associated with robotic assisted partial nephrectomy (RAPN) has been significantly reduced when compared to its open and conventional laparoscopic counterparts (3-5). How RAPN compares with CA from an oncological and functional perspective is of significant interest.

The objective of our study was to systematically review the world literature comparing oncological outcomes, morbidity, renal function and peri-operative outcome between CA and RAPN for renal masses suspected to be a malignancy.

Materials and Methods

Evidence acquisition

Criteria for considering studies for this review

All randomised trials and observational studies comparing Laparoscopic (LCA) and Percutaneous Cryotherapy (PCA) with Robotic Assisted Partial Nephrectomy (RAPN) were considered for potential inclusion.

Search strategy and study selection

The systematic review was performed in accordance with The Cochrane Guidelines and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)(6). Bibliographic databases searched were MEDLINE (2000- September

2016), EMBASE (2000- September 2016), Cochrane Central Register of Controlled Trials - CENTRAL (in The Cochrane Library - Issue 1, 2016), CINAHL (2000- September 2016). As well as hand-searching Individual urological journals, citation and reference lists were also evaluated. The search was conducted on 24/03/2017. All studies comparing CA with RAPN were evaluated. No language restrictions were applied. Animal studies were excluded. Search terms included (not limited to): “renal cell carcinoma”, “RCC”, “small renal mass”, “SRM”, “cryotherapy”, “cryoablation”, “robotic”, “partial nephrectomy”. Boolean operators (AND, OR) were employed to augment the search process. Medical Subjecting Heading (MeSH) phrases included: [Nephrectomy] [Cryotherapy], [Carcinoma, Renal Cell], [Neoplasm, Kidney], [Robotics] and [Robotic Surgical Procedures].

Primary Outcomes Measures:

1. Oncological-Recurrence Rates and Survival Outcomes
2. Overall Complication Rates
3. Clavien 3 and Higher Complication Rates

Secondary Outcomes Measures:

1. Renal function Outcomes
2. Peri-operative Outcomes

Quality Assessment of Evidence

Study quality was assessed according to the method of randomisation, allocation concealment, adequate descriptions of numbers, and reasons for patient withdrawal, as detailed in the *Cochrane Handbook for Systematic Review of Interventions* (7).

The GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) (GRADE) was used to rate the quality of evidence.(7)

Data extraction and analysis

Two reviewers (BR, PJ) independently identified all studies that appeared to fit the inclusion criteria for full review. Disagreement was resolved by consensus. Comparable data from each study was combined in a meta-analysis where possible. A Mantel-Haenszel Chi-square test was used for continuous data and expressed as the mean difference (MD) with 95% CI and for dichotomous data an Inverse Variance was used and expressed as odds ratio (OR) or risk ratio (RR) with 95% CI. P value was considered significant if <0.05. Heterogeneity was analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (6). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity respectively. A fixed-effect model was used unless statistically significant high heterogeneity (I^2 > 75% was considered as significantly high heterogeneity) existed between studies. A random-effects model was employed if heterogeneity existed. If the data available was deemed not suitable for a meta-analysis, it has been described in a narrative fashion.

Results

Systematic Review

Literature Search:

Supplementary Figure 1. shows the PRISMA chart. A total of 241 potential publications were identified. 11 studies were shortlisted for comprehensive evaluation. Of these, 4 were included in the review (8-11). All four studies were

observational comparative studies. Three of these studies were from the USA (8,10,11) and one was from the UK (9). All the 4 studies were relatively recent studies, published between 2012 and 2017. Two studies compared LCA and PCA with RAPN (8,11). 2 studies compared LCA with RAPN (9,10). 3 studies had prospectively maintained their databases (8-10). Caputo et al performed a matched pair analysis (8). Guillotrreoua et al analysed their prospectively maintained database retrospectively (10). Tangho et al was only study that was a purely retrospective study (11). Weiberg et al's study, a nationwide inpatient sample from the USA, was excluded from this review (12). The authors were concerned that this database may contain data from the 3 American studies (8,10,11) in this review and therefore inclusion of this database may potentially corrupt the results accordingly.

Demographics: (See Table 1)

A total of 581 and 521 patient underwent CA and RAPN respectively. Caputo et al was a matched pair analysis and hence Age, ASA, Nephrometry score, Tumour size, renal function and BMI were equally matched for the two cohorts. Two studies (8,11) reported the age in median (Range/IQR) and two studies reported age in in mean (SD)(9,10). Hence a cumulative analysis wasn't possible. In the 3 non-matched studies the RAPN cohort was younger than the CA cohort with a larger tumour size, which was statistically significant in each individual study (8-11). 3 studies reported Nephrometry scores (8,9,11). Two studies used the RENAL nephrometry score (8,9). Tanagho et al weren't clear what Nephrometry score was employed (11). Three studies had clear data on on pre-operative creatinine and eGFR (8-11). All four studies reported on BMI which was similar for both cohorts (8-11).

Primary Outcomes:

Oncological Outcomes:

Guillotreau et al had the longest oncological follow up for CA with median (IQR) of 44.5 months (SD18.8)(10). Tanagho et al had the longest oncological follow up for RAPN with a mean (SD) of 21.9 months (SD18.8)(10). Caputo et al defined tumor recurrence in the CA group "as an area of new contrast enhancement within a previous completely treated ablation site appearing >3 months after treatment" (8). Guillotreau et al defined local recurrence for LCA "as an enlarging or persistently enhanced treatment site on follow-up imaging"(10). The other 2 studies did not provide definitions of local recurrence.

Recurrence Rates: (Supplementary Figure 2)

All the studies reported on recurrence rates and were suitable for meta-analysis (8-11). A fixed model was used for analysis as there was a low degree of heterogeneity across all sub-groups (I^2=0% for LCA +PCA vs. RAPN, I^2=16% for LCA vs. RAPN, I^2=0% for Overall). There was a statistically significant difference in recurrence rates between the 2 techniques, favouring the RAPN cohort:

LCA+PCA vs. RAPN: Risk Ratio (M-H, Random, 95% CI), 28.02 [4.10, 191.57], p-0.0007

LCA vs. RAPN: Risk Ratio (M-H, Random, 95% CI), 20.36[2.69, 154.11], p-0.004

Overall: Risk Ratio (M-H, Random, 95% CI), 23.39[5.70, 96.05], p<0.00001

Survival Outcomes (Table 2): 2 studies reported on survival outcomes (8,11). Both studies reported superior Disease Free Survival with RAPN. Caputo et al on matched pair analysis reported no difference in cancer specific and overall mortality between the 2 cohorts at a median follow-up of 30.1 months and 13 months for CA

and RAPN respectively (8). In the study by Tanagho et al, there was a trend towards better 5 year cancer specific and overall survival in the RAPN cohort, however it did not achieve statistical significance (11).

Overall Complication Rates: (Supplementary Figure 3)

All the studies reported on overall complication and were suitable for meta-analysis. A fixed model was used for analysis as there was a low degree of heterogeneity across all sub-groups (I^2=16% for LCA +PCA vs. RAPN, I^2=0% for LCA vs. RAPN, I^2=0% for Overall). There was no statistically significant difference in overall complication rates across all subgroups between the two techniques:

LCA+PCA vs. RAPN: Risk Ratio (M-H, Random, 95% CI), 0.78 [0.50, 1.22], p-0.28

LCA vs. RAPN: Risk Ratio (M-H, Random, 95% CI), 0.89 [0.63, 1.25], p-0.49

Overall: Risk Ratio (M-H, Random, 95% CI), 0.84 [0.64, 1.11], p-0.22

≥Clavien 3a Complication Rates: (Supplementary Figure 4)

All four studies reported on ≥Clavien 3a complication rates and were suitable for a meta-analysis. A fixed model was used for analysis as there was a low degree of heterogeneity across all sub-groups (I^2=0% across all sub-groups). There was no statistically significant difference in ≥Clavien 3a complication rates across all subgroups between the 2 techniques:

LCA+PCA vs. RAPN: Risk Ratio (M-H, Random, 95% CI), 0.45[0.16, 1.32], p-0.15

LCA vs. RAPN: Risk Ratio (M-H, Random, 95% CI), 1.03[0.40, 2.61], p-0.96

Overall: Risk Ratio (M-H, Random, 95% CI), 0.71[0.36, 1.41], p-0.33

Secondary Outcomes:

Renal function and peri-operative outcomes (Table 3): The data reporting on renal function outcomes were heterogeneous. Regardless of reporting method employed, there was a general trend towards better preservation of renal function with the CA cohort. However, this achieved statistical significance only in 1 study (11). The other peri-operative outcomes are summarised in Supplementary Table 1.

Quality Assessment of studies (Supplementary Table 2)

Caputo et all was judged to have a low risk of selection bias as a matched pair analysis was performed (8). The remaining 3 studies had a high risk of selection of bias as they were non-matched, non-randomised studies. All studies had a high risk of both performance and detection bias.

Adopting the GRADE approach, the quality of evidence for recurrence rates, overall complication and Clavien 3 or higher complications were 'moderate', 'low' and 'very low' respectively.

Discussion:

This meta-analysis highlights that RAPN has significantly lower recurrences rates when compared to CA. The overall recurrence rates in the CA cohort was 11.5% compared to 0% in the RAPN cohort. Our findings are consistent with results published by Klatte et al (13). The authors performed a meta-analysis of 13 studies comparing both conventional laparoscopic and robotic assisted partial nephrectomy with LCA and reported local recurrence rates of 9.4% vs. 0.4% (13). These results impress upon the perception that extirpative surgical techniques such as PN, regardless of approach employed, ensure a far superior clearance of the local tumour in comparison with ablative counterparts. Whilst it is reassuring that none of the studies reported any local recurrence in the RAPN cohort, the authors would

recommend viewing this result with caution. The impact on oncological survival and mortality outcomes aren't as profound though, as most studies suggested equivalent outcomes between the 2 cohorts. Whether this reflects the relatively short oncological follow-up and confounding factors such as tumour size, tumour complexity of the studies in this review, remains unclear. A further issue with evaluating survival outcomes for CA is the inability to determine with confidence, benign disease in patients who had pre-ablative negative renal biopsies for malignancy. A recent non-comparative multi-institutional retrospective study from the European Registry for Renal Cryoablation (EuRECA) did report fairly acceptable survival outcomes in 514 patients who underwent LCA for T1a renal masses (14). They reported a 5- and 10-year Disease Free Survival of 90.4% (95% CI 95.2–98.4) and 80.0% (95% CI 67.2–88.3) respectively. The 5-and 10-year Overall Survival in this study was 83.2% (95% CI 78.2–87.2) and 64.4% (95% CI 44.5–78.7), respectively. A total of 5 patients (1.0%) died due to renal cancer-specific causes after a medium (IQR) follow-up of 36.4 months (11.6–36.7).

One would intuitively assume that both PCA and LCA are less morbid than PN. Interestingly, the outcomes of this review do not support this hypothesis. This review suggests equivalence between the 2 cohorts for both overall complication and major complication rates (≥3a or higher) on meta-analysis. However, the meta-analysis by Klatte et al reported twice as many complications in the PN cohort (13). The authors did not stratify complication based on seriousness and hence we were unable to infer the proportion of major complications from this analysis. The likely rationale for this observation is the approach employed for PN. The Klatte et al meta-analysis used a combination of laparoscopic and robotic PN in their meta-analysis, whereas we only compared CA to RAPN. LAPN is significantly more challenging procedure

when compared to RAPN and carries a higher morbidity (3,4). Apart from technical benefits of the robotic platform such as manoeuvrability and vision, the approach has also allowed significant evolution and sophistication of renorraphy techniques, consequently reducing warm ischemia times and overall morbidity (15). Another possible explanation for this observation could be that the poor quality of evidence for both overall and Clavien 3 and higher complications. Hence this data must be viewed with a degree of caution.

Despite the methodological limitations of the studies in this review, largely due to the lack of randomised control trials (RCTs), it is not inconceivable that RAPN achieves superior local tumour clearance with comparable morbidity with CA (16). Furthermore, it must be borne in mind that in the event of tumour progression in CA, salvage surgical intervention can be challenging (17,18). Therefore, if a nephron sparing approach is indicated for suspected renal masses, RAPN should be the approach of choice. CA may be a substitute to RAPN in a select group of patients in whom there is a high risk of future metachronous tumours, patients with intermediate life expectancy, anaesthetic fitness or renal function status and where RAPN may perhaps be deemed as a less preferable option by the treating clinician (19,20) .

Our review highlights the paucity of high quality evidence in this important area and hence conclusions can only be drawn with a degree of conjecture. This review also observed the lack of standardised reporting making meta-analysis impossible for certain key outcomes such as renal function. Future comparative studies between RAPN and CA should address the impact of these techniques on renal function. However there is a need for international consensus on reporting standards for these outcomes. It is also vital to ascertain what consequent effect individual techniques

related renal function comprise has on overall survival (21). The American Urological Association (AUA) Guidelines recommend one or more of the following criteria to define local recurrence: tumour with enhancement after ablation, visually enlarging lesion in the same area of treatment with or without contrast enhancement, failure of an ablated lesion to regress over time or development of new satellite or port site soft tissue nodules (22). In this review, none of the studies used all the parameters listed above to define 'local recurrence' in the CA cohort. It is therefore plausible that reported local recurrence rates are underestimated in the CA cohort.

RCTs are the highest level of evidence, which could serve to establish the true superiority of RAPN vs. CA and help conclusively answer this important clinical question. RCTs will address the limitations in contemporary literature that have been outlined above. However, the authors would like to raise the concern of equipoise. Despite the data not being of the desired quality, RAPN does appear to be a superior procedure when compared to CA. There have been previous attempts with trials such as the CONSERVE trial attempting to answer this question (23). The CONSERVE trial was a feasibility multicentre randomised control trial attempted to compare partial nephrectomy with cryoablataion and radiofrequency ablation for small renal masses. The study was however was unable to recruit the desired number, as patients were unwilling to take part in a randomised trial of this nature, reflecting the challenges and perhaps ethical consideration with surgical trials where there appears to be superior technique.

Conclusion:

The local recurrence rates of RAPN are significantly lower than CA. The morbidity profile for the 2 procedures appear to be similar. This must be viewed with a degree of caution due to the methodological limitations of the studies eligible for inclusion in this review. If a nephron sparing approach is indicated for suspected renal masses, RAPN should be the approach of choice. CA may be a substitute to PN in a select group of patients where RAPN isn't feasible.

Acknowledgments:

Nil

Disclosures:

No competing financial interests exist

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Table 1-Demographics

Study	Type	Comparator	n	Age in years	Nephrometry Score	Tumour Size (cm)
Caputo 2017	Prospectively maintained Database Matched Pair Analysis	LCA+PCA vs. RAPN	31 VS. 31	**Median (IQR)** 68 (64-76) vs. 68 (64-76), (p-0.2)	**Median (IQR)** 8 (6-9) vs.9(7-10) (RENAL) (p-0.10)	**Median (IQR)** 4.3(4.2-4.7) vs. 4.6(4.3-4.9) (p-0.076)
Tanagho 2013	Retrospective	LCA+PCA vs. RAPN	267 vs. 233	**Mean (SD)** 69.3(11) vs.57.4(11.9) (p<0.01)	**Mean (SD)** 6.4(1.7) vs. 7.3(1.9) (p≤0.01)	**Mean (SD)** 2.5(1) vs. 2.9 (1.5) (p<0.01)
Emara 2014	Prospective	LCA vs. RAPN	56 vs.47	**Mean (Range)** 69.75 vs. 60.5 (p<0.001)	**Units Unclear** 5.75(0.23) vs.5.77(0.25) (p-0.962) (RENAL)	**Mean (SEM)** 2.559(0.958) vs.3.278(1.787) (p<0.001)
Guillotreau 2012	Prospective Maintained Database Retrospectively analysed	LCA vs. RAPN	226 vs. 210	**Mean (SD)** 67.4(11.3) vs. 57.8(11.8) (p<0.0001)	**ASA Score, n (%)** • 1-2=42(20) vs.104(49) • 3-4=170(80) vs. 107(51) (p<0.0001)	IAD

IAD-Inadequate Data

Table 2-Oncological Outcomes

Study	Follow-up	Proportion of diagnosed with RCC on histopathological evaluation	Other Oncological Outcomes
Caputo 2017	**Median (IQR) months** 30.1 (13.2-64) vs 13 (3.19-19.2) (p-0.008)	• 71% vs.90% (p-0.085)	• **Recurrence Free Survival** 77% vs. 100% (p-0.019)
Tanagho 2013	**Mean (SD) months** 39.8 (34.3) vs. 21.9 (SD18.8) (p≤0.01)	• 52.3% vs. 79.4% (p≤0.01)	• **5 year Disease Free Survival** 83.1% vs. 100% (p ≤ 0.01) • **5 year Cancer Specific Survival** 96.4% VS. 100% (p-0.41) • **5 year Overall Survival** 77.1% VS. 91.7% (p-0.11)
Emara 2014	**Mean (SEM) months** 31.30(1.802) VS. 15.50(0.946) (p<0.001)	• 69.6% vs. 70%	• **Recurrence Rates:** **3.6% vs. 0%**
Guillotreau 2012	**Median (IQR) months** 44.5 (8.7-66.8) vs 4.8 (1-7.9) (p<0.001)	• 77% vs. 74% (p-0.001)	• **Metastasis Rates** 5.6% vs. 0.6%(p<0.0021)

Table 3-Renal Function Outcomes

Study	Follow-up	eGFR at follow up	% change in eGFR	Other Renal function Data
Caputo 2017	**Median (IQR) months** 6 months (3.0-12) vs 9.63 months (2.1-12) (p-0.8)	**Median (IQR)** 6.0 (3.0–12) vs. 9.63 (2.1–12) p= 0.8	**Median (IQR)** -7(NR) vs. -11 (NR) p=0.5	**Percentage eGFR preservation** • 93%(79-111) vs. 89% (78-103) (p=0.5)
Tanagho 2013	**Mean (SD) months** 35.8(31.1) vs. 11.8 (16.4) (p≤0.01)	**Mean (SD)** 61.3 (27.0) vs. 73.4 (22.4) p<0.01	**Mean (SD)** - 6.0 (29.2) vs. -13.0 (19.7) p<0.01	Nil
Emara 2014	**Mean (SEM) months** 31.30(1.802) VS. 15.50(0.946) (p<0.001)	IAD	IAD	**Percentage eGFR remained at >60ml/min/1.73m^2** • 55.4% vs. 78.7% **Mean increase in creatinine** • 5.4mmmol/l vs.9.214mmom/l (p=0.66)
Guillotreau 2012	6 month	**Mean (SD)** 60.1 (31.4) vs. 76.0 (21.2) p=0.4	**Mean (SD)** -8.9 (36.7) vs. -11.2 (14.2) p=0.7	• Nil

IAD-Inadequate Data

Supplementary Figure Legends:

Supplementary Figure 1-PRISMA Chart

Supplementary Figure 2-Meta-Analysis-Recurrance Rates

Supplementary Figure 3-Meta-Analysis-Overall Complication Rates

Supplementary Figure 4-Meta-Analysis-Clavien 3 and Higher Complication Rates

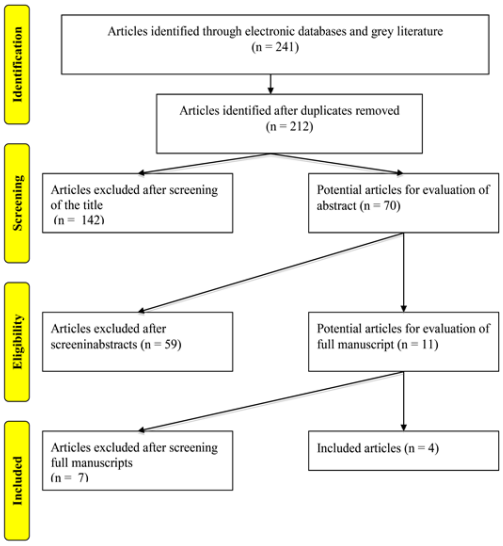

Figure 1 PRISMA Chart.tif

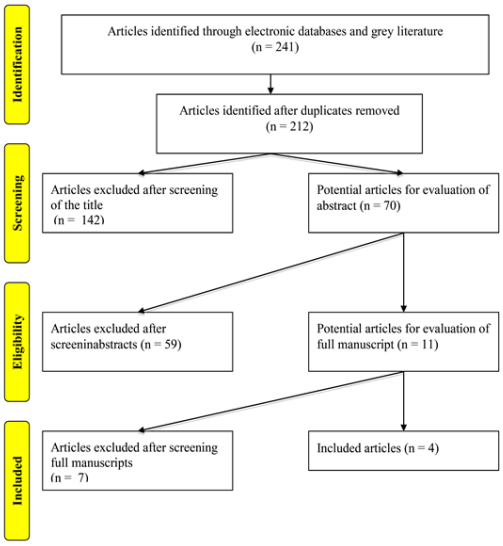

Figure 1 PRISMA Chart_bestsetConverted.png

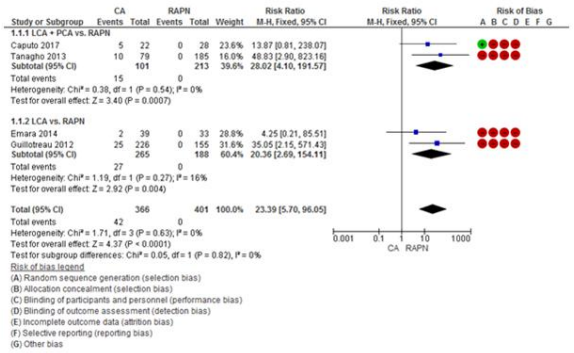

Figure 2 Recurrence Rates.tif

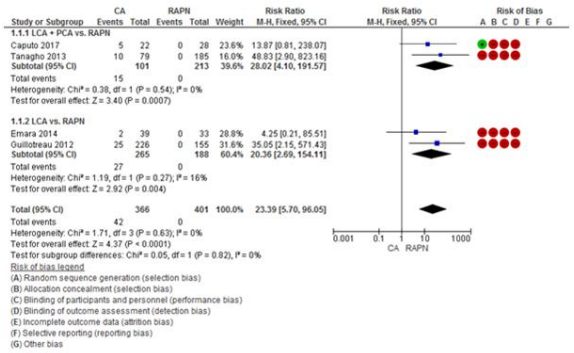

Figure 2 Recurrence Rates_bestsetConverted.png

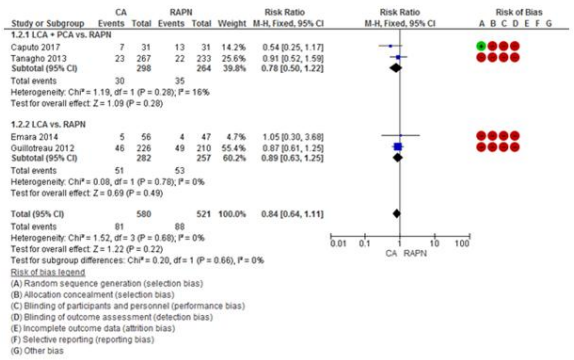

Figure 3 Overall Complication.tif

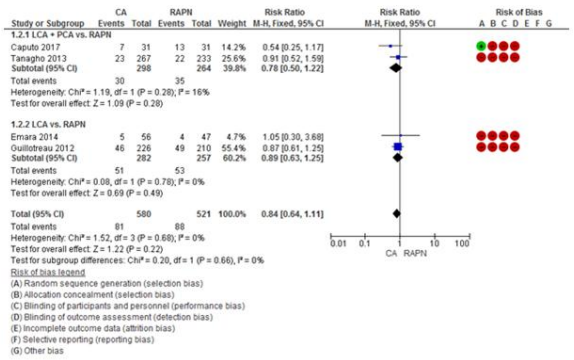

Figure 3 Overall Complication_bestsetConverted.png

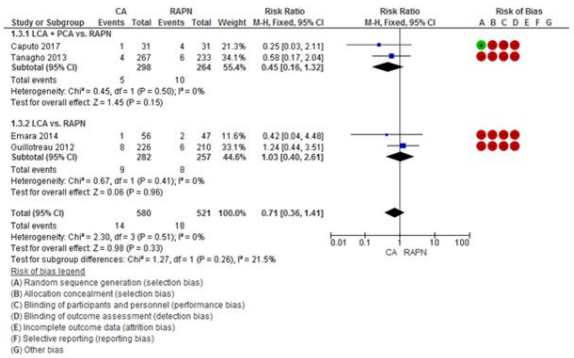

Figure 4 Clavien 3.tif

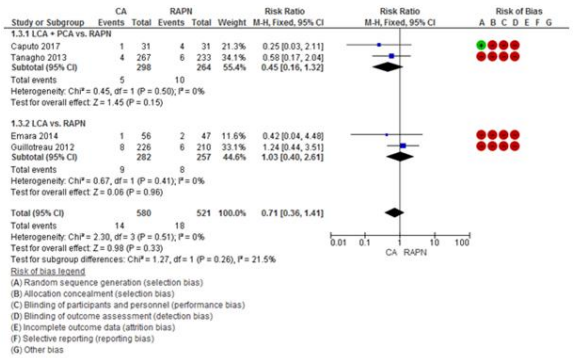

Figure 4 Clavien 3_bestsetConverted.png