

ORIGINAL RESEARCH

Comparison of survival outcomes following radiotherapy versus radical hysterectomy in patients with stage IIA cervical squamous cell carcinoma

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Abstract

This study explored the differences in survival outcomes of cervical squamous cell carcinoma (SCC) patients diagnosed with stage IIA who underwent radical hysterectomy (RH) versus radiotherapy (RT). Eligible stage IIA cervical SCC cases were screened from the C4 database. They were divided into RH and RT groups based on their treatments and in a 1:2 ratio utilizing propensity score matching (PSM). Their 5-year overall survival (OS) and disease-free survival (DFS) before and after PSM were compared. Before PSM analysis, the results showed that patients from the RT group ($n = 421$) had significantly poorer 5-year OS and DFS rates compared with the RH group ($n = 761$) (OS: 77.2% vs. 85.6%, $p < 0.001$, HR = 1.789; DFS: 74.9% vs. 80.0%, $p = 0.006$, HR = 1.447). After stratification in a 1:2 ratio, PSM analysis results showed that the 5-year OS and DFS rates of stage IIA1 patients from the RT group ($n = 226$) were significantly poorer than the RH group ($n = 429$) (OS: 78.1% vs. 87.2%, $p < 0.001$, HR = 2.203; DFS: 78.2% vs. 83.7%, $p = 0.011$, HR = 1.681), while no significant difference in 5-year OS and DFS rates were observed between the RT ($n = 173$) and RH ($n = 266$) groups (OS: 75.2% vs. 83.8%, $p = 0.054$; DFS: 71.4% vs. 79.5%, $p = 0.070$) of stage IIA2 patients. RH was associated with better OS and DFS outcomes than RT in cervical SCC patients diagnosed with stage IIA disease. Subgroup analyses showed that RH had superior OS and DFS benefits than RT in stage IIA1 cases, while no significant difference in survival was observed for stage IIA2 patients.

Keywords

Cervical cancer; Radical hysterectomy; Radiotherapy; Overall survival; Disease-free survival

1. Introduction

Cervical cancer is one of the most common cancer in women, with nearly 570,000 new cases and 311,000 related deaths worldwide in 2018 [1]. For early-stage patients, both radical

hysterectomy (RH) and radiotherapy (RT) were shown to have similar therapeutic effects but different incidences and types of complications [2]. RT can be selected and was shown effective in all cervical cancer stages and was shown to provide a 5-year overall survival rate ranging between 78% to 91%

[3, 4]. Comparatively, surgery can provide more pathological information, which can stratify cervical cancer patients based on their risk of recurrence to undergo postoperative complementary treatments, and has been associated with a 5-year overall survival ranging between 54% to 90% [5, 6].

Currently, the efficacy of different treatment methods for cervical cancer remains debatable. Related studies are limited due to a lack of detailed histological classification in the cases analyzed. The recent 2022 National Comprehensive Cancer Network (NCCN) guidelines recommend RH combined with pelvic lymphadenectomy (category 1) or pelvic external beam radiation therapy (EBRT) plus brachytherapy for cervical cancer patients staged as IB1, IB2 and IIA1, while for those staged as IB3 and IIA2, definitive pelvic EBRT combined with concurrent platinum-based chemotherapy plus brachytherapy (category 1) or RH combined with pelvic lymphadenectomy (category 2B) is recommended [7].

In this study, we selected stage IIA patients with cervical squamous cell carcinoma (SCC) from a large cervical cancer database to compare the survival outcomes of patients who underwent RT versus RH. Further stratification of the stage IIA cases was performed to confirm the benefits of the treatments in different stage IIA subgroups.

2. Methods

2.1 Patients

This was a retrospective study performed on data collected from a large multicenter cervical cancer database, using previously described methods [8–12]. Briefly, the database contains the data of a total of 46,313 cervical cancer patients who underwent surgery or RT from January 2004 to December 2016 at 37 hospitals in mainland China.

2.2 Patients selection criteria

2.2.1 Inclusion criteria

(1) The RT group: patients aged ≥ 18 years; classified as clinical stage IIA based on the 2009 The International Federation of Gynecology and Obstetrics (FIGO) criteria; histologically diagnosed as SCC; initial treatment RT; treatment including external irradiation + brachytherapy; receive a standardized radiotherapy dose; paclitaxel-based chemotherapy regimens with carboplatin/other platinum/5FU/others, following related guidelines and drug instructions; completed the treatment cycles; contained survival data.

(2) The RH group: patients aged ≥ 18 years; classified as clinical stage IIA based on the 2009 FIGO criteria; histologically diagnosed as SCC; initial treatment open surgery, Querleu-Morrow B (QM-B) or QM-C hysterectomy + pelvic lymphadenectomy \pm paraaortic lymphadenectomy; without neoadjuvant chemo-/radiotherapy; underwent standard postoperative treatment following related guidelines [7]; pelvic external irradiation with/without concurrent cisplatin-based chemotherapy for those with ≥ 2 medium postoperative risk factors (*i.e.*, tumor size ≥ 4 cm, T stage $\geq 1/2$, and lymphovascular space invasion); chemotherapy regimens included paclitaxel+carboplatin, paclitaxel + other platinum, platinum + 5FU, or platinum + other, following

related guidelines and drug instructions; contained survival data.

2.2.2 Exclusion criteria

Cases that did not meet the above criteria; pregnant women; accidental discovery of cervical cancer; carcinoma of the cervical stump; and synchronous or metachronous cancer.

2.3 Observation indicators

The study endpoints were 5-year overall survival (OS; time period from diagnosis to death from any cause) and disease-free survival (DFS; time period from diagnosis to death or recurrence).

2.4 Statistical methods

The SPSS v24.0 software (IBM, Chicago, IL, USA) was used for data analyses. Data are expressed as mean \pm standard deviation ($x \pm s$) and enumeration data as a percentage (%). The mean value of the data was compared using an independent t-test. Intergroup comparisons were performed using the chi-square test. Non-parametric rank-sum test was used for classified or rank variables. To reduce selection bias, propensity score matching (PSM) using nearest neighbor matching, 1:2 ratio, and calipers of width equal to 0.1 of standard deviations was conducted [13]. OS and DFS curves were plotted using the Kaplan-Meier method, and the log-rank test was used to compare the patients' survival. The Cox proportional hazards risk regression model was employed for multivariate analysis to identify independent factors associated with patients' survival and obtain related risks and confidence interval (CI) values. A two-sided $p < 0.05$ was used to determine significant differences.

3. Results

3.1 Data screening

Based on the screening criteria, 3159 patients were selected for this study, of whom 538 were assigned to the RT group and 2621 to the RH group (Fig. 1). Then, we performed the 1:2 PSM analysis to adjust the baseline data, after which 421 and 761 patients were assigned to the RT and RH groups, respectively. There were 140 patients who could not be classified because their specific stage of IIA was unknown. Subgroup analysis using FIGO stages assigned 286 stage IIA1 patients to the RT group and 1857 to the RH group. Following 1:2 PSM, 226 and 429 patients were grouped into the RT and RH groups. Further, 252 stage IIA2 patients were classified into the RT group and 624 into the RH group. Following 1:2 PSM, 173 and 266 patients were categorized into the RT and RH groups.

3.2 Survival differences between the RT and RH groups

We observed that baseline characteristics such as tumor diameter and age were imbalanced between the RT and RH groups. To eliminate confounding factors interference, a 1:2 PSM followed by survival analysis was conducted. Before matching, 3159 cases were eligible (RT group, $n = 538$ and RH group, $n =$

TABLE 1. Data of patients with stage IIA cervical cancer before and after matching.

	Unmatched		<i>p</i>	Matched		<i>p</i>
	RH (n = 2621)	RT (n = 538)		RH (n = 761)	RT (n = 421)	
Age (years)	52.13 ± 9.46	55.31 ± 10.46	<0.001	54.30 ± 9.32	54.30 ± 9.78	0.991
Tumor size (cm)	3.43 ± 1.21	4.23 ± 1.40	<0.001	3.98 ± 1.22	4.07 ± 1.23	0.217

RH, radical hysterectomy; RT, radiotherapy.

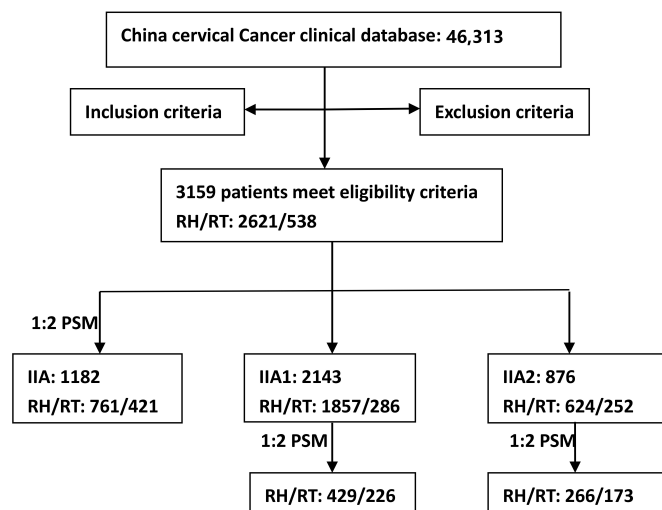


FIGURE 1. Data screening process for this study. RH: radical hysterectomy, RT: radiotherapy; PSM: propensity score matching.

= 2621). The median follow-up of patients from the RT and RH groups was 35 and 48 months, respectively. In addition, we also observed that 97 (18.0%) and 253 (9.7%) patients in the respective groups died within 5 years, demonstrating a 5-year OS of 75.1% and 88.0% ($p < 0.001$) and a DFS of 74.0% and 81.8% ($p < 0.001$), respectively. Multivariate analyses showed that the RT group was associated with a higher risk of death or recurrence than the RH group (death, HR = 1.960, $p < 0.001$; recurrence/death, HR = 1.484, $p = 0.001$).

After 1:2 PSM, 421 patients were categorized into the RT group and 761 into the RH group, with a median follow-up of 35 and 47 months, respectively, during which 85 (20.2%) and 127 (16.7%) patients in the respective groups died within 5 years. The 5-year OS rates were 77.2% and 85.6% ($p < 0.001$) and DFS rates were 74.9% and 80.0% ($p = 0.006$), respectively. Multivariate analyses showed that the RT group had a higher risk of death or recurrence than the RH group (death, HR = 1.789, $p < 0.001$; recurrence/death, HR = 1.447, $p = 0.009$) (Table 1, Fig. 2).

3.3 Subgroup analysis of oncological outcomes before and after PSM: stage IIA1 cervical cancer

In stage IIA1 patients, we found that the baseline information between the RT (n = 286) and RH group (n = 1857) groups was imbalanced. To eliminate confounding factors interference, a

1:2 PSM followed by survival analysis was conducted.

Before matching, there were 286 patients in the RT group and 1857 in the RH group, with a median follow-up of 35 and 47 months, respectively. In addition, 48 (16.8%) and 159 (9.6%) people in the respective groups died within 5 years of diagnosis, resulting in a 5-year OS rate of 77.8% and 89.0% ($p < 0.001$) and DFS of 77.5% and 83.1% ($p < 0.001$), respectively. Multivariate analyses showed that the RT group had higher risks of death or recurrence than the RH group (death, HR = 2.703, $p < 0.001$; recurrence/death, HR = 1.843, $p < 0.001$).

Following 1:2 PSM, 226 and 429 patients were categorized into the RT and RH groups, and their respective followed up for a median of 34 and 47 months, during which 36 (15.9%) and 40 (9.3%) patients died within 5 years, respectively. The 5-year OS and DFS rates were 78.1% and 87.2% ($p < 0.001$) and 78.2% and 83.7% ($p = 0.011$), respectively. Multivariate analyses showed that the RT group had higher risks of death or recurrence than the RH group (death, HR = 2.203, $p = 0.001$; recurrence/death, HR = 1.681, $p = 0.012$) (Table 2, Fig. 3).

3.4 Survival outcomes of stage IIA2 cervical cancer patients before and after PSM

The baseline information of stage IIA2 patients between the RT (n = 252) and RH (n = 624) groups was imbalanced; thus, to eliminate confounding factors interference, a 1:2 PSM followed by survival analysis was performed.

Before matching, there were 252 patients in the RT group and 624 in the RH group, with a median follow-up of 34 and 48 months, during which 49 (19.4%) and 78 (12.5%) patients from the respective groups died within 5 years of treatment, resulting in a 5-year OS and DFS rates of 72.5% and 85.3% ($p < 0.001$) and 69.9% and 78.8% ($p = 0.004$), respectively. Multivariate analyses showed that the risks of death of the RT group were higher than the RH group (HR = 1.622, $p = 0.012$) but had similar recurrence risks ($p = 0.067$).

Following 1:2 PSM, 173 and 266 patients were categorized into the RT and RH groups and had a median follow-up of 35 and 50 months, respectively. In addition, 30 (17.3%) and 36 (13.5%) patients in the respective groups died within 5 years of diagnosis, resulting in a 5-year OS and DFS rates of 75.2% and 83.8% ($p = 0.054$) and DFS of 71.4% and 79.5% ($p = 0.070$), respectively. Multivariate analyses showed that the RT and RH groups had similar risks of death and recurrence (death, $p = 0.054$; recurrence/death, $p = 0.072$) (Table 3, Fig. 4).

TABLE 2. Data of patients with stage IIA1 cervical cancer before and after matching.

	Unmatched			Matched		
	RH (n = 1857)	RT (n = 286)	<i>p</i>	RH (n = 429)	RT (n = 226)	<i>p</i>
Age (years)	52.53 ± 9.45	58.25 ± 10.20	<0.001	55.89 ± 9.10	56.45 ± 9.13	0.456
Tumor size (cm)	3.09 ± 1.00	3.51 ± 1.10	<0.001	3.39 ± 0.96	3.45 ± 0.93	0.49

RH, radical hysterectomy; RT, radiotherapy.

TABLE 3. Data of patients with stage IIA2 cervical cancer before and after matching.

	Unmatched			Matched		
	RH (n = 624)	RT (n = 252)	<i>p</i>	RH (n = 266)	RT (n = 173)	<i>p</i>
Age (years)	50.96 ± 9.09	51.98 ± 9.76	0.142	50.70 ± 8.38	50.51 ± 8.93	0.824
Tumor size (cm)	4.38 ± 1.27	5.06 ± 1.23	<0.001	4.91 ± 0.95	4.95 ± 1.03	0.623

RH, radical hysterectomy; RT, radiotherapy.

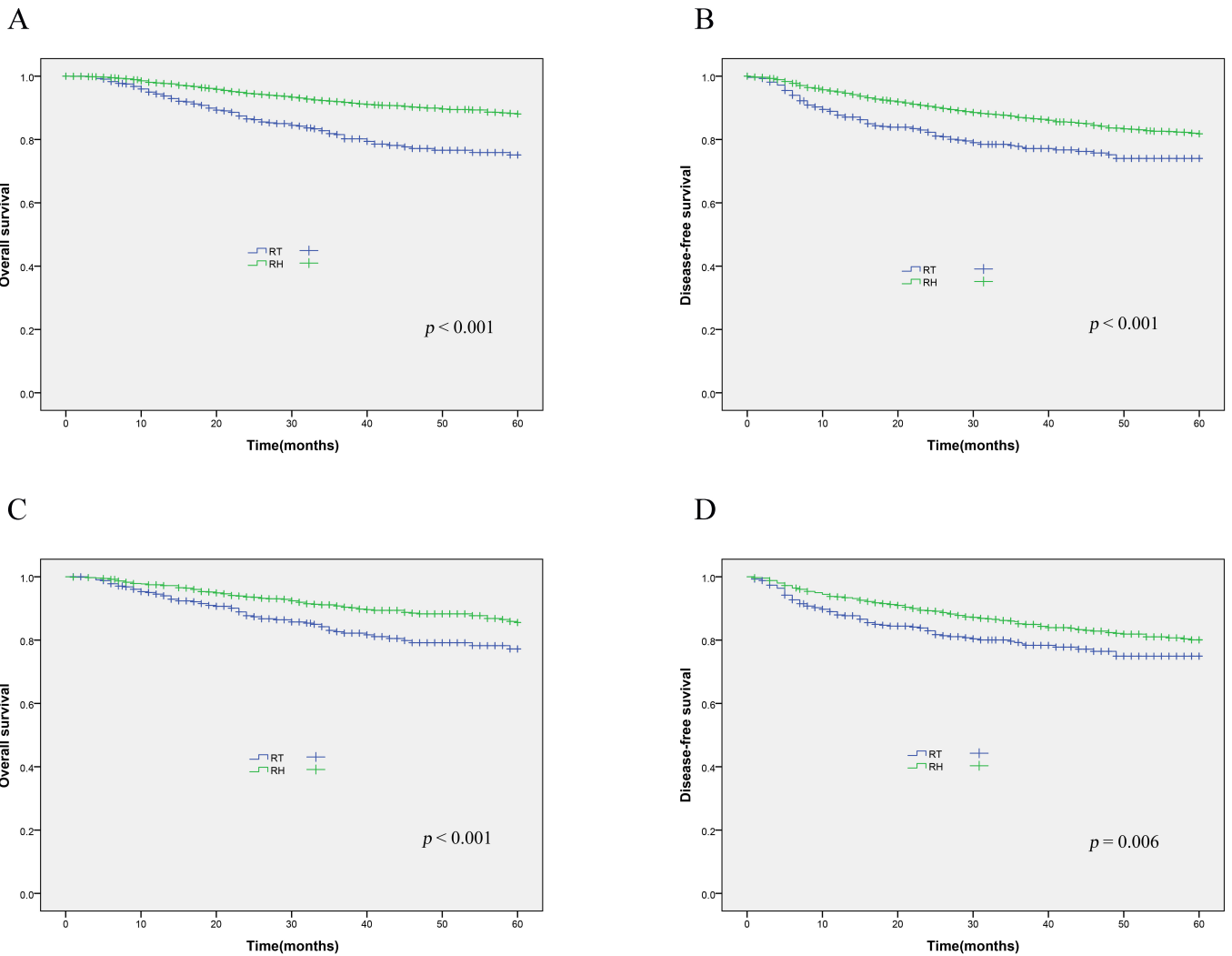


FIGURE 2. Survival curves before and after matching for stage IIA cervical cancer patients who met the study criteria. (A) Before matching, Overall survival. (B) Before matching, Disease-free survival. (C) After matching, Overall survival. (D) After matching, Disease-free survival. RT, radiotherapy; RH, radical hysterectomy.

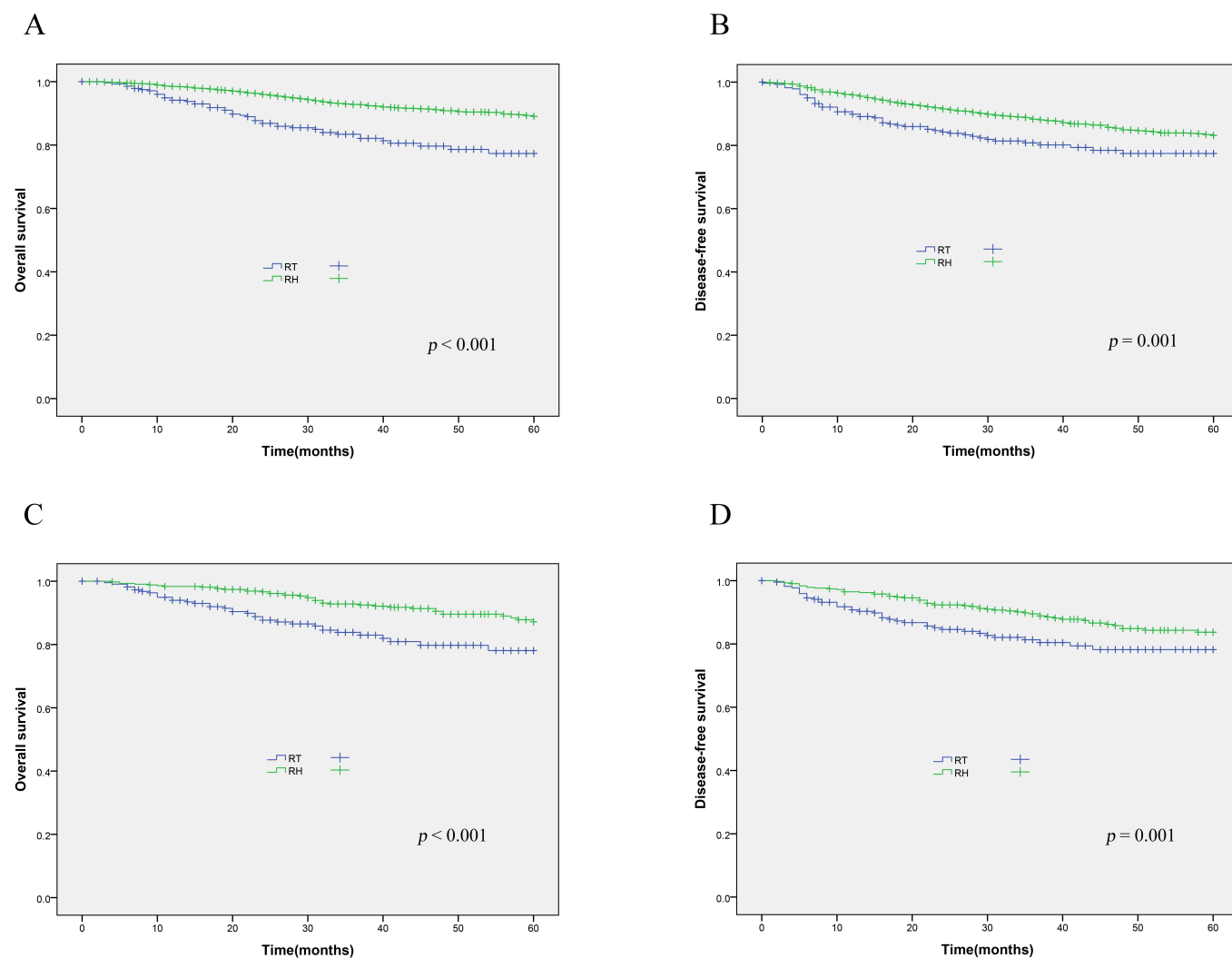


FIGURE 3. Survival curves before and after matching for stage IIA1 cervical cancer patients who met the study criteria. (A) Before matching, Overall survival. (B) Before matching, Disease-free survival. (C) After matching, Overall survival. (D) After matching, Disease-free survival. RT, radiotherapy; RH, radical hysterectomy.

4. Discussion

There is currently a controversy about which treatment between RT and surgery has superior treatment outcomes for stage IIA cervical cancer. Previous studies have yielded different results; however, owing to a limited number of stage IIA patients, it was difficult to obtain an objective conclusion. Our study showed that the survival outcomes were better for stage IIA cervical SCC patients in the RH group (with standard treatment after surgery) than those in the RT group. After eliminating interference of confounding factors using PSM, we found that the RH group with standard treatment after surgery had significantly better survival outcomes than the RT group, with a 5-year OS of 77.2% and 85.6% ($p < 0.001$) and DFS of 74.9% and 80.0% ($p = 0.006$), respectively, further analysis showed that the RT group had higher risks of death or recurrence than the RH group.

Before and after matching, our results showed that stage IIA1 patients (tumor diameter ≤ 4 cm) from the RH group had significantly higher 5-year OS and DFS rates than those from the RT group. Comparatively, the 5-year OS and DFS rates of

stage IIA2 patients (tumor diameter > 4 cm) from the RH group were significantly better than those from the RT group before matching but were not significantly different after matching.

Our preliminary report comprising 1654 stage IIA patients showed that stage IB1-IIA2 cervical cancer patients who underwent laparotomy surgery with standard postoperative treatment had significantly better 5-year OS and DFS compared with nonsurgical treatment (with RT as the main treatment), regardless of the tumor diameter. However, it should be noted that the pathological types of this study included adenocarcinoma and adenosquamous carcinoma [12]. Previous studies have shown that the surgical treatment of adenocarcinoma was better than RT [2], so including adenocarcinoma and adenosquamous carcinoma cases may have impacted the study outcomes. In this study, laparotomy was performed in the RH group to rule out deviation [14–16]. A previous study showed that minimally invasive RH for early cervical cancer resulted in lower DFS and OS compared with open RH [14]. To remove confounding factors, the surgical approach of this study was open RH.

Previous literature indicated that survival following RT

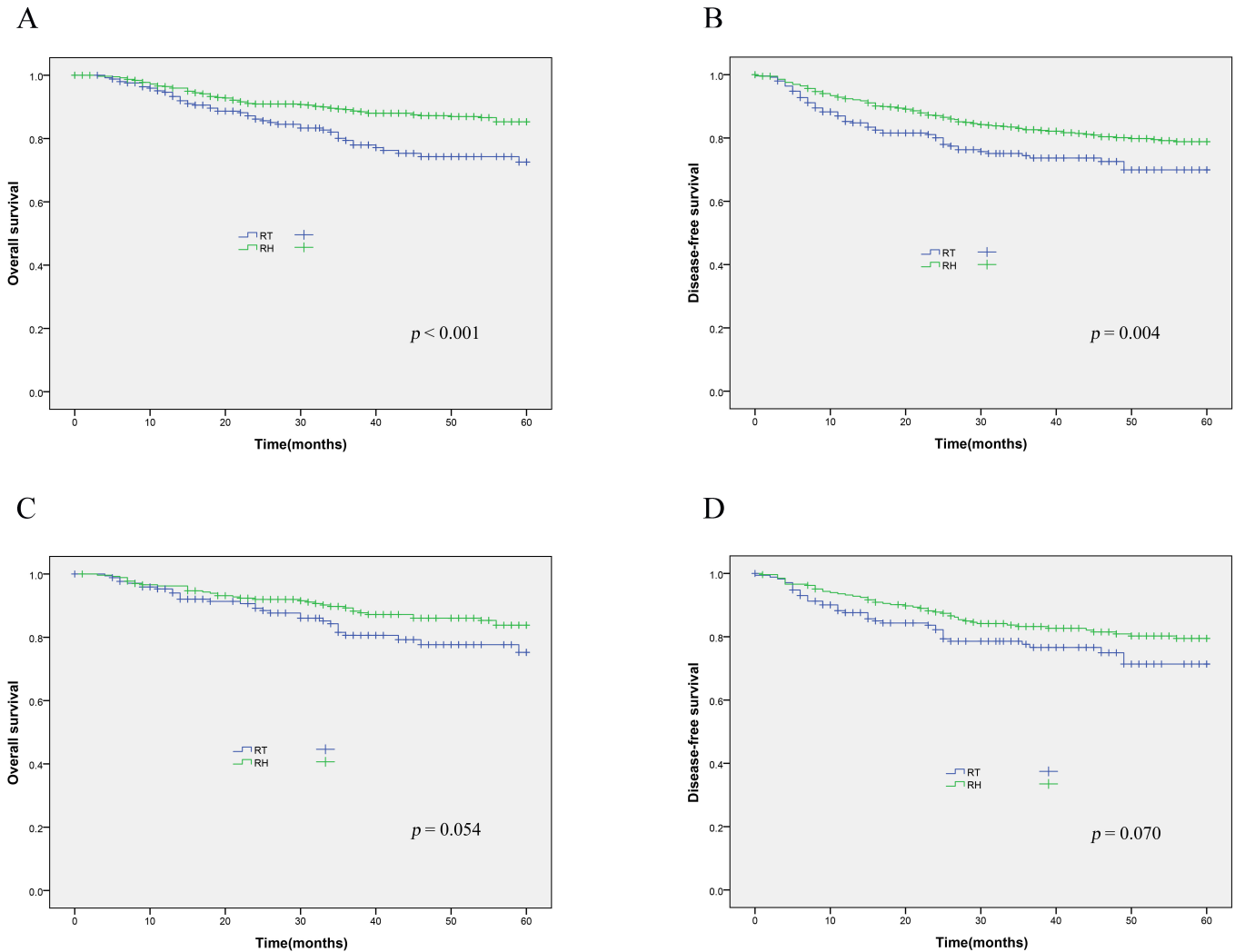


FIGURE 4. Survival curves before and after matching for stage IIA2 cervical cancer patients who met the study criteria. (A) Before matching, Overall survival. (B) Before matching, Disease-free survival. (C) After matching, Overall survival. (D) After matching, Disease-free survival. RT, radiotherapy; RH, radical hysterectomy.

was similar to surgery [2, 17–19]. In a previously published prospective study ($n = 337$ patients), the investigators observed no difference in the 5-year OS and DFS rates between the RT and RH groups, regardless of the tumor size [2]. In 2017, Landoni *et al.* [17] reported no difference in survival between the RT and surgery groups from a single-center prospective study with a 20-year follow-up on stage IB1-IIA2 cervical cancer patients. Further, Wu *et al.* [18] reported that stage IB1 and IIA1 cervical cancer patients had similar survival outcomes irrespective of whether undergoing RT or surgery.

However, some studies suggested surgery was better than RT [12, 20, 21]. In 2009, in a retrospective study by Bansal *et al.* [20] on 4885 stage IB-IIA cervical cancer patients, the authors reported that the mortality rate of patients who underwent RT was higher than those with surgery. Further, for cases with a tumor diameter <4 cm and between 4 and 6 cm, RT still showed a higher mortality rate than surgery; however, no difference in survival rates between surgery and RT was found for patients with a tumor diameter >6 cm.

The results of our study were concordant with Liu Ping *et al.* [12], Bansal N *et al.* [20] and Brewster WR *et al.* [21] but

inconsistent with Landoni F *et al.* [17], Yamashita H *et al.* [19] and Wu S *et al.* [18]. The reasons for these differences might be: (1) Impact of the number of cases: there were 337 and 152 cases in the studies of Landoni F *et al.* [17] and Yamashita H *et al.* [19], respectively. However, only 39 and 24 patients were in stage IIA, and robust comparisons could not be conducted. In contrast, 1654 patients were classified as FIGO IIA in the studies of Liu Ping *et al.* [12], Bansal N *et al.* [20], and Brewster WR *et al.* [21]. From a total of 4885 patients (4012 underwent surgery and 873 received RT) and 1039 patients (741 patients underwent surgery and 298 patients received RT), we found that their results were similar to those obtained in this study. (2) Influence of the pathological type: Landoni F *et al.* [17] found that for cervical adenocarcinoma, surgery was better than RT, but pathological types were not included in the analysis in the study of Wu S *et al.* [18]. However, the study by Bansal *et al.* [20] yielded similar results with our study, possibly due to the elimination of the influence of pathological types. (3) Details on the adjuvant treatment used in the studies of Landoni F *et al.* [17], Yamashita H *et al.* [19] and Wu S *et al.* [18] was RT, and chemotherapy was not recorded. According

to guidelines and related studies, standardized treatment after surgery might affect survival outcomes, which may lead to deviation. In this study, patients were treated according to the NCCN guidelines, and 78.4% received adjuvant treatment (16.7% RT alone, 13.6% chemotherapy alone, 25.4% concurrent radiotherapy and chemotherapy, and 22.7% RT + chemotherapy). In this study, we performed PSM to reduce the effects of confounding factors, indicating that the reported results might be more reliable than previous literature.

To date, this study represents the largest cohort study to investigate the survival outcomes of RT versus surgery in stage IIA cervical SCC patients. Our results showed that surgery was superior to RT in stage IIA1 cervical SCC, but surgery had similar outcomes to RT in stage IIA2 cervical SCC patients. RT has fewer life-threatening complications than surgery, while the advantage of surgery is that it provides more detailed pathological parameters and preserves ovarian endocrine function in young patients. In addition, the quality of sexual life postsurgery was reported to be higher than after RT [22].

5. Conclusions

Altogether, based on current evidence, we recommend radical surgery for young patients with stage IIA cervical SCC. However, considering that this was a retrospective study, the tumors were classified based on a 4 cm diameter threshold according to guidelines, there was no additional subdivision, and the median follow-up between the two groups was significantly different, indicating the presence of potential selection bias, larger-scale randomized controlled studies are still needed to confirm these results.

AUTHOR CONTRIBUTIONS

CLC and JHL—developed the study concepts, designed the work and revised the manuscript. MWL, PL, DBW and HD—participated in the study design, wrote the manuscript and performed quality control of data. XMZ, YZ, QHX, BLC, ZMC, QBL and HLW—generated, collected and analysed the data and prepared the manuscript. XNB—validated the manuscript. All authors reviewed and approved the final version.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the Ethics Committee of Nanfang Hospital of Southern Medical University (ID: NFEC-2017-135) and was registered on the International Clinical Trials Registry Platform Search Portal (identifier: clinical trial number ChiCTR1800017778; <http://apps.who.int/trialsearch/>).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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