Bayesian network analysis of open, laparoscopic and Robot-assisted Radical cystectomy.

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Abstract

Background

We performed the conventional meta-analysis and network meta-analysis to evaluate the safety and efficacy of Robot-assisted Radical cystectomy (RARC) versus laparoscopic radical cystectomy (LRC) versus open radical cystectomy (ORC) for bladder cancer (BCa).

Methods

A systematic search of PubMed, Cochrane Library and Embase was performed up to until Dec 20, 2019. Outcome indexes include: oncologic outcomes: the recurrence rate, mortality; pathologic outcomes: Lymph node yield (LNY), Positive lymph node (PLN), positive surgical margins (PSM); perioperative outcomes: operating time (OP), estimated blood loss (EBL), blood transfusion rate, the length of hospital stay, and the time to regular diet. And Postoperative 90-day complications.

Results

59 articles describing 8 RCTs, 25 Prospective study, 26 Retrospective study (6944 patients) were analyzed. No significant differences were found between RARC, LEC and ORC in two oncologic outcomes: the recurrence rate and mortality. However, for the recurrence rate, patients with LRC has the highest probability, ORC has the second highest probability, and RARC has the lowest probability. For the mortality, patients with ORC has the highest probability, LRC has the second probability, and RARC has the lowest probability. In three pathologic outcomes: direct meta-analysis indicates that ORC is more than RARC or LRC in PSM and RARC is more than ORC in LNY. On the other hand, network meta-analysis indicates that ORC is more than RARC in PSM. No significant differences were found between RARC, LEC and ORC in other pathologic outcomes: LNY and PLN. for LNY, patients with RARC has the highest probability, ORC has the second highest probability, and LRC has the lowest probability by our network meta-analysis. For PLN, patients with ORC has the highest probability, LRC has the second probability, and RARC has the lowest probability by our network meta-analysis. With respect to perioperative outcomes, direct meta-analysis indicates that RARC is shorter time than LRC or ORC in OP. On the other hand, network meta-analysis indicates that patients with ORC have significantly longer OP than LRC or RARC. Direct meta-analysis and network meta-analysis both indicate that ORC is more than RARC or LRC in EBL, ORC is longer than RARC or LRC

Conclusion

The conventional meta-analysis and network meta-analysis suggest that RARC is a safest and most effective surgical approach in the treatment of BCa and LRC ranks second. However, large sample size and more high-quality studies are still needed to further improve and verify.

Introduction

In recent years, the incidence and mortality of bladder cancer have increased significantly[1], ORC is the gold standard for muscle or non-muscle invasive bladder cancer[2]. However, its bleeding volume, operating time, the length of hospital stay and complications are significantly higher than MIRC[3, 4]. With innovation of surgical techniques, the overall survival of RARC or LRC is comparable to ORC [5]. Its safety and feasibility have been widely recognized. LRC has a history of more than 20 years. However, with the application of the robot in the clinic, RARC has obvious advantages compared with LRC in terms of bleeding volume, operation time, the length of hospital stay and complications [6]. So far, no literature has used direct and indirect comparisons to expound outcome indexes between the three approaches. Therefore, this article aims to apply network meta-analysis to compare oncology-related indicators between the three surgical approaches.

Methods

Literature search and selection

The methodology involved in this meta-analysis was based on the Preferred Reporting Items for Systematic Reviews and meta-analysis (PRISMA) statement (Table 1). The systematic literature was searched by databases such as PubMed, Cochrane Library and Embase, in addition, relevant journals were manually searched. And the Population, Intervention, Comparator, Outcomes (PICO) methodology. PICO was defined as follows: population consisted of patients had biopsy-proven clinical stage T1–T4, N0–N1, M0 bladder cancer or refractory carcinoma in situ (P), RARC or LRC or ORC: (I) or (C). the recurrence rate, mortality, OP, EBL, LNY, PLN, PSM, blood transfusion rate, the length of hospital stay, the time to regular diet, Postoperative 90-day complications (O). Retrieval Strategy was in the Search Strategy. Search the database until Dec 20, 2019. Assistance strategy by manual search found as much detailed article information as possible. After reading the full text, the data were extracted. Data extraction includes: first author, publication year, age (If mentioned), study area, type, sample size, sampling method, main observation indicators, etc.

Data extraction and quality evaluation

Two researchers independently reviewed the retrieved literature according to the inclusion and exclusion criteria. When disagreements were encountered, the third researcher was required to participate in the discussion to determine whether to include. If the following inclusion criteria were met, the studies were included in the network analysis: (1) patients were diagnosed with bladder cancer based on their pathological data; (2) patients in group had a history of ORC, LRC and RARC. (3) Outcome indexes should include at least one of the following, operating time, estimated blood loss, length of hospital stay, blood transfusion rate, PSM, positive lymph node, lymph node yield, the time to regular diet, complications. (4) It was limited a randomized controlled trial or a retrospective case control or a prospective cohort design. (5) The studies were Limited to English. Any study that did not conform the above criteria was excluded.

Statistical analysis

Statistical analysis was performed using Stata 12.0 and GeMTC 0.14.3 software. For meta-analysis, the heterogeneity test was $P < 0.1$, $I^2 > 50\%$, the random effect model was used; the heterogeneity test was $P > 0.1$, $I^2 < 50\%$, the meta-analysis was performed using a fixed utility model. The combined r values and 95% CI of each study were calculated, and the characteristics of each study result were displayed by the forest map. The Begg's test and Egger's test were used to test the publication bias. The $P < 0.05$ was considered statistically significant. For network analysis, fill in the extracted data information in the Excel table, the multiple three-arm trials were Sorted out a two-arm trial format, and a net-like relationship diagram comparing multiple interventions was drawn by Stata 12.0 software. Calculate Relative Odds Ratio and implement inconsistency test to evaluate the closed-loop consistency in the network relationship. According to the Z test, if the lower limit of 95% Confidence Interval (CI) is 1, $P > 0.05$, it is considered that is no inconsistency, the consistency model is used for network meta-analysis, otherwise, it is inconsistency, the inconsistency model is used for network meta-analysis. Use GeMTC 0.14.3 software and 4 Markov chain simulations, set the number of tuning iterations to 20,000, the number of simulation iterations to 50,000, and the thinning interval to 10. A close to 1 indicates that the model is satisfied with convergence; draw a rank probability map and predict the possible rank probability.

Results

Literature search results

A total of 2324 articles were retrieved according to the customized search strategy and 16 additional articles. 735 articles that were repeatedly published and cross-published were deleted. After reading the text and abstract, 1339 articles were excluded. After the remaining 206 articles were searched for full text, reading and quality assessment, 59 articles (6944 participants)[2, 6-63] were eventually included (Table 2). The methodological quality evaluation of 59 articles included in this study can be found in Table 3.

Direct meta-analysis

The summary odds ratios (ORs) of the outcomes (two oncologic outcomes: the recurrence rate and mortality; three pathologic outcomes: LNY, PLN and PSM; perioperative outcomes: OP, EBL, blood transfusion rate, the length of hospital stay and the time to regular diet; Postoperative 90-day complications) for each two direct comparison were calculated. The network plot of the outcomes indexes included in this meta-analysis (Figure 1) and the results of direct meta-analysis were showed in Table 4. Patients with ORC exhibited increase of OP compared to those with LRC (OR = 0.68, 95% CI = 0.56,0.80, $P < 0.0001$); Patients with ORC or LRC exhibited increase of OP compared to those with RARC (OR = 0.70, 95% CI = 0.60-0.79, $P < 0.0001$; OR = 0.39, 95% CI = 0.13-0.65, $P = 0.003$). Patients with RARC or LRC exhibited decrease of EBL compared to those with ORC (OR = -1.12, 95% CI = (-1.22, -1.02), $P < 0.0001$; OR = -1.14, 95% CI = (-1.28, -1.00), $P < 0.0001$). Patients with RARC exhibited increase of LNY compared to those with LRC (OR = 0.58, 95% CI = 0.29-0.87, $P < 0.0001$). Patients with RARC or LRC exhibited decrease of the length of hospital stay compared to those with ORC (OR = -0.62, 95% CI (-0.72, -0.51), $P < 0.0001$; OR = -0.42, 95% CI (-0.54, -0.30), $P < 0.0001$). Patients with RARC or LRC exhibited decrease of PSM

compared to those with ORC (OR = 0.41, 95% CI = 0.28 - 0.60, $P < 0.0001$; OR = 0.41, 95% CI = 0.22-0.77, $P = 0.006$). Patients with RARC exhibited decrease of the time to regular diet compared to those with ORC (OR = 0.82, 95% CI = 0.69 - 0.97, $P = 0.018$). When $I^2 > 50\%$, the random effects model is applied to these comparisons.

Network meta-analysis

Table 5 summarizes all the studies within the multiple networks and shows the results of the mixed network comparisons. Patients with ORC exhibited a significantly longer of operating time than those with LRC or RARC (OR = -46.28, 95% CrI = -66.92, -27.08; OR = -65.71, 95% CrI = -84.76, -46.51). Patients with ORC exhibited a significantly more of estimated blood loss than those with LRC or RARC (OR = 414.44, 95% CrI = 289.22, 538.67; OR = 556.12, 95% CrI = 428.74, 681.33). Patients with RARC exhibited a significantly less of estimated PSM than those with ORC (OR = 0.30, 95% CrI = 0.13, 0.68). Patients with LRC or RARC exhibited a significantly less of estimated the length of hospital stay than those with ORC (OR = -1.79, 95% CrI = -2.82, -0.76; OR = -1.65, 95% CrI = -2.67, -0.62). Patients with RARC exhibited a significantly less of estimated the time to regular diet than those with ORC (OR = 1.64, 95% CrI = 1.18, 2.27). However, the recurrence rate, mortality, LNY, PLN, blood transfusion rate and postoperative 90-day complications showed no statistical significance in Table 5. But the magnitude of the probability can be shown in Figure 2-7. For the recurrence rate, Figure 2 shows that the probability of LRC is the largest, ORC is the second, and RARC is the smallest. For the mortality, Figure 3 shows that the probability of ORC is the largest, LRC is the second, and RARC is the smallest. For LNY, Figure 4 shows that the probability of RARC is the largest, ORC is the second, and LRC is the smallest. For PLN, Figure 5 shows that the probability of ORC is the largest, LRC is the second, and RARC is the smallest. For the blood transfusion rate, Figure 6 shows that the probability of ORC is the largest, RARC is the second, and LRC is the smallest. For the postoperative 90-day complications, Figure 7 shows that the probability of LRC is the largest, ORC is the second, and RARC is the smallest. As suggested by Table 6-a, no significant inconsistency between indirect and direct evidence was presented with respect to the mortality, OP, EBL, LNY, PLN, PSM, blood transfusion rate, the length of hospital stay, the time to regular diet, and Postoperative 90-day complications and thereby a consistent model was used in our analysis. As suggested by Table 6-b, significant inconsistency between indirect and direct evidence was presented with respect to the recurrence rate (ORC VS RARC) and thereby a inconsistent model was used in our analysis.

Discussion

BCa is the second most common malignant tumor in the urinary system, behind prostate cancer[1]. With the development of science and technology, the application of minimally invasive surgery in radical bladder cancer surgery has become more and more mature. Compared with ORC, RARC and LRC have many advantages[64, 65]. Notably, Reports on RARC, LRC and ORC all are direct evidence from traditional meta-analysis, but network meta-analysis contains all the research and is more convincing. There is not

only direct evidence from traditional meta-analysis but also network meta-analysis about comparing the three surgical approaches of RARC, LRC, and ORC.

One study showed that RARC, LRC and ORC have no difference for two oncologic outcomes: the recurrence rate and mortality[30]. However, For the probability of network meta-analysis, patients with LRC has the highest probability, ORC has the second highest probability, and RARC has the lowest probability for the recurrence rate. patients with ORC has the highest probability, LRC has the second probability, and RARC has the lowest probability for the mortality.

Menon et al [66] firstly reported RARC in 2003. Since then, the research results of many scholars [67–69] have shown that compared with ORC and LRC, RARC can complete a more detailed anatomy, which can cure tumors, preserve function and control urine to achieve better result. Reducing the operative time is considered to be beneficial for surgeons to improve the efficiency of surgery, and for patients to reduce estimated blood loss, accelerate postoperative recovery, and reduce complications. Direct evidence from conventional meta-analysis indicates that RARC is shorter than LRC or ORC in OP. On the other hand, our network meta-analysis indicates that ORC have significantly longer OP than LRC or RARC. Direct evidence from conventional meta-analysis and our network meta-analysis both indicate that ORC is more than RARC or LRC in EBL, ORC is longer than RARC or LRC in the time to regular diet, and ORC is longer than RARC or LRC in the length of hospital stay. The possible reason is RARC has a wide three-dimensional field of vision, a flexible wrist with 7 degrees of freedom, and an ergonomic operating console, the operator is less prone to fatigue[70].

However, there are not statistically significant for blood transfusion rate and postoperative 90-day complications between direct meta-analysis and our network meta-analysis. But for blood transfusion rate, patients with ORC has the highest probability, RARC has the second highest probability, and LRC has the lowest probability by our network meta-analysis. For the 90-day postoperative complication, the probability of patients with LRC is the largest, ORC is the second, and RARC is the smallest by our network meta-analysis.

On the other hand, we have to consider the outcome indexes of the three surgical approaches. At the beginning of minimally invasive surgery, ORC's surgical effect is better than MIRC. However, as surgeons become more proficient with MIRC, MIRC is even better than ORC at this stage[6].

Three pathologic outcomes include PSM, LNY and PLN. Direct evidence from conventional meta-analysis indicates that ORC is more than RARC or LRC in PSM and RARC is more than ORC in LNY. On the other hand, our network meta-analysis indicates that ORC is more than RARC in PSM. The possible reason is that the advantages of RARC's 3D field of view and 7 degrees of freedom make the operation under the microscope more refined, which is an improvement on the original traditional surgical technology, which has broadened the scope of traditional surgery[70].

However, there both are not statistically significant for LNY and PLN in our network meta-analysis. But for LNY, patients with RARC has the highest probability, ORC has the second highest probability, and LRC has

the lowest probability by our network meta-analysis. For PLN, patients with ORC has the highest probability, LRC has the second probability, and RARC has the lowest probability by our network meta-analysis.

Compared LRC and ORC, RARC can better perform some difficult operations such as adhesion decomposition, hemostasis and suture and so on. The deep lymph nodes of the pelvic cavity during the operation have the characteristics of clear vision, flexible operation, fine and stable. At the same time, RARC saves operation time, reduces patient pain, accelerates patient recovery, and reduces complications. Therefore, RARC is more worthy of clinical promotion in countries and regions with conditions.

Conclusion

The conventional meta-analysis and network meta-analysis suggest that RARC is a safest and most effective surgical approach in the treatment of BCa and LRC ranks second. However, large sample size and more high-quality studies are still needed to further improve and verify.

Abbreviations

LNy = Lymph node yield, PLN = Positive lymph node, PSM = positive surgical margins, OP = operating time, EBL = estimated blood loss, BCa = Bladder Cancer, MIRC = Minimally Invasive Radical cystectomy, ORs = odds ratios

Declarations

Ethics approval and consent to participate:

The authors declare that there is no involving Ethics.

Consent for publication:

Yes

Competing interests:

The authors declare that there is no conflict of interest.

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Lin Dong, Chen Lin: Project development,

Lin Dong, Tinghui Hu, Xiaoxi Mou: Data Collection,

Tao Wu, Cui Shu: Manuscript writing

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Tables

Due to technical limitations, the tables are only available as a download in the supplemental files section.

Figures

Figure 1: The network plot of the three surgical approaches for BCa included in this meta-analysis.

Figure 1

The network plot of the three surgical approaches for BCa included in this meta-analysis.

Figure 2

Figure 2

shows that the probability of LRC is the largest, ORC is the second, and RARC is the smallest.

Figure 3

Figure 3

For the mortality, Figure 3 shows that the probability of ORC is the largest, LRC is the second, and RARC is the smallest.

Figure 4

Figure 4

For LNY, Figure 4 shows that the probability of RARC is the largest, ORC is the second, and LRC is the smallest. For PLN,

Figure 5

Figure 5

Shows that the probability of ORC is the largest, LRC is the second, and RARC is the smallest.

Figure 6

Figure 6

Shows that the probability of ORC is the largest, RARC is the second, and LRC is the smallest.

Figure 7

Figure 7

For the postoperative 90-day complications, Figure 7 shows that the probability of LRC is the largest, ORC is the second, and RARC is the smallest.

Supplementary Files

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