Meta-analysis of curative effect of minimally invasive radical hysterectomy and open radical hysterectomy with primary chemo-radiation in patients with cervical cancer

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► *Original article*

ABSTRACT

Background: The comparative analysis of minimally invasive radical hysterectomy (MIRH) and open radical hysterectomy (ORH) in cervical cancer (CC) patients undergoing primary chemoradiation has yielded divergent and contentious study conclusions. ***Materials and Methods:*** A comprehensive literature search was conducted across PubMed, Web of Science core database, Nature, Science Direct, and others, covering the period from January 2007 to the present. ***Results:*** Ten relevant articles were identified, encompassing 4,148 CC patients who underwent radical hysterectomy, with 1,949 (47.0%) undergoing MIRH and 2,199 (53.0%) undergoing ORH. Among these patients, 767 experienced recurrence, and 223 succumbed to the disease. The analysis revealed a slightly higher recurrence rate in patients who underwent MIRH versus ORH [OR=1.25, 95% CI=1.02~1.54, Z=2.16, P=0.03], demonstrating statistical significance (P<0.05). However, the mortality rate in MIRH patients was marginally superior to in ORH patients [OR=1.02, 95% CI=0.76 ~ 1.37, Z=0.11, P=0.91] (P>0.05). MIRH was associated with a slightly lower complication rate versus ORH [OR=0.40, 95% CI=0.28 ~ 0.57, Z=5.02, P<0.00001], and a significantly reduced incidence of perioperative blood transfusions [OR=0.19, 95% CI=0.05 ~ 0.58, Z=4.18, P<0.0001]. ***Conclusion:*** The findings suggest that ORH is linked to lower recurrence and mortality rates versus minimally invasive surgery, establishing its potential advantage in the treatment of CC.

INTRODUCTION

Cervical cancer (CC) represents a malignant tumor affecting the uterine cervix in women and ranks as the second most prevalent malignancy jeopardizing women's health in China [1, 2]. Recent statistics reveal that in 2015, the number of new CC cases in China surpassed 90,000, resulting in up to 30,000 deaths. The incidence of CC has been on the rise, particularly among women aged 36 to 50 years, indicating a trend towards younger age groups [3]. Within the spectrum of malignant tumors affecting the female reproductive system in China, CC holds the highest incidence [4, 5]. Numerous factors contribute to the initiation and progression of CC, with a significant proportion of patients found to be infected with high-risk human papillomavirus (HPV) [6]. Early-stage CC patients often present with symptoms such as vaginal bleeding and drainage. However, due to the mild nature of these early signs or symptoms, timely detection is challenging. Consequently, most CC cases are diagnosed at advanced stages [7, 8]. Recent advancements in medical capabilities have facilitated early detection and treatment of CC in clinical practice [9]. When managing CC patients, physicians must consider various factors, including clinical stage, age, fertility plans, overall health status, and medical infrastructure, to formulate personalized treatment plans [10]. Presently, surgical resection is a common approach for treating early-stage CC patients in China [11, 12].

Currently, radical hysterectomy remains the primary clinical intervention for early-stage CC [13, 14]. This procedure involves the removal of the lesion along with lymph node dissection. In clinical practice, when performing radical hysterectomy for early-stage CC patients, the choice between transabdominal and abdominal surgery is typically made [15, 16]. Historically, open radical hysterectomy (ORH) combined with pelvic lymphadenectomy was frequently employed. While this approach demonstrated effective clinical outcomes by allowing removal of pelvic lymph nodes, the abdominal cavity, and the entire uterus, it also resulted in substantial trauma and an elevated risk of postoperative complications, significantly impacting patients' quality of life [17, 18]. In recent years, with the ongoing advancement of minimally invasive techniques, laparoscopic surgery has gained considerable attention and become increasingly popular in the treatment of CC [19-21]. The utilization of laparoscopic hysterectomy not only achieves the goal of

minimizing trauma and facilitating rapid patient recovery but also boasts high levels of safety and feasibility. Nevertheless, there are still lingering controversies regarding the selection between these two treatment modalities in the clinical management of CC.

In summary, both minimally invasive radical hysterectomy (MIRH) and ORH find extensive application in the clinical treatment of CC with primary chemoradiation. However, variations persist in the assessment of the therapeutic efficacy of MIRH and ORH in CC patients. To comprehensively evaluate the impact of MIRH and ORH on individuals with CC, further systematic investigations are warranted. The uniqueness of meta-analysis lies in its ability to integrate results from multiple independent studies, enhancing statistical power to comprehensively assess both consistency and variability among different studies. This comprehensive research approach can provide decision-makers with more compelling evidence, guiding clinical practice. In this study, our focus was on the application of novel minimally invasive surgical techniques in hysterectomy, systematically comparing the efficacy of MIRH with traditional ORH in the treatment of CC. This research aimed to offer healthcare professionals and patients a more comprehensive range of treatment options.

MATERIALS AND METHODS

Literature search

Literature searches were conducted across databases, including PubMed, Web of Science core database, Nature, and Science Direct, spanning from January 2007 to the present. Keywords such as "minimally invasive radical hysterectomy," "open radical hysterectomy," and "cervical cancer," were employed, combined using "or" and "and." No language restrictions were applied in the literature search.

Criteria for enrolling and excluding the literatures

Criteria for literature inclusion were as follows: (1) articles published between January 2007 and January 2023; (2) articles focusing on the efficacy of MIRH and ORH in patients with CC; (3) studies with a minimum sample size of 15; (4) inclusion of available data, such as relative risk (RR) or odds ratio (OR), along with 95% confidence intervals (CI).

Exclusion criteria comprised: (1) review articles, conference reports, experience lectures, individual case reports, and commentaries; (2) studies unrelated to the subject; (3) studies lacking a control group or presenting non-comparable samples between groups; (4) preference for the highest quality literature when multiple articles presented the same dataset; (5) small sample size studies; (6)

incomplete study type descriptions and incorrect randomization controls; (7) repeated reporting of literature; (8) those with unavailable full texts from authors; (9) inability to extract valid outcome data; (10) adherence to specific exclusion requirements.

Quality evaluation

Independently, two investigators reviewed the retrieved literature, assessed the full texts, and extracted relevant data. Any disagreements or disputes were resolved through discussion or with the assistance of a third investigator. The quality of the included literature was evaluated using the Jadad scale, considering factors such as (1) randomization in controlled studies, (2) appropriateness of the randomization method, (3) implementation of double-blind tests, (4) appropriateness of the double-blind method, and (5) handling of patient loss to follow-up or withdrawal during the study, including elucidation of reasons and utilization of intention-to-treat analysis methods. A score of 1 was assigned for "Yes" and 0 for "No," resulting in a total score ranging from 0 to 5. Studies with score of less than 2 were categorized as low-quality, while those with a score greater than 2 were considered high-quality.

Additionally, the Cochrane Handbook of Reviews 4.2.6 was employed for further quality evaluation, assessing (1) whether it was a randomized trial, (2) the presence of allocation concealment, (3) utilization of a blinded trial, (4) completeness of result data, (5) existence of selective reporting results, and (6) identification of any other deviations from standard practices.

Data extraction

Two investigators independently reviewed the literature, focusing on case-control or cohort studies and assessing data completeness. Each literature was then subjected to a quality assessment, with exclusion criteria applied for repeated reports, poor quality, and articles lacking sufficient reporting information for utilization. Data extraction adhered to predefined tables, a database was established, and data underwent thorough verification. In cases of incomplete reporting, authors were contacted to confirm availability, and studies without available data were excluded. Any discrepancies between the two investigators were resolved through discussion with a third party. Data extraction took place after obtaining full-text articles, and the gathered information was inputted into Microsoft Excel for organization. Extracted indicators covered fundamental details from the literature, encompassing article title, study type, initial author, and publication year. Additionally, essential information about study subjects, like grouping method, sample size, patient age, and pertinent indicators, along with outcome indicators such as serum uric acid level, serum hemoglobin level, serum

bilirubin level, and neonatal low body weight, were considered in the analysis.

Statistical analysis

A meta-analysis was carried out on the data obtained from the selected articles using Review Manager 5.3. The heterogeneity analysis of the extracted indicators from the included literature was executed using I^2 and P values in the Peto test. In cases where I^2 was ≥ 50% or $P \leq 0.05$, signifying substantial heterogeneity, the analysis was conducted employing the random effects model (REM). Conversely, if $I^2 < 50\%$ or $P > 0.05$, suggesting no substantial heterogeneity, the fixed-effects model (FEM) was utilized for analysis. Sensitivity analyses for the extraction measures of the included literature were performed through subgroup analyses. Binary categorical variables were defined using RR, OR, or risk difference (RD), and continuous variables were delineated using weighted mean difference (WMD) or standard mean difference (SMD). Each effect size was reported with a 95% CI. Statistical significance between groups was acknowledged at $P < 0.05$.

RESULTS

Literature search results and overview analysis

A total of 1,026 relevant articles were identified, with 592 retrieved from the Medline database, 146 from the EMbase database, and 288 from the Elton B. Stephens Company (EBSCO) database. After excluding 756 duplicate articles, an additional 159 were eliminated due to obvious non-compliance with inclusion criteria upon reviewing titles and abstracts. Following a thorough assessment of full texts, 101 articles were excluded, and ultimately, 10 articles meeting the predefined enrollment criteria were included in the analysis [22-31] (figure 1, table 1).
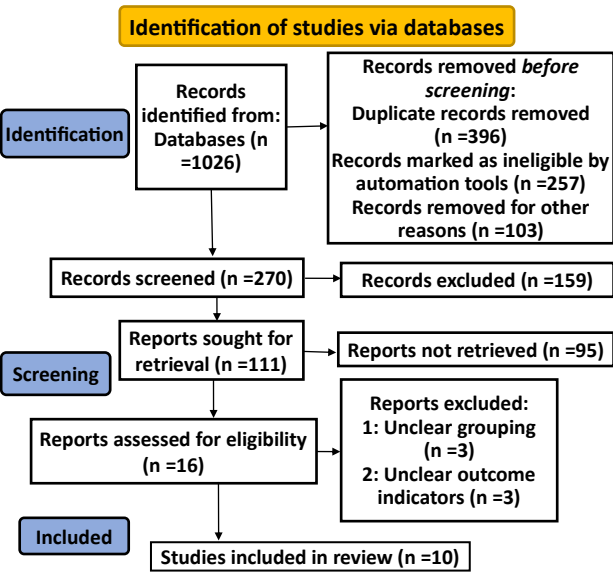
Table 1. Basic data of included literatures

First author (Ref.)	LRH	ORH	Publishing time	Country	Region
Nam [22]	263	263	2012	Korea	Asia
Bogani [23]	65	65	2014	Italy	Europe
Ditto [24]	60	60	2015	Italy	Europe
Shah [25]	109	202	2017	USA	North America
Alfonzo [26]	232	232	2019	Sweden	Europe
Wallin [27]	149	155	2017	Sweden	Europe
Cusimano [28]	475	483	2019	USA	North America
Chiva [29]	291	402	2020	Spain	Europe
Salvo [30]	288	358	2019	USA	North America
Levine [31]	82	44	2020	USA	North America

Evaluation of risk of bias of included literatures

The risk of bias assessment for the seven included articles was conducted using Cochrane Handbook 5.3, and the results were depicted in risk of bias plots (figures 2 and 3). The presentation of the findings was carried out through Review Manager 5.3.
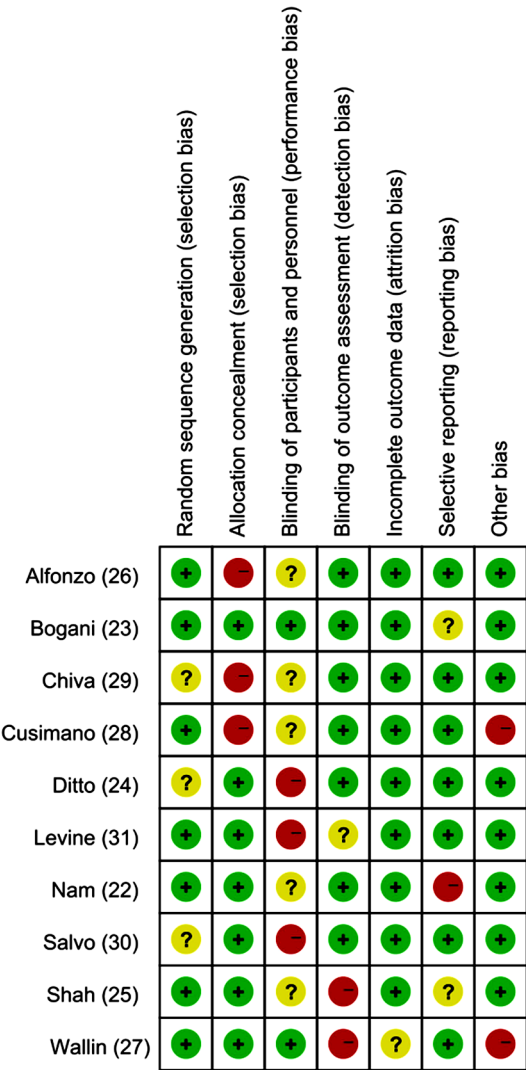

Figure 1. The method for literature inclusion and exclusion.

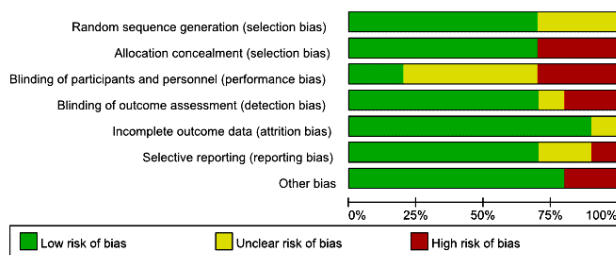**Figure 2.** Bias risk assessment chart of the literatures.

Figure 3. Bar chart for bias risk assessment of the included literatures.
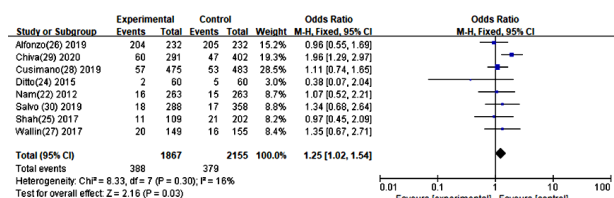

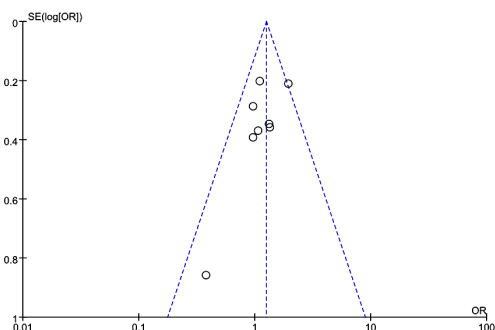**Figure 4.** Forest map for comparison of recurrence of patients.

Figure 5. Funnel plot of recurrence comparison of patients.

Analysis of recurrence

A meta-analysis was conducted to demonstrate the contrast between MIRH and ORH for recurrence in patients with CC. Heterogeneity analysis revealed $I^2=16\%$ and $P=0.30$, leading to the selection of the FEM for subsequent analysis. The meta-comprehensive model analysis indicated an OR of 1.25 with a 95% CI of 1.02 ~ 1.54, Z=2.16, and $P=0.03$. The number of patients with recurrent CC who underwent MIRH was slightly superior to those who underwent ORH, and this difference reached statistical significance ($P<0.05$). The forest plot illustrating the comparative analysis of recurrence in CC patients with primary chemoradiation undergoing MIRH and ORH is presented in figure 4. As depicted in figure 5, the funnel plot exhibits essential symmetry, with data points distributed evenly on either side of the central axis. This suggests the absence of significant publication bias.
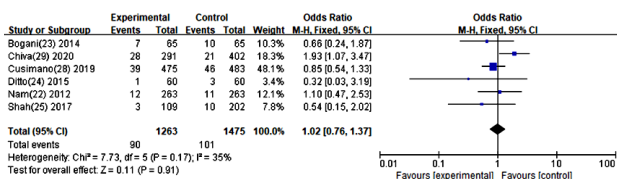

Figure 6. Forest map for deaths.

Analysis of death

A meta-analysis was conducted to compare deaths between CC patients undergoing MIRH and those undergoing ORH. Heterogeneity analysis revealed $I^2=35\%$ and $P=0.17$, leading to the selection of the FEM for subsequent analysis. The meta-comprehensive model analysis indicated an OR of 1.02 with a 95% CI of 0.76 ~ 1.37, Z=0.11, and $P=0.91$. The number of deaths in CC patients treated with MIRH was slightly superior to those treated with ORH ($P>0.05$). The forest plot illustrating the comparative analysis of deaths in CC patients receiving MIRH and ORH is presented in figure 6. However, the funnel plot exhibits asymmetry (figure 7), with most data points concentrated on the left side of the central axis. This suggests the potential presence of publication bias.
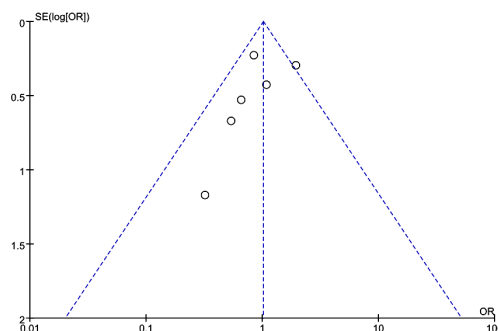

Figure 7. Comparison of deaths of patients receiving different treatment methods.

Analysis of postoperative complications in the two groups

The incidence of postoperative complications in patients with CC treated with MIRH and ORH was compared. Heterogeneity analysis revealed $I^2=0\%$ and $P=0.41$, leading to the selection of the FEM for subsequent analysis. The meta-comprehensive model analysis indicated an OR of 0.40 with a 95% CI of 0.28 ~ 0.57, Z=5.02, and $P<0.00001$. The results demonstrated that the incidence of postoperative complications in CC patients treated with MIRH was slightly inferior to in those treated with ORH ($P<0.05$). The forest plot comparing the incidence of postoperative complications in CC patients receiving MIRH versus ORH is presented in figure 8. However, the funnel plot exhibits asymmetry, with most data points concentrated on the left side of the central axis (figure 9). This implies the potential presence of publication bias.
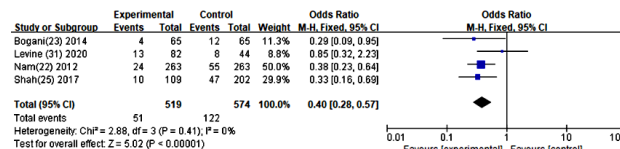

Figure 8. Postoperative complications in patients treated with MIRH and ORH.

Analysis of perioperative blood transfusion

The perioperative blood transfusion was compared between patients with CC treated with MIRH and ORH. Heterogeneity analysis revealed $I^2=0\%$ and $P=0.91$, leading to the selection of the FEM for subsequent analysis. The meta-comprehensive

model analysis indicated an OR of 0.19 with a 95% CI of 0.05 ~ 0.58, Z=4.18, and *P*<0.0001. The results demonstrated that the number of perioperative blood transfusions in CC patients treated with MIRH was slightly inferior to in those treated with ORH (*P*<0.05). A forest plot comparing perioperative blood transfusion in CC patients receiving MIRH versus ORH is presented in figure 10. As depicted in figure 11, the funnel plot exhibits essential symmetry, with data points distributed evenly on either side of the central axis. This implies the absence of marked publication bias.
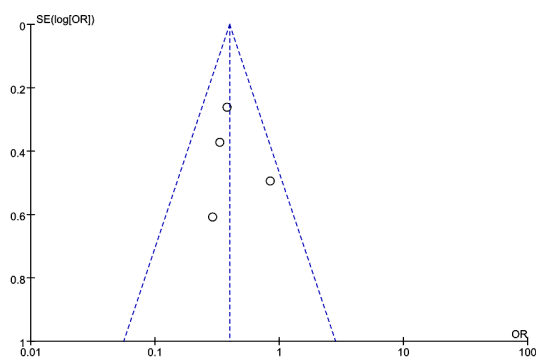

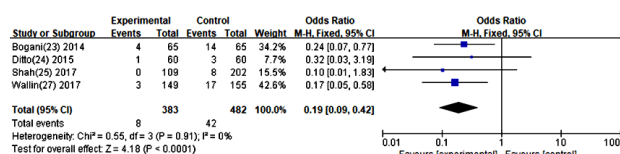**Figure 9.** Postoperative complications in patients.

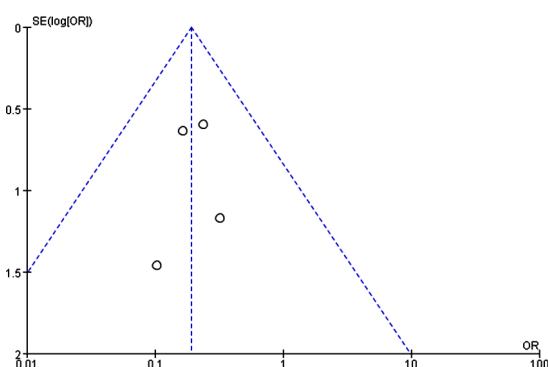**Figure 10.** Perioperative blood transfusion in patients treated with MIRH and ORH.

Figure 11. Perioperative blood transfusion in patients.

DISCUSSION

Approximately a century ago, hysterectomy was introduced as a treatment for CC. Over time, advancements in medical technology have significantly improved postoperative morbidity and mortality, contributing to enhanced overall patient survival. The widespread adoption of minimally invasive surgery, characterized by reduced trauma, fewer postoperative complications, and faster patient recovery, has marked the pinnacle of surgical techniques for gynecological tumors. However, certain studies have raised concerns about the

overall survival rate of MIRH being shorter than that of open surgery. This debate has prompted investigations into the factors contributing to MIRH's elevated recurrence rate and heightened risk of death [32]. Despite the attention given to these concerns, there is limited research exploring potential differences in pathological outcomes between the two surgical methods. Only a small number of studies have indicated no significant difference in the positive rate of the vaginal cuff or resection margin. In this analysis, ten relevant articles were selected, involving 1,949 (47.0%) patients who underwent MIRH and 2,199 (53.0%) patients who underwent ORH among a total of 4,148 CC patients undergoing radical hysterectomy with primary chemoradiation. The results showed that there were 767 patients with recurrence and 223 patients who died. The number of patients receiving MIRH who relapsed was slightly superior to that of patients receiving ORH [OR=1.25, 95% CI=1.02 ~ 1.54, Z=2.16, *P*=0.03] (*P*<0.05); the number of patients receiving MIRH who died was slightly superior to that of patients receiving ORH [OR=1.02, 95% CI=0.76 ~ 1.37, Z=0.11, *P*=0.91], giving a difference with *P*>0.05; three retrospective studies found that the effect of MIRH on postoperative recurrence or death may be related to the tumor size of patients [33-35]. In addition, another explanation for heterogeneity is that it may be related to the technique of minimally invasive surgery.

In the study by Nitecki *et al.* (2020) [36], it was observed that MIRH, relative to open surgery, was associated with an increased risk of recurrence and death in early-stage CC. Similarly, a domestic study also indicated that MIRH was associated with poorer survival outcomes versus open surgery [37]. Patients undergoing MIRH exhibited a slightly lower incidence of complications versus those undergoing ORH [OR=0.40, 95% CI=0.28 ~ 0.57, Z=5.02, *P*<0.00001]. Additionally, patients undergoing MIRH had a slightly lower rate of perioperative blood transfusions than those undergoing ORH [OR=0.19, 95% CI=0.05 ~ 0.58, Z=4.18, *P*<0.0001]. The utilization of laparoscopic techniques for tissue visualization and magnification has demonstrated the potential to enhance disease staging and improve the accuracy of lymphadenectomy. The application of laparoscopy in CC has been advocated as a viable alternative to ORH and pelvic lymphadenectomy. Numerous case-control studies have provided support for the hypothesis that perioperative complications, blood transfusions, and hospital stay duration can be reduced without compromising clinical outcomes.

In summary, MIRH demonstrates superior performance over ORH in reducing complications and perioperative transfusions. However, MIRH is associated with higher risks of recurrence and mortality versus ORH. Nevertheless, these conclusions should be interpreted cautiously as there

are existing controversies and uncertainties, requiring further research for confirmation and additional support. It's important to note that we did not conduct a detailed analysis of individual patient information and disease staging data, which may impact the comprehensiveness and accuracy of the conclusions. Future studies could enhance their assessments of the merits and drawbacks of both surgical approaches by expanding sample sizes, delving deeper into patient characteristics and disease progression, and considering the incorporation of more long-term follow-up data for a more profound understanding of treatment durability.

CONCLUSION

Based on meta-analysis, the difference of treatment effect between MIRH and ORH in patients with CC with primary chemoradiation was investigated. The MIRH had superior risk of recurrence and death compared with ORH. In conclusion, MIRH had superior risk of recurrence and death versus ORH, so ORH has more advantages for CC treatment, which provides a reference.

***Data availability statement*:**
Data not stored in public storage. Data sharing is not applicable to this article as no new data were created or analyzed in this study.

***Ethical statement*:** This study does not require review and/or approval from an ethics committee as it did not involve clinical or animal experiments.

***Declaration of competing interest*:** The authors declare that they have no conflict of interest.

***Author contribution statement*:** All authors listed have significantly contributed to the development and the writing of this article.

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