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Laparoscopic vs Percutaneous Cryotherapy for Renal Tumors: A Systematic Review and Meta-Analysis

Abstract

Background: Cryoablation has emerged as an alternative to the more invasive partial nephrectomy for small renal masses. The approach can be carried out by two techniques, either laparoscopic cryoablation (LCA) or percutaneous cryoablation (PCA) with CT guidance. We aimed to compare between the two procedures.

Materials and Methods: A systematic review and meta-analysis was conducted, including studies comparing the two techniques. Outcomes included incomplete ablation, late local recurrence, cancer-specific survival, procedure time, transfection rates, hospital stay, and complications.

Results: A total of 1475 patients were included, 788 patients in the laparoscopic group and 687 patients in the percutaneous group. There was statistical difference favoring the laparoscopic group with regard to having less incomplete ablation (p=0.0008) and higher cancer-specific survival patients (p=0.04). However, there was longer hospital stay in the LCA group (p<0.00001) and was found to be more costly than the PCA group. There was significantly more Clavien-I complications in the PCA group (p=0.001) and more Clavien-III complications in the LCA group (p=0.001). Otherwise, there were no differences in any other outcome parameter.

Conclusion: LCA was found to have less incomplete tumor ablation rates and higher cancer-specific survival rates, however, higher hospitalization time, more major complications (Clavien III), and was costlier compared with PCA.

Keywords: cryoablation, cryotherapy, renal cancer, small renal masses, laparoscopy

Background

Renal Cell Cancer represents 2% of all adult cancers. In Europe, there were 84,000 new renal cell cancer diagnosed in 2012 that resulted in 34,700 deaths.1 Because of increased utilization of cross-sectional imaging, the number of incidental tumors has increased. Two-thirds of newly diagnosed renal tumors are stage T1a.2 Partial nephrectomy is the standard of care for the management of T1a renal tumors.3 It offers the benefit of renal function preservation and solid local cancer control and with minimally invasive techniques offer less morbidity. 4-5 Ablative therapies have emerged as an alternative treatment modality to partial nephrectomy. Renal tumors are treated in situ by a heating or freezing technique. Ablative treatment is minimally invasive, associated with fewer complications, shorter hospitalization time, and quicker recovery compared to partial nephrectomy.6 Cryoablation uses subzero temperatures to destroy cancer cells through direct injury caused by ice crystals formation and microcirculatory failure.7 Renal cryoablation has evolved considerably since it was first used to treat renal cell tumors over 20 years ago. It is performed through a laparoscopic cryoablation (LCA) or percutaneous cryoablation (PCA) image-guided approach. The purported advantages of a percutaneous approach over LCA are short hospitalization.
time, faster recovery, less pain relief requirement, and reduced cost, with a comparable oncologic outcome. This has led more centers to adopt PCA rather than LCA.

In this systematic review and meta-analysis, we reviewed the contemporary literature to compare the outcome, complications, and cost of both laparoscopic and percutaneous image-guided cryotherapy to treat small renal masses. We only included comparative studies of both procedures to reduce the risk of bias, as opposed to conducting a comparison of reported series of individual procedures.

Methodology

Search strategy and study selection

A review of the literature and meta-analysis was conducted using Cochrane guidelines and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist. The search strategy was conducted to find studies for inclusion using the following databases: MEDLINE (1990–May 2017), EMBASE (1990–May 2017), Cochrane Register of Controlled Trials—CENTRAL, (in The Cochrane Library—Issue 1, 2017). Clinicaltrials.gov, Google Scholar, and individual urologic journals.

Search terms used included: “renal masses,” “percutaneous,” “renal tumors,” “laparoscopic,” “laparoscopy,” “cryotherapy,” and “cryoablation.”

Mesh phrases included:

- (“Kidney Neoplasms”[Mesh]) AND (“Cryotherapy”[Mesh])
- (“Cryotherapy”[Mesh]) AND (“Tomography, X-Ray Computed”[Mesh]) AND (“Laparoscopy”[Mesh])
- (“Laparoscopy”[Mesh]) AND (“Cryotherapy”[Mesh]) AND (“Kidney Neoplasms”[Mesh])

Studies in languages other than English were included if data were extractable. If data were not provided or clarified and the data were not extractable, the study was excluded.

Two reviewers (O.A. and M.L.) identified all studies that appeared to fit the inclusion criteria for full review. Two reviewers (O.A. and M.L.) independently selected studies for inclusion in the review. Any disagreements were referred to a third reviewer (F.X.K.).

Data extraction and analysis

All studies comparing laparoscopic cryotherapy to percutaneous CT-guided cryotherapy for small renal masses were included. The primary outcome was to assess the difference between the two procedures regarding oncologic outcomes: incomplete ablation, local recurrence, and cancer-specific survival. Secondary outcomes were to assess the procedure-related outcomes: operative time, transfusion rates, hospital stay, and complications.

We defined residual tumor or incomplete ablated tumor as an enhancing lesion at the site of ablation on the first postoperative CT scan, while late local recurrence was defined as enhancing lesion at the site of ablation following at least one contrast CT scan showing no residual tumor.

Results

The literature search yielded 128 studies, of which 109 were excluded due to irrelevance based on titles and abstracts (Fig. 1). Full articles were evaluated in 19 studies, of which 12 were included in the systematic review. Of the 12 studies included, 6 were from the same centers, therefore, their data were only included if unique to that study, therefore

![Flowchart of article selection process of the review.](image-url)
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Study or Subgroup       Laparoscopic   CT-Guided   Odds Ratio M-H, Fixed, 95% CI
                       Events Total   Events Total   Weight
Denveris 2009          1   24       3   20      7.1%  0.23 (0.02, 2.30)
Firby 2004             1   24       1   19      23%  0.78 (0.08, 7.30)
Hinshaw 2005           4   60       3   30      8.0%  0.96 (0.13, 6.90)
Kim 2014               2   167      9   123     11.6%  0.15 (0.03, 0.73)
MacLennan 2009         2   40       5   30      21.5%  0.14 (0.02, 0.78)
Mars 2016              1   97       9   90      9.9%  0.10 (0.01, 0.94)
Siddiqui 2010          0   52       2   101     3.8%  0.30 (0.02, 0.60)
Zargar 2015            19  275      9   137     23.3%  1.08 (0.41, 2.74)
Total (95% CI)          755  555   525  430     80.0%  0.82 (0.20, 3.20)
Total events            30   41
Heterogeneity: Chi^2 = 10.47, df = 7 (P = 0.18), I^2 = 23%
Test for overall effect: Z = 3.18 (P = 0.0018)

Incomplete ablation

Study or Subgroup       Laparoscopic   CT-Guided   Odds Ratio M-H, Fixed, 95% CI
                       Events Total   Events Total   Weight
Hinshaw 2005           1   60       0   30      1.9%  1.04 (0.06, 19.80)
Kim 2014               20  145      8   110     17.8%  2.29 (0.82, 6.20)
Mars 2010              2   81       0   89      10.3%  0.28 (0.01, 2.30)
Siddiqui 2010          5   84       10  81      20.5%  0.32 (0.10, 1.03)
Zargar 2015            30  275      20  137     34.2%  0.84 (0.40, 1.78)
Total (95% CI)          905  445   460  340     100.0%  1.04 (0.50, 2.15)
Total events            96   32
Heterogeneity: Chi^2 = 0.73, df = 4 (P = 0.73), I^2 = 54%
Test for overall effect: Z = 0.17 (P = 0.86)

Recurrence rates

Study or Subgroup       Laparoscopic   CT-Guided   Odds Ratio (Non-event) M-H, Fixed, 95% CI
                       Events Total   Events Total   Weight
Bard 2007              50  506      20  206     39.3%  0.99 (0.95, 1.05)
Kim 2014               81  91       99  99      52.9%  0.60 (0.30, 1.00)
Siddiqui 2010          275 275    135 135     26.3%  0.10 (0.00, 2.05)
Zargar 2015            77  77       57  57      26.4%  1.30 (0.60, 2.74)
Total (95% CI)          418  418   347  347     100.0%  0.30 (0.16, 0.57)
Total events            491  202
Heterogeneity: Chi^2 = 0.66, df = 2 (P = 0.80), I^2 = 45%
Test for overall effect: Z = 2.04 (P = 0.04)

Cancer specific survival

Study or Subgroup       Laparoscopic   CT-Guided   Odds Ratio (Non-event) M-H, Fixed, 95% CI
                       Events Total   Events Total   Weight
Iyer 2014              124 124     100 100     34.5%  1.09 (0.54, 2.21)
Zargar 2015            217 217     110 110     52.2%  1.09 (0.56, 2.10)
Total (95% CI)          420 420   210 210     100.0%  1.09 (0.72, 1.64)
Total events            527 222
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.94), I^2 = 0%
Test for overall effect: Z = 0.33 (P = 0.74)

5-year Recurrence free survival

FIG. 2. Oncologic outcomes. (a) Incomplete ablation. (b) Recurrence rate. (c) Cancer-specific survival. (d) 5-year recurrence-free survival.

Reducing the actual number of studies with extractable data to 8.
All the included studies were published within the last 8 years.
All the included studies were retrospective cohort comparisons with no randomization and all reported on individual center's experience with laparoscopic and percutaneous cryotherapy.

Characteristics of the included studies

Although literature search was conducted between 1990 and 2015, all of which were from centers in the United States, and the majority of the studies were single-center studies.
In total, there were 1475 patients, 788 patients (age range of 56-80 years) in the LCA group and 687 patients (age range of 36-82 years) in the PCA group. Four studies included patients with masses 0.7 cm in size, while one included masses 0.7 cm in size and the remaining included patients with masses 0.7 cm in size.
Although all the studies reported on the patients and procedure demographics, only four studies depicted the data for
**FIG. 3.** Comparison between LCT and PCT (a) Total complications that developed (b) Clavien Classification I (c) Clavien Classification II (d) Clavien Classification III (e) Clavien Classification IV.
Table 1.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Age</th>
<th>Sex (male)</th>
<th>BMI</th>
<th>Tumor size for Rx</th>
<th>Tumor Size (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bandi et al.</td>
<td>58 vs 20</td>
<td>66 vs 68</td>
<td>31 vs 21</td>
<td>30 vs 31</td>
<td>&lt;4 cm</td>
<td>2.7 vs 2.2</td>
</tr>
<tr>
<td>Himshaw et al.</td>
<td>60 vs 30</td>
<td>67.4±11 vs 67 ± 10.8</td>
<td></td>
<td></td>
<td>&lt;4 cm</td>
<td>2.4±0.83 vs 2.1±0.73</td>
</tr>
<tr>
<td>Bandi et al.</td>
<td>19 (24) vs 18 (19)</td>
<td>NS vs NS</td>
<td>NS vs NS</td>
<td>NS</td>
<td>NS</td>
<td>3 vs 2.7</td>
</tr>
<tr>
<td>Finley et al.</td>
<td>81 (97) vs 99</td>
<td>NS vs NS</td>
<td>NS vs NS</td>
<td>NS</td>
<td>&lt;3</td>
<td>1.9±0.7 vs 2.1±0.7</td>
</tr>
<tr>
<td>Sidana et al.</td>
<td>52 vs 101</td>
<td>NS vs NS</td>
<td>24 vs 65</td>
<td>46 vs 83</td>
<td>&lt;3 cm</td>
<td>2.2 vs 2.4</td>
</tr>
<tr>
<td>Tsvi et al.</td>
<td>72 (79) vs</td>
<td>NS vs NS</td>
<td>NS vs NS</td>
<td>NS</td>
<td>&lt;7 cm</td>
<td>NS</td>
</tr>
<tr>
<td>Zargar et al.</td>
<td>123 (140)</td>
<td>275 vs 157</td>
<td>201 vs 93</td>
<td>28.4±8.97 vs 30.3±7.43</td>
<td>&lt;3</td>
<td>NS</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>145 (167) vs 118 (123)</td>
<td>69.3±11.6 vs 72.5±10.3</td>
<td>87 vs 73</td>
<td>29.1±6.1 vs 32.3±9.3</td>
<td>&lt;3</td>
<td>2±0.8 vs 2±7.1</td>
</tr>
<tr>
<td>Strom et al.</td>
<td>84 vs 61</td>
<td>65.7±10 vs 68.6±12.8</td>
<td>73 vs 93</td>
<td>29.8±6.6 vs 29.9±6.6</td>
<td>&lt;4 cm</td>
<td>2.5±0.8 vs 2±7.1</td>
</tr>
<tr>
<td>Malcolm et al.</td>
<td>46 vs 20</td>
<td>18 vs 19</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Derweesh et al.</td>
<td>34 vs 26</td>
<td>18 vs 19</td>
<td></td>
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</tr>
</tbody>
</table>

The body mass index, PCA = percutaneous cryotherapy; LCA = laparoscopic cryotherapy; NS = not stated.

Figure 2 depicts the studies that reported on the oncologic outcome measures. All studies reported on incomplete ablation, five on local recurrence rates, four on cancer-specific survival,

and all studies reported the 5-year recurrences-free survival, however, only two studies had comparable data. The analysis of the results showed that the LCA group had a lower local recurrence rate (p<0.01; OR: 1.59; CI: 1.24, 2.02) and a higher cancer-specific survival (p<0.05; OR: 1.95; CI: 1.15, 3.29). However, there was no difference in the 5-year recurrences-free survival (p=0.92; OR: 1.09; CI: 0.72, 1.64).

Regarding the incomplete ablation, in total, 3.9% (30/755) of the LCA and 7.4% (41/555) of the PCA patients had incomplete tumor ablation. Of these, 37 of the 41 patients with incomplete PCA ablation had effective repeated PCA, 3 had radical nephrectomies, and 1 went on to active surveillance. One of the radical nephrectomy patients had the PCA repeated before his nephrectomy and the tumor remained incompletely ablated, leading to a nephrectomy. In the LCA group, the 30 patients with incomplete ablation underwent a variety of procedures: 10 had effective PCA, 3 nephrectomies, 11 active surveillance, and 2 partial nephrectomies, while 1 patient died of an unrelated illness before any subsequent treatment.

There was no significant difference between the two groups regarding overall complications (lap: 81.86 vs CT: 98.07) (p=0.46; OR: 0.88; CI: 0.63, 1.23), CD-II complications (lap: 26/647 vs CT: 165/588) (p=0.16; OR: 1.69; CI: 0.83, 3.08), or CD-IV complications (lap: 5647 vs CT: 4558) (p=0.59; OR: 1.39; CI: 0.42, 4.64). However, there were significantly more CD-I complications in the PCA group (lap: 3/2067 vs CT: 9.15; CI: 51/558) (p=0.001; OR: 0.45; CI: 0.23, 0.7) and more CD-III complications in the laparoscopic group (lap: 3/2567 vs CT: 1.4; CI: 6/558) (p=0.001; OR: 3.99; CI: 1.72, 9.28).

The studies that reported on metastasis found no difference between the two groups (lap: 0.9% [3/335] vs CT: 1.2% [2/167]) (p=0.75; OR: 0.74; CI: 0.12, 4.51). There was no difference regarding transfusion rates (lap: 2.3% [5/250] vs CT: 2.6% [5/192]) (p=0.84; OR: 1.04; CI: 0.52, 3.41), however, there was a shorter length of hospital stay in the PCA group (PCA mean stay: 1 vs LCA mean stay 3) (p<0.00001; MD: 1.06; CI: 0.8, 1.32).

Methodologic quality assessment

All the studies were nonrandomized retrospective studies comparing between LCA and PCA. The majority of the studies were single-center studies, with only three involving more than one center. Only Finley and colleagues did not clearly describe their statistical methods.
and colleagues did not mention their procedural techniques for LCA and PCA. Six studies had multiple publications of varying aspects of their study and did not mention whether or not these patients were the same patients in each publication or a different cohort.11,13,15,17,20

There was specific patient selection bias in three of eight studies, from which patient data were extracted into the meta-analysis.13,15,20 Hinshaw and colleagues had larger tumors in the LCA group.13 Zargar and colleagues had patients with higher BMI and more comorbidity in the PCA group.15 Kim and colleagues had older patients, higher BMI, and larger tumors in the PCA group and more patients with multiple tumors in the LCA group.14 Finley and colleagues and Sidana and colleagues did not mention a comparison between their basic patient demographic parameters.14,19 Three studies reported no difference regarding patient characteristic between the groups.8,21,22 Otherwise, all the studies mentioned their results with no publication or reporting bias, no missing data were identified, and no other risk of bias was found.

Discussion

Summary of the main results

Oncologic outcomes: there were significantly fewer tumors that were incompletely ablated and a higher cancer-specific survival rate in the LCA group. There was no difference between the two groups regarding late local recurrence rates. No difference in the 5-year recurrence-free survival was found.

Safety outcomes: there was no difference between the two groups regarding overall complications, however, subdividing the complications into the Clavien–Dindo classification, we found that there was more CD-1 complications in the PCA group and more CD-III complications in the LCA group, implying that LCA is associated with a higher risk of significant complications. No difference between the two regarding CD-II or CD-IV complications, and no deaths were reported related to the procedures.

There was no difference between the two groups regarding transfusion rates; however, the PCA group had shorter length of hospital stay. There was no difference between the two groups regarding distant metastasis.

Incomplete ablation. There were strikingly different management strategies for the two treatments following incomplete ablation. The majority of patients in the LCA group who had incomplete ablation went on to have either PCA or opted for observation, while nearly all of those with incomplete ablation in the PCA group were managed by repeat PCA.

Cost analysis. Of the included studies, only one had a cost comparison analysis between the two groups. Hinshaw and colleagues found that the PCA group was significantly cheaper per patient by nearly half ($23,618 vs $14,175).15

Two other published studies also found similar results favoring PCA to be the cheaper procedure.23,24 Both studies took into consideration multiple variants such as fees, consumables, theatre costs, hospital stays, and pathology costs. While Link and colleagues used a modular approach to take into consideration impact of postoperative imaging and recurrence rates with subsequent treatments to predict a cost model.23,24 All predictions and direct comparisons found PCA to be the cheaper of the two procedures.15 Furthermore, Link and colleagues also found that both PCA and LCA were cheaper than laparoscopic or open partial nephrectomies.24

Strengths and limitations of review

This is the first systematic review and meta-analysis comparison between LCA and PCA and was conducted to the highest standards using Cochrane and Prisma guidelines with an impartial look into the resulting data analysis.19 The main limitation of the review is the fact that there is limited comparative studies (8) with even more limiting numbers in some of the subgroup analyses. Furthermore, all the studies were retrospective in nature with varying degrees of risks of bias. Although there was no difference between the two groups with regard to their ages or tumor sizes, the results indicate that the patients undergoing PCA had higher BMI’s. Furthermore, it is plausible that many patients underwent PCA rather than LCA due to their comorbidities and lack of fitness, which would increase case ascertainment bias between the two groups. However, all these studies were set up not to be randomized and do declare the fault of a retrospective look on their results. A further risk of bias is with the mentioning of the incomplete ablation outcomes, specifically no mention of outcomes of subsequent management results after the initial incomplete ablation. However, those studies did not mention that they would present this specific data set. Most of the studies were conducted in single centers. However, despite these limitations, this represents the reported literature and gives a detailed understanding and overview of the difference between the two procedures. The total number of procedures reported was considerable and roughly equally divided between the two groups.

Future direction

The studies included in this review demonstrate the shortcomings of retrospective comparative studies. The only randomized controlled trial of needle ablation vs partial nephrectomy (CONSERVE) to date failed to recruit in its feasibility phase and so was not completed.29 EuRBCA (European Renal CryoAblation), a prospective, multicenter registry, including both laparoscopic and image-guided cryoablation, is currently accruing patients according to a strict protocol that includes comorbidities and nephronary scores. The results of this registry should shed further light and provide more robust evidence for LCA and PCA results.

An interesting point regarding the two procedures is the increasing skill set of radiologists to perform these procedures in more complex cases. Furthermore, patients undergoing cryoablation tend to have more comorbidity and might not be good surgical candidates from the outset. In addition, with the advent of robotic partial nephrectomy, many laparoscopic surgeons have moved away from laparoscopic partials. Furthermore, more complex partial nephrectomy is being conducted with the robotic system, as an alternative to previously cryoablation. These points increase the likelihood that PCA use will continue for a selected patient cohort, while LCA might be replaced by robotic CA or even robotic partial nephrectomy. Only time will tell.

Conclusion

LCA had less incomplete tumor ablation rates and higher cancer-specific survival rates. PCA was effective as second
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...line treatment for failed LCA or PCA. The advantages of percutaneous image-guided cryoablative therapy over LCA are short hospitalization and reduced cost. There were no complications in the PCA group and no CD-III complications in the LCA group. Otherwise, there was no difference between the two procedures in any other parameters.

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References
25. UK CR. A Feasibility Study for a Multicentre Randomised Controlled Trial to Compare Surgery With Needle Ablation Techniques in People With Small Renal Masses (4 cm) (CONSERVE), clinicaltrials.gov 2015.

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Abbreviations Used
BMI = body mass index
CD = computed tomography
LCA = laparoscopic cryoablation
PCA = percutaneous cryoablation
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