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Research Article

Comparison of the oncological outcomes of Q-M Type B/C2 abdominal radical RH for FIGO 2018 stage IA1 (LVSI+)-IA2 cervical cancer: A multicentre retrospective study

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Abstract

Purpose: To compare the survival outcomes of abdominal Querleu-Morrow (Q-M) type B and Q-M type C2 radical hysterectomy(RH) for International Federation of Gynecology and Obstetrics(FIGO) 2018 stage IA1 (lymphovascular invasion [LVSI]+)-IA2 cervical cancer to explore the appropriate surgical procedures.

Method: Based on the Clinical Diagnosis and Treatment of Cervical Cancer in China (Four C) database, the real-world study and matched cohort study conditions were used to assess the 5-year overall survival (OS) and disease-free survival (DFS) of patients with cervical cancer classified as the new FIGO 2018 stage IA1 (LVSI+)-IA2 who underwent abdominal type B and type C2 RH from 2004 to 2018.

Results: (1) A total of 203 patients (160 with Q-Mtype BRH; 43 with Q-M type C2 RH) were enrolled. The median follow-up time was 55 months (Q-M type B vs Q-M type C2: 55 months vs 53 months). (2) In the whole study population, 5-year OS/DFS were not significantly different between the groups (OS: 97.8% vs 100%, P=0.397; DFS: 97.1% vs 100%, P=0.370). All patients with Q-M type C RH survived without tumour recurrence. (3) After 1:4 propensity score matching, 125 patients with Q-M type BRH and 41 patients with Q-M type C2RH were included. There was no significant difference in 5-year OS/DFS between the groups (OS:97.5% vs 100%, P=0.433; DFS:98.2% vs 100%, P=0.449). All patients with Q-M type C2RH survived without tumour recurrence. (4) According to the analysis of postoperative exhaust time, defecation time and catheter stopping time, the postoperative defecation time was significantly lower in theQ-M type B group than in the Q-M type C group.

Conclusion: Compared with abdominal Q-M type C2 RH, Q-M type B RH is more beneficial to patients with cervical cancer classified as the new FIGO 2018 stage IA1 (LVSI+)-IA2.

Keywords: Cervical cancer; Abdominal radical hysterectomy; Q-M Type B; Q-M Type C2; Survival outcome.

Introduction

In 2018, the guidelines of the International Federation of Obstetrics and Gynecology (FIGO) for the staging of cervical cancer were revised; these guidelines includes the results of imaging examination and postoperative pathology for the first time, and all cases of lymph node metastasis were classified as stage IIIC. In addition, the extent of horizontal infiltration in the middle stage (2009 FIGO stage IA) was removed as a factor affecting the staging, and it was considered that the measurement of the width of infiltration is greatly influenced by human factors [1]. This updated system classifies the cases by the depth of infiltration in the middle of 2009 FIGO stage IB1 (horizontal infiltration depth <5 mm but >7 mm) as FIGO2018 stage IA. According to the first edition of the clinical practice guide for cervical cancer by the National Comprehensive Cancer Network (NCCN) in 2021, Querleu-Morrow (Q-M) type Bradical hysterectomy (RH) can be selected for patients with lymphovascular invasion (LVSI) (+) cervical cancer in stage IA1, and Q-M type C2 RH is recommended for patients with IA2 cervical cancer who do not retain reproductive function [2]. Q-M type C2 RH has a larger range of parametrial resection than Q-M type B RH, so it has a higher incidence of perioperative complications [3-6]. Due to the removal of the high-risk factor for lymph node metastasis, we need to explore whether Q-M type B RH can be used in patients with cervical cancer in FIGO 2018 stage IA1 (LVSI+)-IA2.

In this study, patients who underwent abdominal Q-M type B/Q-M type C2 RH for FIGO 2018 stage IA1 (LVSI+)-IA2 cervical cancer were selected from the Four C database. Real-world and matched cohort study conditions were used to compare the 5-year overall survival (OS) and disease-free survival (DFS) of patients with cervical cancer who underwent abdominal Q-M type B and Q-M type C2 RH for FIGO 2018 stage IA1 (LVSI+)-IA2 cervical cancer.

Methods

Data collection

Analysis of the Four C Database was conducted for a multicentre, retrospective cohort study and was approved by the Ethics Committee of Nanfang Hospital, Southern Medical University (Ethics No. NFEC-2017-135) with International Clinical Trial Registration No. CHiCTR1800017778, (International Clinical Trials Registry Platform Search Port, http://apps.who.int/trialsearch/). The methods of Four C data collection and database construction can be found in the published articles of this team [7-10]. Due to the long time span of patient enrolment, the cases in this database were staged by the FIGO 1994 system before 2009 and the FIGO 2009 system after 2009. All cases were restaged according to the revised FIGO 2018 system after entering the database.

Inclusion criteria and exclusion criteria

The inclusion criteria were as follows: (1) age ≥18 years old; (2) pathological diagnosis of cervical cancer by cervical biopsy; (3) postoperative histopathological type of squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma; (4) FIGO 2018 stage IA1 (LVSI+)-IA2; (5) surgical approach: laparotomy; (6) Q-M type B or Q-M type C2RH + pelvic lymphadenectomy ± para-aorticlymphadenectomy/biopsy. (7) the lymphadenectomy/biopsy; (7) complete postoperative pathological report with negative lymph node status; and (8) follow-up.

The exclusion criteria were as follows:

(1) did not meet the above criteria or (2) pregnancy complicated with cervical cancer, stump cancer or other malignant tumours.

Case-control matching

To eliminate the influence of baseline differences, this study included the following variables for Propensity Score Matching (PSM): Age, parametrial invasion, vaginal margin, depth of cervical myometrial invasion, pathological type, LVSI, postoperative adjuvant treatment, and FIGO stage (2018) to balance the baseline between groups and reduce the possible bias and the influence of confounding factors.

Observation indicators

The main long-term oncological outcome indicators were OS and DFS. The fifth year after the operation was taken as the cut-off point. OS was defined as the date of diagnosis to death of any cause or the last effective follow-up; DFS was defined as death/recurrence of any cause or the last effective follow-up from the date of diagnosis to the occurrence of any cause.

Definition of surgery type

The types of surgery in this study were based on the Q-M classification [11], and the types of operations recorded in the clinic were reclassified according to this classification [12].

Statistical analysis

SPSS 23.0 software (IBM Corporation, Armonk, NY, USA) was used for statistical analysis. The measurement data are expressed as the mean ± standard deviation, Student's t-test was used for inter-group comparisons, the counting data are expressed as percentages (%), and the inter-group rates were compared by the chi-square test or Fisher's exact probability method. The follow-up time was expressed as the median; survival curves for the two groups were generated by the Kaplan-Meier (K-M) method and compared by the log-rank test; the independent risk factors were analysed by a multi-factor Cox regression model, and the related hazard ratios and confidence intervals were calculated. The PSM score was determined by a logical regression model. Differences with $P < 0.05$ were considered statistically significant. The specific statistical methods can be found in the articles published by our team [7-10].

Results

Study Population

Data for a total of 63926 patients with cervical cancer in 47 hospitals in China from 2004 to 2018 were collected. Among them, 160 patients aged 43.33 ± 7.915 years underwent Q-M type BRH, and 43 patiens aged 41.95 ± 7.813 years underwent Q-M type C2RH. The median follow-up time was 55 months (Q-M type B vs Q-M type C2: 55 months vs 53 months). The data filtering process is shown in Figure 1.

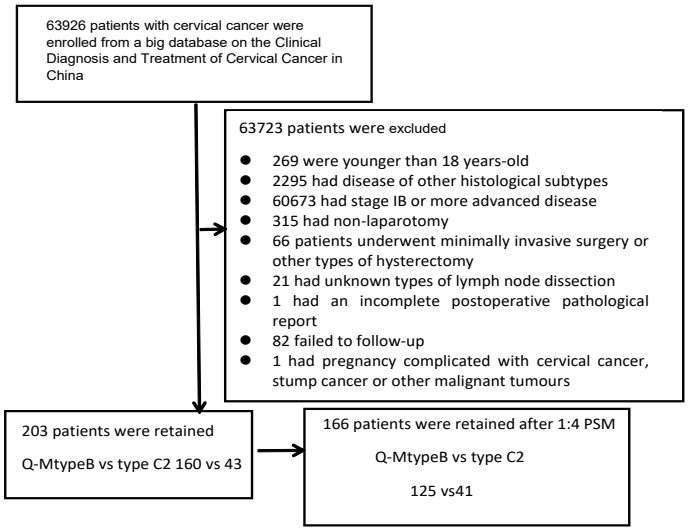

Figure 1: Data screening flow chart.

Table 1: Characteristics of patients with FIGO 2018 IA1 (LVSI+)-IA2 stage cervical cancer before and after 1:4 PSM.

Variables	Before matching		P value	After matching		P value
	Q-M type B (N=160)	Q-M type C2 (N=43)		Q-M type B (N=125)	Q-M type C2 (N=41)	
Age, years	43.33 ± 7.915	41.95 ± 7.813	0.703	43.01 ± 98.143	42.07 ± 7.853	0.939
Histological subtype			0.506			0.573
Squamous-cell carcinoma	149 (93.1%	42 (97.7%)		117 (93.6%)	40 (97.6%)	
Adenocarcinoma	9 (5.6%)	1 (2.3%)		6 (4.8%)	1 (2.4%)	
Adenosquamous carcinoma	2 (1.3%)	0 (0%)		2 (1.6%)	0 (0%)	
Postoperative adjuvant therapy			0.056			0.420
No treatment	147 (91.9%)	34 (79.1%)		114 (91.2%)	34 (82.9%)	
Simple chemotherapy	4 (2.5%)	3 (7.0%)		2 (1.6%)	1 (2.4%)	
Radiotherapy and chemotherapy	9 (5.6%)	6 (14.0%)		9 (7.2%)	6 (14.6%)	
Vaginal margin			0.316			0.404

Negative	159 (99.4%)	42 (97.7%)		124 (99.2%)	40 (97.6%)	
Positive	1 (0.6%)	1 (2.3%)		1 (0.8%)	1 (2.4%)	
Parametrial involvement						
Negative	160 (100%)	43 (100%)		125 (100%)	41 (100%)	
Positive	0	0		0	0	
LVSI			0.910			0.977
Negative	146 (91.3%)	39 (90.7%)		113 (90.4%)	37 (90.2%)	
Positive	14 (8.7%)	4 (9.3%)		12 (9.6%)	4 (9.8%)	
Depth of tumour invasion			0.048			0.467
≤1/2	118 (73.8%)	25 (58.1%)		89 (71.2%)	25 (61.0%)	
＞1/2	11 (6.9%)	2 (4.7%)		5 (4.0%)	2 (4.9%)	
Unknown	31 (19.3%)	16 (37.2%)		31 (24.8%)	14 (34.1%)	
FIGO stage of disease			0.460			0.420
IA1	4 (2.5%)	2 (4.7%)		3 (2.4%)	2 (4.9%)	
IA2	156 (97.5%)	41 (95.3%)		122 (97.6%)	39 (95.1%)	

According to the results of the baseline analysis between the two groups, there was a significant difference in the depth of cervical invasion between the two groups. An additional 1:4 PSM step was performed between the two groups, and a total of 166 patients were included after pairing. A total of 125 patients aged 43.01 ± 8.143 years were included in the Q-M type BRH group. Forty-one patients aged 42.07 ± 7.853 years were included in the Q-M type C2RH group. The median follow-up time was 54.5 months (Q-Mtype B group vs Q-Mtype C2 group: 55 months vs 54 months). The baseline between the two groups was balanced in terms of age, paracentral invasion, vaginal stump invasion, LVSI, cervical invasion and postoperative adjuvant therapy (Table 1).

Comparison of oncology outcomes between the initial real world study and 1:4 psm groups

In the real-world study, K-M survival analysis showed that there was no significant difference in the 5-year OS and DFS between the Q-M type B RH group and the Q-M type C2 RH group (OS:97.1% vs 100%, p=0.370; DFS: 100% vs 100%, p=0.397) (Figures 2a,2b). Because there was no death in the Q-M type C2 group, independent risk factors could not be analysed by Cox multivariate analysis.

The results of K-M survival analysis after 1:4 PSM showed that there was no significant difference in 5-year OS and DFS between the Q-M type B RH group and the Q-M type C2 RH group (OS: 97.5% vs 100%, p=0.433; DFS: 98.2% vs 100%, p=0.449), and the results were the same as those in the real-world study (Figures 2C, 2d). Because there was no death in the Q-M type C2 group, independent risk factors could not be analysed by Cox multivariate analysis.

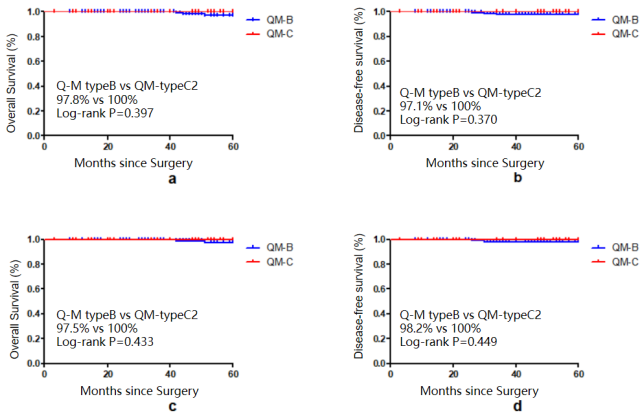

Figure 2: a,b: The 5-year OS and DFS of the initial real-world study group; **c, d:** the 5-year OS and DFS after 1:1 PSM.
Survival Analysis of Patients with FIGO 2018 IA1 (LVSI+)-IA2 stage Cervical Cancer Before and After 1:4 PSM.

Analysis of related indexes in the perioperative period

In this study, the perioperative-related indexes of the Q-M type B RH group and the Q-M type C2 RH group were statistically analysed, and the results are shown in Table 2. The results showed that the postoperative exhaust time, defecation time and catheter stopping time in the Q-M type B RH group were less than those in the Q-M type C2 RH group, and there was a significant difference in the postoperative defecation time between the two groups, suggesting that the postoperative recovery in the Q-M type B group was better than that in the Q-M type C2 group.

Table 2: Analysis of related indexes in the perioperative period.

	Q-M type B (n=160)	Q-M type C2 (n=43)	P
Postoperative exhaust time	2.75 ± 0.770	2.88 ± 0.905	0.714
Defecation time	4.18 ± 1.274	5.04 ± 2.274	0.030
Catheter stopping time	9.11 ± 3.587	9.43 ± 3.327	0.489
Discharge with cathetertime	10.38 ± 3.788	7.50 ± 2.393	0.203
Postoperative residual urine volume	93.44 ± 139.077	69.25 ± 45.632	0.391

Discussion

In this multicentre, retrospective, cohort study, there was no significant difference between the 5-year OS and DFS in the real-world study of FIGO 2018 stage IA1 (LVSI+)-IA2 cervical cancer patients who underwent abdominal Q-M type BRH and Q-M type C2RH. To further reduce the deviation and confounding factors, 1:4 PSM was carried out, and the same conclusion was drawn.

The FIGO 2018 staging system considers the results of imaging examination and postoperative pathology, and the main differences from the FIGO 2009 staging system are as follows: (1) the width of interstitial infiltration is no longer considered for IA; (2) for stage IB sub-staging, the tumour size is increased to the boundary of 2 cm; (3) all patients with lymph node metastasis examined by imaging or postoperative pathology are classified into the new stage IIIC and then divided into stage IIIC1 (pelvic lymph node metastasis) and stage IIIC2 (abdominal para-aortic lymph node metastasis) according to the location of the positive lymph nodes.

Different stages affect the treatment and choice of cervical cancer. According to the 2021 NCCN guidelines, cervical conization + pelvic lymphadenectomy or radical cervicectomy + pelvic lymphadenectomy is recommended for patients with reproductive needs and stage IA1 (LVSI+)-IA2 cervical cancer. For those with stage IA1 (LVSI+) disease without reproductive needs, Q-M type BRH is recommended.Q-M type Bor Q-M type C2RH is feasible for stage IA2 cervical cancer patients without reproductive demand [2]. Compared with Q-M type C2 RH, Q-M type BRH has the advantages of a lower scope of parametrial resection, a shorter operation time, faster postoperative recovery and a lower recurrence rate. Therefore, it is particularly important to choose the operation with the least trauma and quickest recoveryto improve the quality of life of patients.

The FIGO 2018 staging system modifies the definition of stage IA disease. If the lesions with infiltration width >7 mm and infiltration depth <5 mm are classified as IB1 stage according to FIGO 2009 staging in and reduced to IA stage in the FIGO 2018 staging system, do cervical cancer patients with new FIGO 2018 stage IA1 (LVSI+)-IA2 disease still need Q-M type C2 RH surgery? We further explored whether the outcome differs among patients with FIGO 2018 stage IA1 (LVSI+)-IA2 disease undergoing Q-M type B vs Q-M type C2RH.

Ditto et al [14] analysed stage IA2, IB1 and IIA1 cervical cancer. The survival results of patients who underwent Piver II and III RH showed that the 5-year OS of the type II group was better after the operation (95.2% vs 86.8%) and that the 5-year DFS of the two groups was similar (91.2% vs 82.9%), which was different from the results of this study. The reasons for the difference may be that the former study (1) used the FIGO 2009 staging system, (2) was not limited to patients with stage IA2 disease and (3) included patients with minimally invasive surgery. PlottiF et al [15] compared the oncological outcomes of IA-IIA stage patients with Q-M type B/Q-M type C2RH cervical cancer, and the results showed that there was no difference in oncological outcome between the two groups. Compared with Q-M type C2RH for cervical cancer, Q-M type B RH had a shorter operation time, lower blood loss, faster postoperative recovery and a lower incidence of postoperative bladder dysfunction. In this study, the postoperative defecation, defecation and catheter stopping time of the Q-M type B group was lower than that of the Q-M type C2 group, and the difference in postoperative defecation time between the two groups was statistically significant, suggesting that the Q-M type B group recovered faster after the operation. Photopulos GJ et al [16] compared perioperative-related indexes and postoperative complications between Q-M type BRH and Q-M type C2 RH. The results showed that Q-M type BRH had the advantages of rapid recovery, a lower incidence of postoperative complications such as fistula and a low recurrence rate. Sun H et al [13] pointed out that there was no difference in the 2-year DFS between Q-M type BRH and Q-M type C2 RH(100% vs 97.9%). The operation time, intraoperative blood loss and postoperative exhaust time with Q-M type BRH were less than those with Q-M type C2 RH, which was consistent with the conclusion of this paper. The follow-up time was 2 years after the operation, but a longer follow-up was needed to assess the oncological outcomes , and the staging system was still the FIGO 2009 system. Some studies have pointed out that the revised new FIGO 2018 staging system can better reflect the survival of patients with cervical cancer [17,18]. For patients with FIGO 2009 stage IB1 disease but stage IA disease according to FIGO 2018, we should re-explore the suitable mode of operation. Based on real-world data from China and the balancing of any possible confounding factors, this paper discusses suitable surgical methods for patients with cervical cancer classified as the new FIGO 2018 stage IA1 (LVSI+)-IA2 stage by laparotomy.

Limitations

There are some limitations to this study. First, this study included case data from 47 hospitals in China with some missing clinical data. Second, there is a certain deviation in the surgical level and experience of surgeons. Third, the time span of patient enrolment was long, and the surgeons' learning curves should be considered. Fourth, this study did not analyse and compare the complications and quality of life. Fifth, the number of cases included in this study was relatively small. Only 43 patients with cervical cancer in stage IA1 (LVSI+)-IA2 underwent abdominal Q-M type C2RH surgery, and all of them survived. Independent risk factors were not further analysed, and subsequent data can be added for further analysis.

Although there are some limitations to our study, this multicentre, large-sample study can effectively reflect the practical value of the new FIGO 2018 stagein the treatment of cervical cancer in China, and PSM was used to strictly control the confounding factors. Therefore, we think that the results of this study have high credibility.

In short, for FIGO 2018 stage IA1 (LVSI+)-IA2 cervical cancer, there was no significant difference in the 5-year OS or DFS of the Q-M type BRH group and that of the Q-M type C2RH group, but the postoperative recovery in the Q-M type B RH group was better than that in the Q-M type C2RH group. It is suggested that for the above mentioned stages of cervical cancer, the use of Q-M type BRH surgery may benefit patients, and long-term follow-up may further verify the conclusion of this study.

Declarations

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Author contributions: All authors approved the final version. Pengfei Li contributed to the literature review, study question, prepared the first draft of the report and contributed to subsequent versions.,Li Wangparticipated in the drafting of the original version of this manuscript. Yijia Lu and Zhihua Liu performed the literature search, data collection, data analysis and interpretation and drafted and revised the manuscript. Li Wang, Shan Kang, Bin Zhu, Zhong Lin and Xiaohong Wang, Ben Ma, Zhonghai Wang, Xiaonong Bin and Jinghe Lang performed the data analysis and interpretation. Chunlin Chen and Ping Liu participated in the protocol development, study-supervision and study design. Chunlin Chen is the guarantor. All authors participated in reviewing the writing and editing the manuscript.

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