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Original Research

Abdominal Radical Hysterectomy as an Alternative Treatment Option for Patients with Cervical Cancer without Access to Radiotherapy Facilities

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Abstract

Background: To compare the oncological outcomes of Chinese patients with International Federation of Gynecology and Obstetrics (FIGO) 2018 stage IIIC cervical cancer (CC) receiving radical chemoradiotherapy (R-CT), abdominal radical hysterectomy (ARH), or neoadjuvant chemotherapy and radical surgery (NACT). **Methods**: Overall, 4086 patients in 47 hospitals from 2004 to 2018 were divided into groups according to stage (4029 with stage IIIC1 and 57 with stage IIIC2). Kaplan-Meier and Cox regression analyses were applied to compare the 5-year overall survival (OS) and disease-free survival (DFS) of the three initial treatments before and after propensity score matching (PSM). **Results**: The 5-year DFS was worse in patients with stage IIIC2 than in those with stage IIIC1 (post-PSM: 68.3% *vs*. 39.9%, $p < 0.001$). For stage IIIC1, the ARH group had better 5-year OS (post-PSM: 71.0% *vs*. 80.0%, $p < 0.001$) and DFS (post-PSM: 67.2% *vs*. 71.0%, $p < 0.001$) than the R-CT group, while the NACT group had worse 5-year DFS (post-PSM: 67.7% *vs*. 55.3%, $p = 0.002$). The 5-year OS (post-PSM: 80.9% *vs*. 70.5%, $p < 0.001$) and DFS (post-PSM: 70.7% *vs*. 54.1%, $p < 0.001$) were better in the ARH than in the NACT group. For stage IIIC2, the 5-year DFS was better in the ARH than in the NACT group (45.4% *vs*. 30.1%, $p = 0.025$). **Conclusions**: The oncological prognosis of patients with stage IIIC1 CC was generally better than that of patients with stage IIIC2, thereby supporting the rationale behind the classification of stage IIIC. In less developed areas, the ARH is a promising alternative treatment option for patients with stage IIIC; nonetheless, the use of NACT is not advisable. **Clinical Trial Registration**: The study was registered at http://apps.who.int/trialsearch/, registration number CHiCTR1800017778.

Keywords: FIGO 2018 IIIC; cervical cancer; radiotherapy; prognosis; abdominal radical hysterectomy

1. Introduction

Cervical cancer (CC) represents a significant global health issue, with an estimated 570,000 cases and 311,000 deaths worldwide in 2018, ranking as the fourth most frequently diagnosed cancer and the fourth leading cause of cancer-related deaths in women [1]. Several studies have indicated lymph node metastasis (LNM) as a poor prognostic factor for CC [2–9]. Tumor staging is high-ranking for overall management and guidance of treatment [10]. The International Federation of Gynecology and Obstetrics (FIGO) staging system [11] is relatively well-recognized for CC and includes a prominent revision to classify patients with LNM as stage IIIC. Patients with pelvic LNM are classified as stage IIIC1, whereas those with para-aortic LNM are classified as stage IIIC2. This classification emphasizes the significance of LNM and its location for prognosis and treatment.

Abdominal radical hysterectomy (ARH) and radical chemoradiotherapy (R-CT) are the primary initial treatments for CC. R-CT improves mortality in CC by approximately 30–50% [12–16] and can be used in all stages of CC; however, it is associated with a range of concomitant complications [17–19]. In contrast, ARH allows for the resection of tumor tissues and metastatic lymph nodes (LNs) to reduce tumor burden and determine LN status, which can guide postoperative adjuvant therapy. In recent years, neoadjuvant chemotherapy and radical surgery (NACT) have also been used to treat CC because of their positive effect in reducing tumor volume and lowering tumor stage. In the FIGO 2018 staging system [11], stage

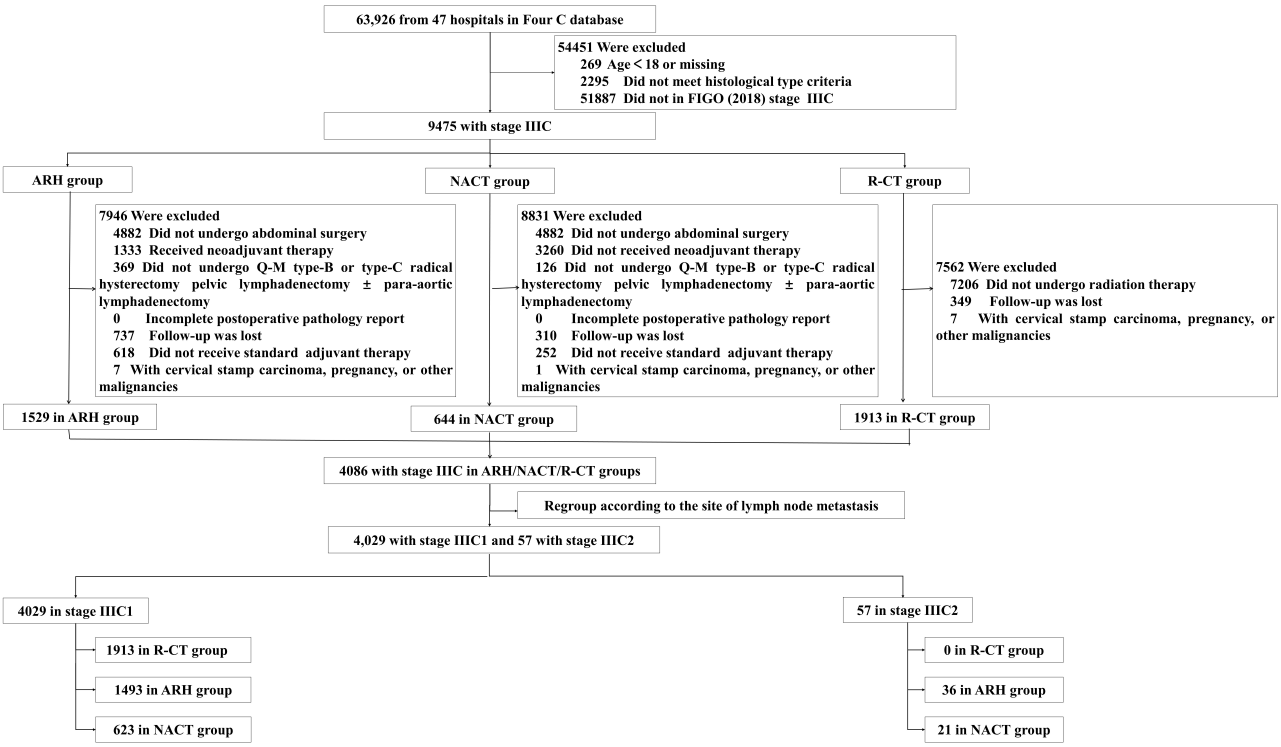

Fig. 1. Patient selection flow diagram. Based on the inclusion and exclusion criteria, 4019 stage IIIC1 cases (R-CT, n = 1913; ARH, n = 1493; and NACT, n = 623) and 57 stage IIIC cases (ARH, n = 36; and NACT, n = 21) were screened from the Chinese 1538 project database. FIGO, international federation of gynecology and obstetrics; R-CT, radical chemoradiotherapy; ARH, abdominal radical hysterectomy; NACT, neoadjuvant chemotherapy and radical surgery.

IIIC CC includes cases of FIGO 2009 stages IA to III CC with LNM. Prior to 2018, the standard initial treatments for FIGO 2009 stages IA to IIA and stages IIB to III CC were ARH and R-CT, respectively. Nevertheless, both the FIGO 2018 [11] and 2023 National Comprehensive Cancer Network (NCCN) [20] guidelines recommend R-CT for stage IIIC CC only, leading to the loss of opportunity for surgery in some patients with FIGO 2009 early-stage CC, which represents a significant departure from past treatment strategies. As a result, the treatment of stage IIIC CC remains controversial.

Overall, less developed regions account for 85% of the incidence and 90% of the mortality of CC [21]. In light of the World Health Organization (WHO) country profile for CC [22], Canada has 11 radiotherapy units per 10,000 cancer patients, whereas China has 4 and Uganda 1, highlighting the lack of radiotherapy resources in such less developed regions. Therefore, options to initial treatment for FIGO 2018 stage IIIC CC is particularly critical in less developed regions with both a high CC prevalence and a lack of radiotherapy resources. Nevertheless, most studies on stage IIIC CC have largely focused on the prognostic and influencing factors, validating their plausibility and causes, whereas fewer studies have focused on treatment strategies, and studies from less developed regions are also lacking. Consequently, this study addresses the treatment strategy for FIGO 2018 Stage IIIC CC in developing countries to provide evidence for the selection of alternative initial treatment options for less developed regions.

2. Materials and Methods

2.1 Data Collection

For this retrospective study, the data used were obtained from the Project 1538 developed through a clinical trial (Project 1538; Ethics Clearance NFEC-2017-135; Clinical trial registration number: CHiCTR1800017778, http://apps.who.int/trialsearch/), which was authorized by the Ethics Committee of Southern Hospital. The database includes 63,926 cases of CC, collected across 47 hospitals in China. Included are patients' clinical information, pretreatment biopsy results, laboratory and imaging information, treatment plans, treatment complications, and postoperative pathology reports. Data were collected by two gynecologists, who received specific training for the clinical trial, using EpiData 3.1 (EpiData Association, Odense, Denmark) for dual data entry and standard interviews for follow-up data by telephone calls or outpatient visits. Details of the data collection and follow-up methods have been previously described [23,24].

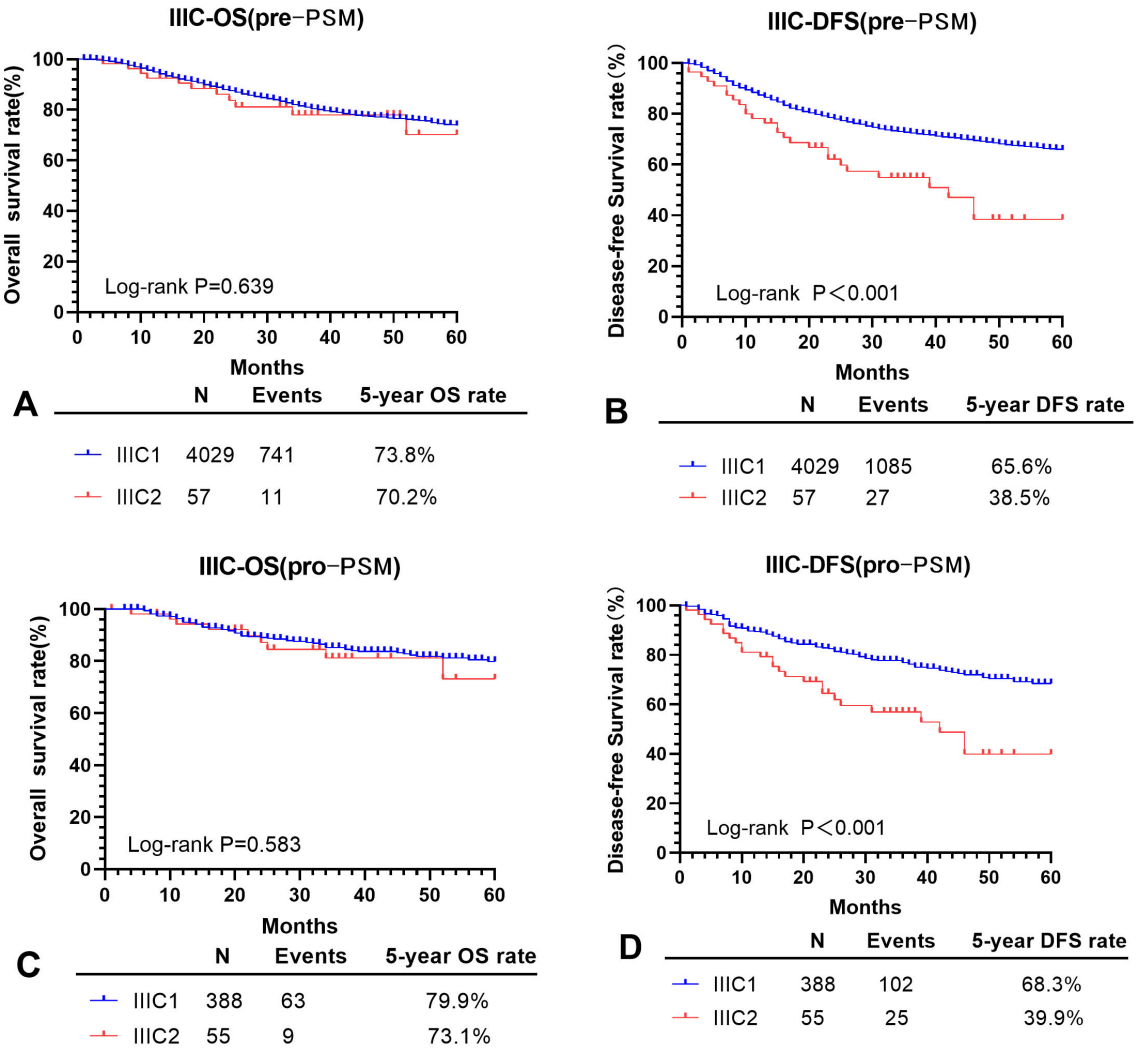

Fig. 2. OS and DFS of stages IIIC1 and IIIC2. Direct comparison of 5-year OS (A) and 5-year DFS (B) for stage IIIC1 and IIIC2. Comparison of 5-year OS (C) and 5-year DFS (D) for stage IIIC1 and IIIC2 after PSM. PSM, propensity score matching; OS, overall survival; DFS, disease-free survival.

2.2 Inclusion and Exclusion Criteria

For our study, the selection criteria for eligible cases were as follows: age ≥18 years; CC detected through cervical biopsy; histological diagnosis of squamous cell carcinoma (SCC), adenocarcinoma (AC), or adenosquamous cell carcinoma (ASC); FIGO 2018 stage IIIC classification; and availability of follow-up data. With regards to initial treatment, the inclusion criteria were as follows: R-CT, external radiation therapy (RT) at a dose of ≥45 Gy/brachytherapy at a dose of ≥40 Gy, on or off concurrent platinum-based chemotherapy (an example of the dose of R-CT: the doses of the external radiation therapy is 1.8–2 Gy per fraction, the doses of the brachytherapy (high dose rate) is 6–7 Gy per fraction, and the total dose of external radiation therapy and brachytherapy is usually ≥85 Gy); ARH, Q-M type-B or type-C radical hysterectomy pelvic lymphadenectomy, with or without para-aortic lymphadenectomy; and NACT, consisting of platinum-based neoadjuvant therapy (2–3 cycles) and radical surgery; and patients with available follow-up data. The patients of stage IIIC2 received extended-field external irradiation radiotherapy, concurrent platinum-based chemotherapy, and brachytherapy. Exclusion criteria consisted of violation of selection criteria, cancer of the uterine cervix stump, and CC combined with other malignancies or pregnancy.

2.3 Outcome Measurement

The outcomes for this study were overall survival (OS) and disease-free survival (DFS), with a cutoff point of 5 years post-treatment. OS is the last point in time from diagnosis to valid follow-up or death for any reason. DFS is the last point in time from diagnosis to follow-up, relapse, or death.

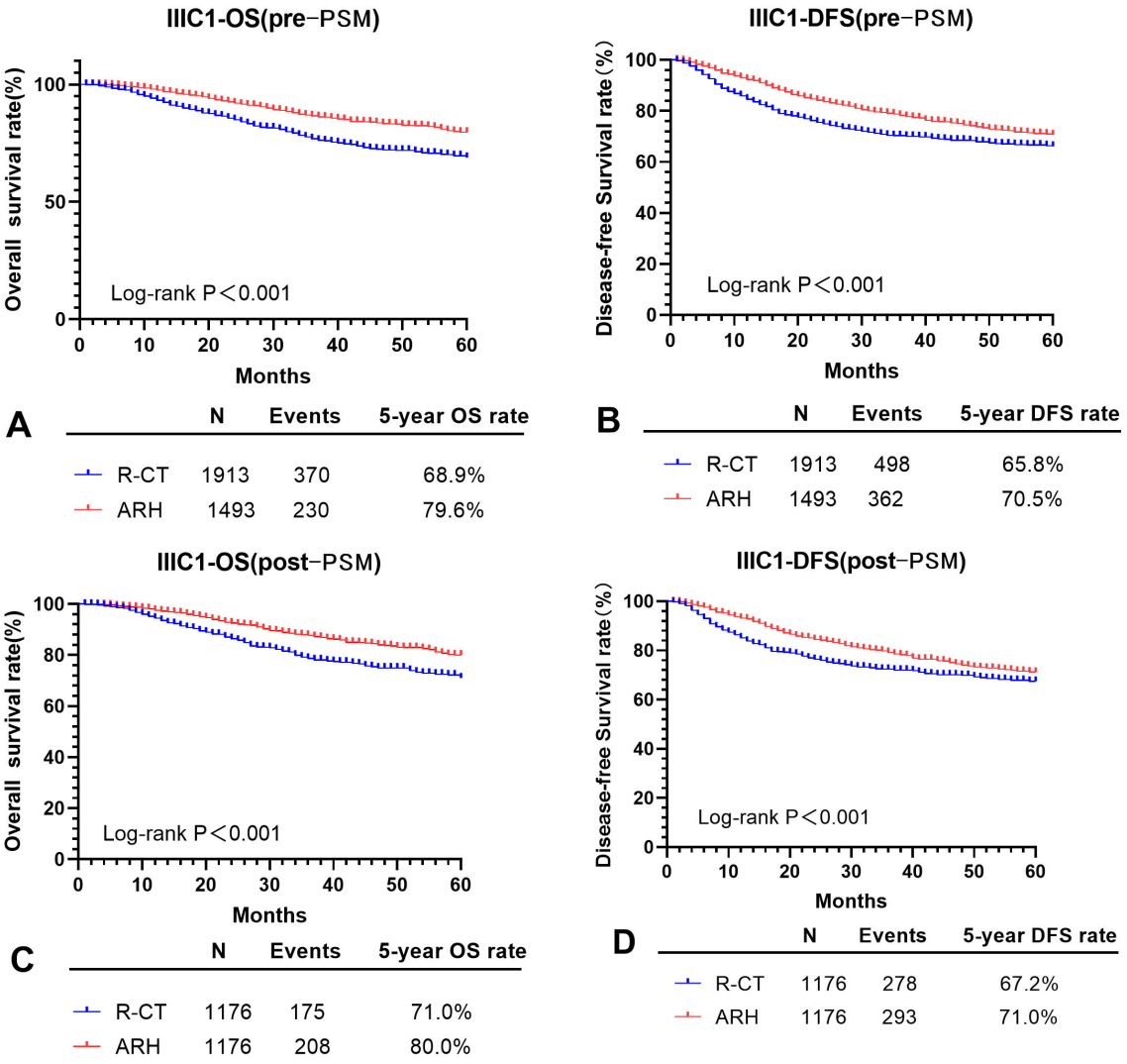

Fig. 3. OS and DFS of the R-CT and ARH groups (stage IIIC1). Direct comparison of 5-year OS (A) and 5-year DFS (B) for R-CT and ARH in stage IIIC1. Comparison of 5-year OS (C) and 5-year DFS (D) for R-CT and ARH in stage IIIC1 after PSM. PSM, propensity score matching; OS, overall survival; DFS, disease-free survival; R-CT, radical chemoradiotherapy; ARH, abdominal radical hysterectomy.

2.4 Statistical Analysis

Continuous variables were described as the mean ± standard deviation, while the independent samples *t*-test was used for between-group comparisons. Categorical values were described as their percentages, and the chi-squared test or Fisher's exact probability test was used, as appropriate, for between-group comparisons. The Kaplan-Meier method was applied for survival analysis. Independent risk factors were established with Cox proportional hazards models along with hazard ration (HR) and 95% confidence interval (CI). Propensity score matching (PSM) was used to minimize the influence of baseline differences between groups. All analyses were performed using SPSS (version 29; IBM Corp., Armonk, NY, USA), with significance set at a p-value < 0.05.

3. Results

3.1 Case Screening Results

Based on the inclusion and exclusion criteria, 4086 CC cases were selected from the Project 1538 database, with no missing values. Fig. 1 exemplifies the patient screening process. The findings from baseline profiling for stages IIIC1 and IIIC2 are presented in **Supplementary Table 1**. The findings from baseline profiling for the R-CT and ARH groups, R-CT and NACT groups, and ARH and NACT groups for stage IIIC1 are described in **Supplementary Tables 2,3,4,** respectively. The findings from baseline profiling for the ARH and NACT groups for stage IIIC2 are depicted in **Supplementary Table 5**.

Table 1. Cox multivariate survival analysis of the stage IIIC.

Variables	5-year OS (pre-PSM)			5-year DFS (pre-PSM)			5-year OS (post-PSM)			5-year DFS (post-PSM)		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Age (years)	1.008	1.000–1.015	0.040	1.001	0.995–1.007	0.772	1.007	0.979–1.036	0.631	0.998	0.997–1.019	0.826
Histological type			<0.001			<0.001			0.016			0.005
SCC	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-
AC	1.689	1.287–2.216	<0.001	1.585	1.264–1.986	<0.001	2.517	1.332–4.759	0.004	2.337	1.399–3.905	0.001
ASC	2.231	1.534–3.245	<0.001	1.592	1.129–2.245	0.008	1.939	0.264–14.268	0.516	0.763	0.105–5.525	0.789
FIGO stage												
Stage IIIC1	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-
Stage IIIC2	1.518	1.13–2.035	0.005	2.112	1.436–3.108	<0.001	1.142	0.558–2.337	0.716	2.295	1.470–3.581	<0.001
Initial treatment modality			<0.001			<0.001			0.020			0.017
R-CT	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-
ARH	0.647	0.599–0.700	<0.001	0.681	0.591–0.785	<0.001	0.424	0.165–1.093	0.076	0.657	0.262–1.648	0.371
NACT	0.730	0.657–0.812	<0.001	1.173	0.995–1.383	0.057	0.789	0.301–2.069	0.630	1.115	0.441–2.822	0.817

PSM, propensity score matching; OS, overall survival; DFS, disease-free survival; CI, confidence interval; HR, hazard ratio; SCC, squamous cell carcinoma; AC, Adenocarcinoma ASC, adenosquamous cell carcinoma; FIGO, international federation of gynecology and obstetrics; R-CT, radical chemoradiotherapy; ARH, abdominal radical hysterectomy; NACT, neoadjuvant chemotherapy and radical surgery.

Table 2. Cox multivariate survival analysis of the stage IIIC1.

	5-year OS (pre-PSM)			5-year DFS (pre-PSM)			5-year OS (post-PSM)			5-year DFS (post-PSM)		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
R-CT and ARH groups												
Age (years)	1.006	0.998–1.014	0.116	1.001	0.994–1.008	0.774	1.007	0.996–1.018	0.230	0.999	0.990–1.008	0.788
Histological type			<0.001			<0.001			<0.001			<0.001
SCC	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-
AC	1.835	1.336–2.521	<0.001	1.645	1.250–2.165	<0.001	2.514	1.683–3.756	<0.001	1.969	1.352–2.867	<0.001
ASC	2.141	1.350–3.394	0.001	1.657	1.092–2.515	0.018	2.884	1.657–5.021	<0.001	2.367	1.439–3.894	<0.001
Initial treatment modality												
R-CT	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-
ARH	0.552	0.464–0.658	<0.001	0.684	0.592–0.791	<0.001	0.603	0.493–0.738	<0.001	0.727	0.616–0.857	0.001
R-CT and NACT groups												
Age (years)	1.007	0.998–1.015	0.116	1.000	0.993–1.008	0.919	1.002	0.988–1.017	0.748	0.994	0.982–1.006	0.335
Histological type			<0.001			<0.001			<0.001			
SCC	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-
AC	1.685	1.166–2.437	0.005	1.639	1.201–2.235	0.002	1.767	1.107–2.820	0.017	2.071	1.419–3.022	<0.001
ASC	2.823	1.777–4.486	<0.001	2.040	1.316–3.160	0.001	3.596	2.060–6.278	<0.001	2.675	1.569–4.559	<0.001

Table 2. Continued.

	5-year OS (pre-PSM)			5-year DFS (pre-PSM)			5-year OS (post-PSM)			5-year DFS (post-PSM)		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Initial treatment modality												
R-CT	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-
NACT	0.940	0.761–1.160	0.564	1.157	0.974–1.373	0.096	1.065	0.850–1.335	0.586	1.308	1.088–1.573	0.004
ARH and NACT groups												
Age (years)	1.010	0.998–1.021	0.090	1.002	0.993–1.011	0.628	1.014	0.996–1.033	0.136	1.000	0.986–1.015	0.998
Histological type			0.004			0.056			0.330			0.465
SCC	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-
AC	1.527	1.084–2.152	0.016	1.342	1.016–1.772	0.038	1.199	0.649–2.214	0.563	1.272	0.803–2.012	0.305
ASC	1.825	1.131–2.945	0.014	1.342	0.874–2.062	0.179	1.905	0.768–4.724	0.164	1.359	0.598–3.085	0.464
Initial treatment modality												
ARH	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-
NACT	1.709	1.366–2.137	<0.001	1.687	1.412–2.016	<0.001	1.750	1.306–2.345	<0.001	1.653	1.312–2.083	<0.001
Hysterectomy type			0.821			0.527			0.785			0.760
Type QM-B	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-
Type QM-C1	0.000	0–2.405×10^{87}	0.927	0.392	0.055–2.799	0.351	0.00	0–2.112×10^{118}	0.946	0.00	0–1.001×10^{91}	0.930
Type QM-C2	1.074	0.858–1.344	0.534	1.057	0.885–1.264	0.539	1.121	0.812–1.546	0.488	1.100	0.853–1.420	0.462
Tumor diameter (cm)			0.252			0.057			0.101			0.112
≤4	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-
>4	1.160	0.929–1.448	0.190	1.132	0.948–1.352	0.172	1.354	0.992–1.849	0.056	1.232	0.965–1.574	0.094
Unknown	1.333	0.875–2.031	0.180	1.456	1.052–2.014	0.023	1.584	0.839–2.985	0.156	1.518	0.914–2.521	0.107
LVSI												
Negative	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-
Positive	1.339	1.085–1.653	0.007	1.070	0.903–1.268	0.436	1.164	0.858–1.579	0.330	1.016	0.796–1.296	0.902
Cervical stromal invasion			0.001			<0.001			0.490			0.521
≤1/2	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-
>1/2	1.976	1.368–2.854	<0.001	1.892	1.427–2.508	<0.001	1.313	0.797–2.162	0.285	1.202	0.828–1.747	0.333
Unknown	1.632	0.881–3.023	0.120	1.543	0.953–2.497	0.078	1.624	0.597–4.418	0.342	1.463	0.669–3.198	0.341
Parametrial involvement												
Negative	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-
Positive	1.615	1.107–2.356	0.013	1.893	1.426–2.513	<0.001	1.646	0.801–3.384	0.175	1.615	0.901–2.894	0.107
Vaginal margin												
Negative	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-	1 (Ref)	-	-
Positive	0.732	0.389–1.379	0.335	1.283	0.867–1.899	0.213	0.234	0.032–1.708	0.152	0.825	0.353–1.925	0.656

PSM, propensity score matching; OS, overall survival; DFS, disease-free survival; CI, confidence interval; HR, hazard ratio; SCC, squamous cell carcinoma; AC, Adenocarcinoma ASC, adenosquamous cell carcinoma; R-CT, radical chemoradiotherapy; ARH, abdominal radical hysterectomy; NACT, neoadjuvant chemotherapy and radical surgery; LVSI, lymphovascular space invasion.

3.2 Comparison of the Oncological Outcomes of Stages IIIC1 and IIIC2

Kaplan-Meier analysis revealed a marked distinction in 5-year DFS between stages IIIC1 and IIIC2 (73.8% *vs.* 70.2%, $p = 0.638$) but not in OS (65.6% *vs.* 38.5%, $p < 0.001$) before PSM; the same result was obtained after PSM (DFS: 68.3% *vs.* 39.9%, $p < 0.001$; OS: 79.9% *vs.* 73.1%, $p = 0.583$) (Fig. 2).

Cox regression analyses (post-PSM) showed that stage IIIC2 was correlated with worse DFS (HR = 2.295, 95% CI 1.470–3.581, $p < 0.001$) compared with stage IIIC1 but not with worse OS ($p = 0.716$). Additionally, the ARH group was not correlated with 5-year OS ($p = 0.076$) or DFS ($p = 0.371$) as opposed to the R-CT group; moreover, the NACT group was not correlated with 5-year OS ($p = 0.630$) or DFS ($p = 0.817$). Finally, age was not correlated with 5-year OS or DFS ($p > 0.05$); compared with SCC, AC was correlated with worse 5-year OS and DFS ($p < 0.05$); however, ASC was not correlated with 5-year OS or DFS ($p > 0.05$; Table 1).

3.3 Comparison of the Oncological Outcomes of the R-CT, ARH, and NACT Groups for Stage IIIC1

Kaplan–Meier analysis revealed notable variations in 5-year OS (pre-PSM: 68.9% *vs.* 79.6%, $p < 0.001$; post-PSM: 72.0% *vs.* 80.0%, $p < 0.001$) and DFS (pre-PSM: 65.8% *vs.* 70.5%, $p < 0.001$; post-PSM: 67.2% *vs.* 71.0%, $p < 0.001$) between the R-CT and ARH groups (Fig. 3). A marked distinction in 5-year DFS (pre-PSM: 65.8% *vs.* 55.5%, $p = 0.012$; post-PSM: 67.7% *vs.* 55.3%, $p = 0.002$) was found between the R-CT and NACT groups but not in 5-year OS (pre-PSM: 68.9% *vs.* 71.2%, $p = 0.634$; post-PSM: 70.7% *vs.* 70.7%, $p = 0.613$; Fig. 4). Furthermore, there were notable variations in the 5-year OS (pre-PSM: 79.6% *vs.* 71.2%, $p < 0.001$; post-PSM: 80.9% *vs.* 70.5%, $p < 0.001$) and DFS (pre-PSM: 70.5% *vs.* 55.5%, $p < 0.001$; post-PSM: 70.7% *vs.* 54.1%, $p < 0.001$) between the ARH and NACT groups (Fig. 5).

Cox regression analyses (post-PSM) showed that the ARH group was correlated with better 5-year OS (HR = 0.603, 95% CI 0.493–0.738, $p < 0.001$) and DFS (HR = 0.727, 95% CI 0.616–0.857, $p = 0.001$) than the R-CT group. Moreover, the study found that compared with SCC, both AC and ASC were correlated with worse 5-year OS and DFS ($p < 0.001$); however, age was not correlated with 5-year OS or DFS ($p > 0.05$; Table 2). Moreover, the NACT group was correlated with worse 5-year DFS compared with the R-CT group (HR = 1.308, 95% CI 1.088–1.573, $p = 0.004$) but not with 5-year OS ($p = 0.586$). Both AC and ASC were correlated with worse 5-year OS or DFS compared with SCC ($p \leq 0.017$); however, age was not correlated with 5-year OS or DFS ($p > 0.05$; Table 2). In addition, the 5-year OS (HR = 1.750, 95% CI 1.306–2.345, $p < 0.001$) and DFS (HR = 1.653, 95% CI 1.312–2.083, $p < 0.001$) were worse in the NACT group than in the ARH group. Nevertheless, other factors, including age, histological type, hysterectomy type, tumor diameter, lymphovascular space invasion (LVSI), cervical stromal invasion, parametrial involvement, and vaginal margin were not correlated with 5-year OS or DFS ($p > 0.05$; Table 2).

3.4 Comparison of the Oncological Outcomes of the ARH and NACT Groups for Stage IIIC2

PSM could not be performed because of the small number of cases in both groups. Kaplan-Meier analysis revealed a marked distinction in 5-year DFS (45.4% *vs.* 30.1%, $p = 0.025$) but not in 5-year OS (69.7% *vs.* 73.9%, $p = 0.750$) between the ARH and NACT groups (Fig. 6).

Cox regression analyses (pre-PSM) showed that the NACT group was related to worse 5-year DFS (HR = 2.526, 95% CI 1.012–6.301, $p = 0.047$) but not to worse 5-year OS ($p = 0.825$) versus the ARH group. Age was also correlated with worse 5-year DFS ($p = 0.040$) but not with 5-year OS ($p = 0.868$). Compared with SCC, AC was correlated with worse 5-year DFS ($p = 0.001$) but not with worse 5-year OS ($p = 0.075$), whereas ASC was not correlated with either 5-year OS or DFS ($p > 0.05$). Overall, hysterectomy type, tumor diameter, LVSI, cervical stromal invasion, parametrial involvement, and vaginal margin were not correlated with 5-year OS or DFS ($p > 0.05$; Table 3).

4. Discussion

The FIGO 2018 IIIC staging system highlights the relevance of LNM in oncology treatment and prognosis. For patients at this stage, the 2018 FIGO [11] and the 2023 NCCN [20] guidelines recommend only R-CT with no alternative treatment options described. However, performing R-CT is often a challenge for underdeveloped areas where radiotherapy facilities are lacking. Consequently, this study focused on FIGO 2018 stage IIIC CC patients to investigate the oncological outcomes of R-CT, ARH, and NACT and to provide a real-world basis for selecting an appropriate alternative initial treatment in less developed areas. We found that different stages and treatments affected the prognosis of stage IIIC CC patients, with higher mortality and risk of recurrence for stage IIIC2 than for stage IIIC1. In addition, for patients with stage IIIC1, ARH showed better oncological outcomes than R-CT and NACT. In contrast, for patients with stage IIIC2, ARH was superior to NACT, but R-CT data were insufficient to conclude whether it was appropriate in the current study. As such, ARH may thus represent a viable alternative treatment option.

4.1 Comparison of the Oncological Outcomes of Stages IIIC1 and IIIC2

Substantial evidence supports para-aortic LNM as a clear adverse prognostic factor [5,18,19,25–29]. Cho *et al.* [25] analyzed stage IIIC CC patients and observed that patients with para-aortic LNM exhibited noticeably worse 5-

Table 3. Cox multivariate survival analysis of stage IIIC2.

Variables	5-year OS			5-year DFS		
	HR	95% CI	*p*	HR	95% CI	*p*
Age (years)	0.993	0.909–1.084	0.868	0.944	0.894–0.997	0.040
Histological type			0.126			0.004
SCC	1 (Ref)	-	-	1 (Ref)	-	-
AC	7.447	0.815–68.093	0.075	11.118	2.639–46.832	0.001
ASC	3.073	0.293–32.184	0.349	0.884	0.108–7.240	0.908
Initial treatment modality						
ARH	1 (Ref)	-	-	1 (Ref)	-	-
NACT	1.194	0.248–5.747	0.825	2.526	1.012–6.301	0.047
Hysterectomy type			0.820			0.176
Type QM-B	1 (Ref)	-	-	1 (Ref)	-	-
Type QM-C1	0.000	0.000	0.990	1.266	0.129–12.424	0.839
Type QM-C2	0.559	0.092–3.406	0.528	0.338	0.106–1.084	0.068
Tumor diameter (cm)			0.933			0.516
$\leq$4	1 (Ref)	-	-	1 (Ref)	-	-
>4	1.254	0.268–5.864	0.773	1.515	0.545–4.209	0.426
Unknown	0.836	0.050–13.968	0.901	0.631	0.110–3.604	0.604
LVSI						
Negative	1 (Ref)	-	-	1 (Ref)	-	-
Positive	0.977	0.210–4.548	0.976	0.730	0.265–2.009	0.543
Cervical stromal invasion			0.803			1.000
$\leq$1/2	1 (Ref)	-	-	1 (Ref)	-	-
>1/2	1.439	0.082–25.145	0.803	1.009	0.209–4.870	0.991
Unknown	-	-	-	0.00	0.000	0.984
Parametrial involvement						
Negative	1 (Ref)	-	-	1 (Ref)	-	-
Positive	0.369	0.046–2.953	0.347	0.489	0.134–1.785	0.279
Vaginal margin						
Negative	1 (Ref)	-	-	1 (Ref)	-	-
Positive	4.361	0.569–33.428	0.156	2.413	0.568–10.261	0.233

OS, overall survival; DFS, disease-free survival; CI, confidence interval; HR, hazard ratio; ARH, abdominal radical hysterectomy; NACT, neoadjuvant chemotherapy and radical surgery; SCC, squamous cell carcinoma; AC, Adenocarcinoma; ASC, adenosquamous cell carcinoma; LVSI, lymphovascular space invasion.

year OS and DFS than those without para-aortic LNM ($p < 0.001$), which was similar to the results of the studies of Guo *et al*. [26] and Yan *et al*. [5]. In the present study, the 5-year DFS was found to be superior in stage IIIC1 compared with that in stage IIIC2, and stage IIIC2 was related to worse 5-year DFS. As such, this research further classified stage IIIC CC patients into stages IIIC1 and IIIC2 subgroups for individualized treatment studies.

4.2 Comparison of the Oncological Outcomes among the Three Treatments for Patients with Stages IIIC1 and IIIC2

Although R-CT is used in patients with all stages of CC to improve the oncological outcomes, it may also damage nearby organs and cause adverse effects [17–19]. Contrastingly, ARH offers several advantages, including avoidance of the adverse effects of R-CT; removal of the primary tumor, infiltrating tissues, and LN; and the possibility of personalized postoperative treatment based on pathological findings. As such, ARH is the preferred treatment option for early CC [10]. However, it was demonstrated by Wu *et al*. [30] and Landoni *et al*. [31] that the therapeutic efficacies of ARH and R-CT are similar. Furthermore, investigations by Yan *et al*. [32] and Jang *et al*. [33] indicated that the prognosis after ARH was significantly better than that after R-CT, which is in keeping with the outcomes of the present research. In the present study, compared with the R-CT group, the ARH group had superior 5-year OS (post-PSM: 71.0% *vs*. 80.0%, $p < 0.001$) and DFS (post-PSM: 67.2% *vs*. 71.0%, $p < 0.001$) and was related to better 5-year OS and DFS (post-PSM: $p < 0.05$) for stage IIIC1. The patients treated with R-CT may develop serious immediate or long-term complications, including impaired ovarian function, damaged vaginal structure and function, and inflammation of the bladder and rectum [17–19], which may affect

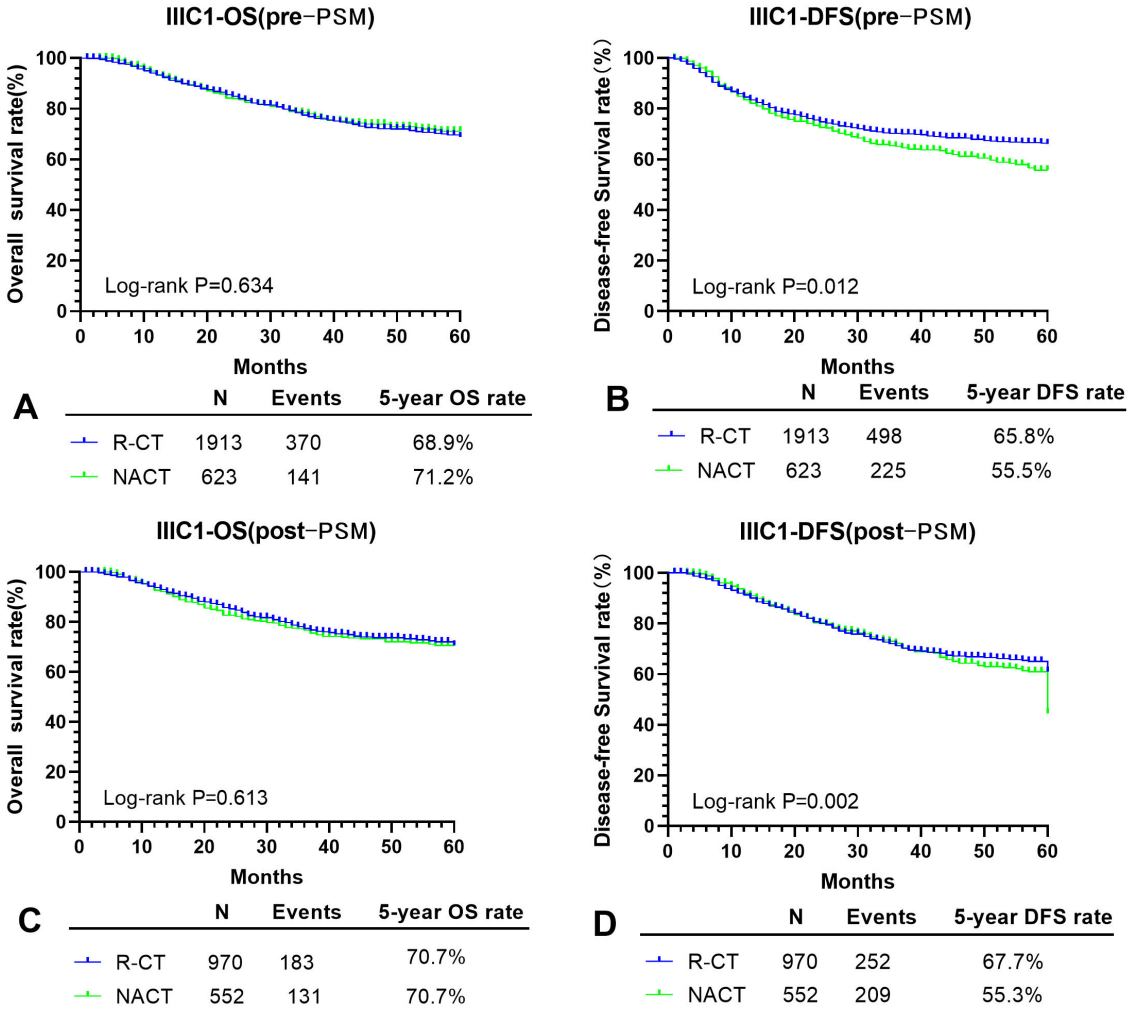

Fig. 4. OS and DFS of the R-CT and NACT groups (stage IIIC1). Direct comparison of 5-year OS (A) and 5-year DFS (B) for R-CT and NACT in stage IIIC1. Comparison of 5-year OS (C) and 5-year DFS (D) for R-CT and NACT in stage IIIC1 after PSM. PSM, propensity score matching; OS, overall survival; DFS, disease-free survival; R-CT, radical chemoradiotherapy; NACT, neoadjuvant chemotherapy and radical surgery.

their physical condition. For tumor treatment, whether it is initial treatment or treatment after the occurrence of recurrence and metastasis, the patient's physical condition is a key component influencing the outcome [34,35]. This may account for the poor treatment outcome in the R-CT group. Considering the undesirable effects of R-CT and the paucity of radiotherapy equipment in developing countries, ARH may be a suitable alternative option, especially for patients who desire to preserve their fertility.

Interestingly, NACT positively lowers tumor stage, reduces tumor burden, and enhances the chance of surgical tumor removal; however, conclusive evidence on whether NACT has a positive effect on the prognosis of CC is still lacking [36–39]. A meta-analysis by Ye *et al.* [40] revealed that oncological outcomes were significantly superior in the NACT group compared with those in the direct surgery group ($p < 0.05$). Similar findings were confirmed by Hu *et al.* [41] and Rydzewska *et al.* [42]. However, a phase III randomized controlled study by Katsumata *et al.* [43] in Japan that included 134 FIGO 2009 patients with stage IB2, IIA2, and IIB (including LNM) CC displayed a distinctively inferior OS in the NACT group compared with that in the radical surgery group (58% *vs.* 80%, $p = 0.015$), leading to the early termination of the study. In the present study, compared with the ARH group, the NACT group experienced the worse 5-year OS and DFS and was correlated with worse 5-year OS and DFS for stage IIIC1 (post-PSM: $p < 0.001$); simultaneously for stage IIIC2, NACT had a worse 5-year DFS and was correlated with a worse DFS (post-PSM: $p < 0.05$). For both stages, NACT showed no oncological advantages over ARH.

Duenas-Gonzalez *et al.* [44] also observed that, compared with R-CT, NACT did not have an improved prognosis for CC. Similar findings were showed in this research,

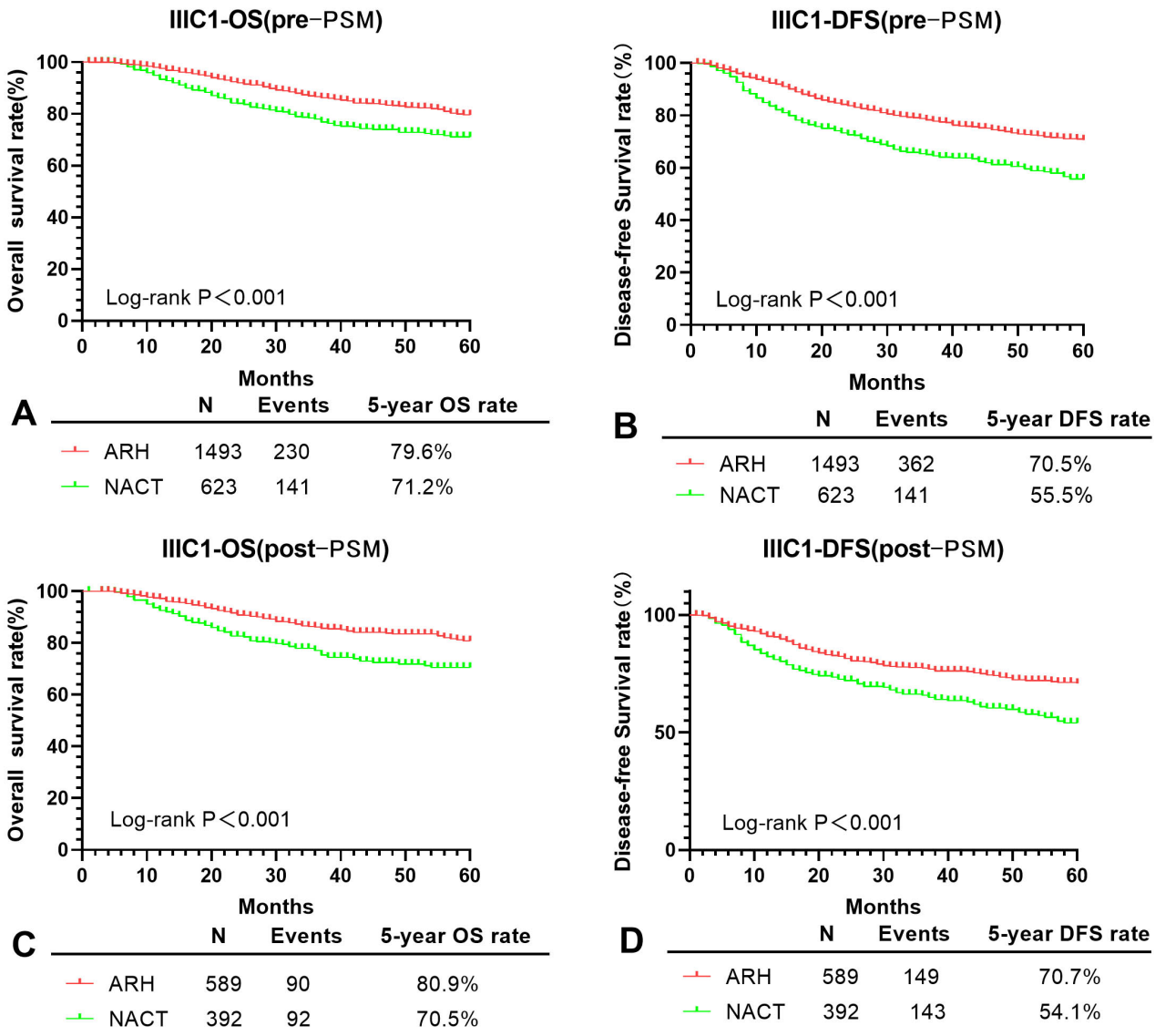

Fig. 5. OS and DFS of the ARH and NACT groups (stage IIIC1). Direct comparison of 5-year OS (A) and 5-year DFS (B) for ARH and NACT in stage IIIC1. Comparison of 5-year OS (C) and 5-year DFS (D) for ARH and NACT in stage IIIC1 after PSM. PSM, propensity score matching; OS, overall survival; DFS, disease-free survival; ARH, abdominal radical hysterectomy; NACT, neoadjuvant chemotherapy and radical surgery.

where for stage IIIC1, R-CT had a better 5-year DFS than NACT, and NACT was also correlated with a worse 5-year DFS (post-PSM: $p < 0.05$). Owing to the lack of R-CT cases, in-depth study is required to investigate the effect of R-CT on stage IIIC2. Nwankwo *et al.* [45] suggested that NACT may introduce confounding pathological factors in surgical specimens, influence postoperative pathological findings, complicate the assessment of the need for postoperative adjuvant therapy, and lead to missed or overtreatment. This may provide an explanation for the inferior effectiveness of NACT compared with ARH and R-CT in this research. As such, NACT should be used with caution for stage IIIC CC.

This current study is notable, as it is one of the largest studies based on the 2018 FIGO staging system for stage IIIC1 and IIIC2 CC from less developed regions. This study is innovative, as it stratified patients based on different LNM locations and compared the oncological prognosis of three commonly used CC treatments. In spite of the wide-ranging application of minimally invasive approaches, abdominal hysterectomy remains a general surgical procedure of intervention [46]. Furthermore, the Laparoscopic Approach to Cervical Cancer (LACC) confirmed that the prognosis of minimally invasive surgery was worse than that of ARH [47]. Therefore, only patients treated with ARH were included in this study. Nevertheless, this study has a few limitations. First, being retrospective, this study may

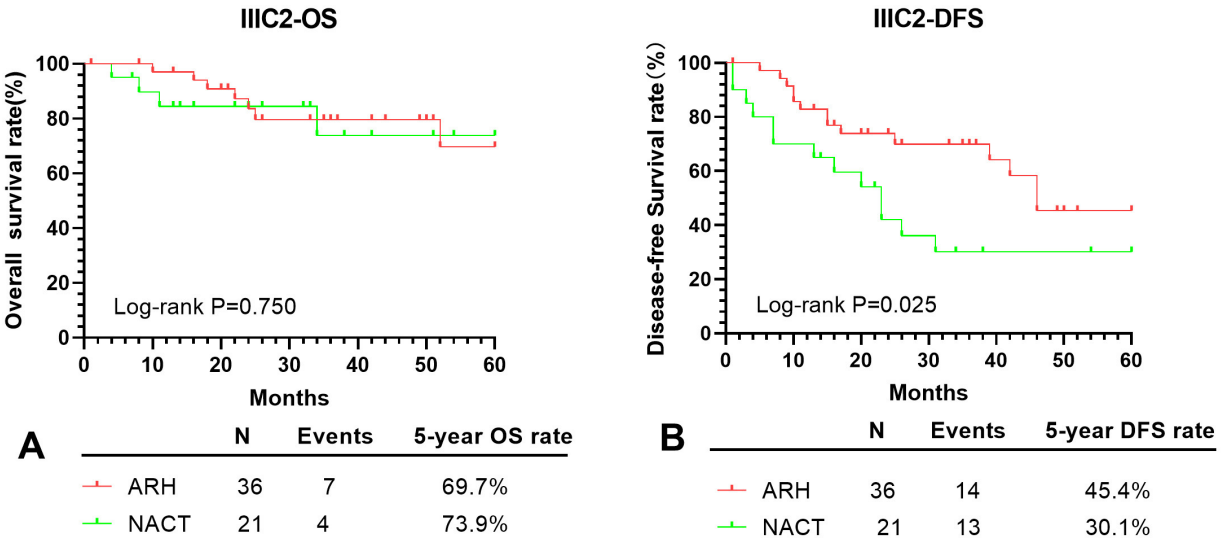

Fig. 6. OS and DFS of the ARH and NACT groups (stage IIIC2). Direct comparison of 5-year OS (A) and 5-year DFS (B) for ARH and NACT in stage IIIC2. OS, overall survival; DFS, disease-free survival; ARH, abdominal radical hysterectomy; NACT, neoadjuvant chemotherapy and radical surgery.

have involved data imbalance between groups. Second, the lack of information on the specific treatment regimen, dose and duration of postoperative adjuvant therapy, R-CT, and NACT was also a shortcoming of the current study. Third, only 57 stage IIIC2 cases and no R-CT cases were available, which may have affected the reliability of the results. Fourth, stratification was performed based on only two LNM locations and did not include LN size and number and other LNM locations.

5. Conclusions

In the present study, the oncological prognosis of patients with stage IIIC1 CC was generally better than that of patients with stage IIIC2, indicating that the rationale behind the classification of stage IIIC is justified. The oncological outcome of ARH was superior to those of R-CT and NACT for stage IIIC1 and superior to that of NACT for stage IIIC2. As such, ARH is an acceptable initial treatment option for patients with stage IIIC in less developed areas; however, consideration should be given to the use of NACT. Given the small number of stage IIIC2 cases analyzed, confirmation of the results of this research is warranted in future prospective studies.

Availability of Data and Materials

The data generated in the present study are not publicly available due to privacy, ethical restrictions and relevance to unpublished research, but may be requested from the corresponding author.

Author Contributions

All authors approved the final version of the study. YY, ZL, SK and BC made equal contributions to this work. YY conceived, structured and mentored the study, translated the data, and created and revamped the manuscript. ZL undertook the search of literature, gathered data, performed data analysis and explanation, and wrote and corrected the manuscript. SK framed and conceived the study, construed the data, and produced and modified the manuscript. BC has performed the literature search, the analysis and interpretation of data and graphs, and prepared and reviewed the manuscript. BL and LW gathered data, performed data analysis and explanation, and contributed resources. JY gathered data and contributed with resources and software. JL conceptualized the study. PL and CC conceptualized, devised and mentored the study. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was carried out in accordance with the ethical principles of the Declaration of Helsinki 1964. Permission for this retrospective study was obtained from the Ethics Committee of the Nanfang Hospital of Southern Medical University (approval number NFEC-2017-135 and clinical trial number CHiCTR1800017778; International Clinical Trials Registry Platform Search Port, https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR1800017778, registered at 14/08/2018), in which they concluded that written informed consent was not necessitated owing to the retrospective nature of the study and the withholding of patient information.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.ceog5010219.

References

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries [published correction appears in CA-A Cancer Journal for Clinicians. 2020; 70: 313]. CA-A Cancer Journal for Clinicians. 2018; 68: 394–424.

[2] Wang W, Zhang F, Hu K, Hou X. Image-guided, intensity-modulated radiation therapy in definitive radiotherapy for 1433 patients with cervical cancer. Gynecologic Oncology. 2018; 151: 444–448.

[3] Wang SC, Lin LC, Kuo YT, Lin YW. Radiographic Number of Positive Pelvic Lymph Nodes as a Prognostic Factor in Cervical Cancer Treated With Definitive Concurrent Chemoradiotherapy or Intensity-Modulated Radiotherapy. Frontiers in Oncology. 2018; 8: 546.

[4] Koh WJ, Abu-Rustum NR, Bean S, Bradley K, Campos SM, Cho KR, *et al*. Cervical Cancer, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network. 2019; 17: 64–84.

[5] Yan DD, Tang Q, Tu YQ, Chen JH, Lv XJ. A comprehensive analysis of the factors of positive pelvic lymph nodes on survival of cervical cancer patients with 2018 FIGO stage IIIC1p. Cancer Management and Research. 2019; 11: 4223–4230.

[6] Miyahara S, Tsuji K, Shimada M, Shibuya Y, Shigeta S, Nagai T, *et al*. The Impact of Histological Subtype on Survival Outcome of Patients with Stage IIB-IVA Cervical Cancer Who Received Definitive Radiotherapy. The Tohoku Journal of Experimental Medicine. 2021; 255: 303–313.

[7] Chen W, Xiu S, Xie X, Guo H, Xu Y, Bai P, *et al*. Prognostic value of tumor measurement parameters and SCC-Ag changes in patients with locally-advanced cervical cancer. Radiation Oncology. 2022; 17: 6.

[8] Qin F, Pang H, Yu T, Luo Y, Dong Y. Treatment Strategies and Prognostic Factors of 2018 FIGO Stage IIIC Cervical Cancer: A Review. Technology in Cancer Research & Treatment. 2022; 21: 15330338221086403.

[9] Brodeur MN, Dejean R, Beauchemin MC, Samouëlian V, Cormier B, Bacha OM, *et al*. Oncologic outcomes in the era of modern radiation therapy using FIGO 2018 staging system for cervical cancer. Gynecologic Oncology. 2021; 162: 277–283.

[10] Benedet JL, Pecorelli S. Why Cancer Staging? International Journal of Gynaecology and Obstetrics. 2006; 95: S3.

[11] Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri. International Journal of Gynaecology and Obstetrics. 2018; 143: 22–36.

[12] Keys HM, Bundy BN, Stehman FB, Muderspach LI, Chafe WE, Suggs CL 3rd, *et al*. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma [published correction appears in The New England Journal of Medicine. 1999; 341: 708]. The New England Journal of Medicine. 1999; 340: 1154–1161.

[13] Morris M, Eifel PJ, Lu J, Grigsby PW, Levenback C, Stevens RE, *et al*. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. The New England Journal of Medicine. 1999; 340: 1137–1143.

[14] Peters WA, 3rd, Liu PY, Barrett RJ, 2nd, Stock RJ, Monk BJ, Berek JS, *et al*. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. Journal of Clinical Oncology. 2000; 18: 1606–1613.

[15] Whitney CW, Sause W, Bundy BN, Malfetano JH, Hannigan EV, Fowler WC, Jr, *et al*. Randomized comparison of fluo-

rouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. Journal of Clinical Oncology. 1999; 17: 1339–1348.

[16] Kim YS, Shin SS, Nam JH, Kim YT, Kim YM, Kim JH, *et al*. Prospective randomized comparison of monthly fluorouracil and cisplatin versus weekly cisplatin concurrent with pelvic radiotherapy and high-dose rate brachytherapy for locally advanced cervical cancer. Gynecologic Oncology. 2008; 108: 195–200.

[17] Hoekman EJ, Knoester D, Peters AAW, Jansen FW, de Kroon CD, Hilders CGJM. Ovarian survival after pelvic radiation: transposition until the age of 35 years. Archives of Gynecology and Obstetrics. 2018; 298: 1001–1007.

[18] Bergmark K, Avall-Lundqvist E, Dickman PW, Henningsohn L, Steineck G. Vaginal changes and sexuality in women with a history of cervical cancer. The New England Journal of Medicine. 1999; 340: 1383–1389.

[19] Gupta S, Maheshwari A, Parab P, Mahantshetty U, Hawaldar R, Sastri Chopra S, *et al*. Neoadjuvant Chemotherapy Followed by Radical Surgery Versus Concomitant Chemotherapy and Radiotherapy in Patients With Stage IB2, IIA, or IIB Squamous Cervical Cancer: A Randomized Controlled Trial. Journal of Clinical Oncology. 2018; 36: 1548–1555.

[20] National Comprehensive Cancer Network. 2023 NCCN clinical practice guideline sinoncology, cervical cancer (version1). 2023. Available at: https://www.nccn.org/ (Accessed: 9 June 2023).

[21] Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri: 2021 update. International Journal of Gynaecology and Obstetrics. 2021; 155: 28–44.

[22] World Health Organization. Cervical cancer country profiles. 2021. Available at: https://www.who.int/teams/noncommunicable-diseases/surveillance/data/cervical-cancer-profiles (Accessed: 9 June 2023).

[23] Li Z, Duan H, Guo J, Yang Y, Wang W, Hao M, *et al*. Discussion on the rationality of FIGO 2018 stage IIIC for cervical cancer with oncological outcomes: a cohort study. Annals of Translational Medicine. 2022; 10: 122.

[24] Ye Y, Li Z, Kang S, Zhan X, Zhang Y, Xu Y, *et al*. Impact of different postoperative adjuvant therapies on the survival of early-stage cervical cancer patients with one intermediate-risk factor: A multicenter study of 14 years. Journal of Obstetrics and Gynaecology Research. 2023; 49: 1579–1591.

[25] Cho WK, Kim YJ, Kim H, Kim YS, Park W. Significance of para-aortic lymph node evaluation in patients with FIGO IIIC1 cervical cancer. Japanese Journal of Clinical Oncology. 2020; 50: 1150–1156.

[26] Guo Q, Zhu J, Wu Y, Wen H, Xia L, Ju X, *et al*. Validation of the prognostic value of various lymph node staging systems for cervical squamous cell carcinoma following radical surgery: a single-center analysis of 3732 patients. Annals of Translational Medicine. 2020; 8: 485.

[27] Feng Y, Liu H, Ding Y, Zhang Y, Liao C, Jin Y, *et al*. Combined dynamic DCE-MRI and diffusion-weighted imaging to evaluate the effect of neoadjuvant chemotherapy in cervical cancer. Tumori. 2020; 106: 155–164.

[28] Yang X, An J, Zhang Y, Yang Y, Chen S, Huang M, *et al*. Prognostic Nomograms Predicting Survival in Patients With Locally Advanced Cervical Squamous Cell Carcinoma: The First Nomogram Compared With Revised FIGO 2018 Staging System. Frontiers in Oncology. 2020; 10: 591700.

[29] Kwon J, Eom KY, Kim YS, Park W, Chun M, Lee J, *et al*. The Prognostic Impact of the Number of Metastatic Lymph Nodes and a New Prognostic Scoring System for Recurrence in Early-Stage Cervical Cancer with High Risk Factors: A Multicenter Cohort Study (KROG 15-04). Cancer Research and Treatment. 2018; 50: 964–974.

[30] Wu SG, Zhang WW, He ZY, Sun JY, Wang Y, Zhou J. Comparison of survival outcomes between radical hysterectomy and definitive radiochemotherapy in stage IB1 and IIA1 cervical cancer. Cancer Management and Research. 2017; 9: 813–819.

[31] Landoni F, Colombo A, Milani R, Placa F, Zanagnolo V, Mangioni C. Randomized study between radical surgery and radiotherapy for the treatment of stage IB-IIA cervical cancer: 20-year update. Journal of Gynecologic Oncology. 2017; 28: e34.

[32] Yan RN, Zeng Z, Liu F, Zeng YY, He T, Xiang ZZ, *et al*. Primary radical hysterectomy vs chemoradiation for IB2-IIA cervical cancer: A systematic review and meta-analysis. Medicine. 2020; 99: e18738.

[33] Jang TK, Shin SJ, Chung H, Kwon SH, Cha SD, Lee E, *et al*. A retrospective comparison of outcome in IB2 and IIA cervical cancer patients treated with primary concurrent chemoradiation versus radical hysterectomy with or without tailored adjuvant therapy. Obstetrics & Gynecology Science. 2017; 60: 549–557.

[34] Nishio S, Kitagawa R, Shibata T, Yoshikawa H, Konishi I, Ushijima K, *et al*. Prognostic factors from a randomized phase III trial of paclitaxel and carboplatin versus paclitaxel and cisplatin in metastatic or recurrent cervical cancer: Japan Clinical Oncology Group (JCOG) trial: JCOG0505-S1. Cancer Chemotherapy and Pharmacology. 2016; 78: 785–790.

[35] D'Oria O, D'Auge TG, Baiocco E, Vincenzoni C, Mancini E, Bruno V, *et al*. The role of preoperative frailty assessment in patients affected by gynecological cancer: a narrative review. Italian Journal of Gynaecology. 2022; 34: 76–83.

[36] Wright JD, Matsuo K, Huang Y, Tergas AI, Hou JY, Khoury-Collado F, *et al*. Prognostic Performance of the 2018 International Federation of Gynecology and Obstetrics Cervical Cancer Staging Guidelines. Obstetrics and Gynecology. 2019; 134: 49–57.

[37] Liu X, Wang W, Hu K, Zhang F, Hou X, Yan J, *et al*. A Risk Stratification for Patients with Cervical Cancer in Stage IIIC1 of the 2018 FIGO Staging System. Scientific Reports. 2020; 10: 362.

[38] Grigsby PW, Massad LS, Mutch DG, Powell MA, Thaker PH, McCourt C, *et al*. FIGO 2018 staging criteria for cervical cancer: Impact on stage migration and survival. Gynecologic Oncology. 2020; 157: 639–643.

[39] Pedone Anchora L, Carbone V, Gallotta V, Fanfani F, Cosentino F, Turco LC, *et al*. Should the Number of Metastatic Pelvic Lymph Nodes be Integrated into the 2018 Figo Staging Classification of Early Stage Cervical Cancer? Cancers. 2020; 12: 1552.

[40] Ye Q, Yang Y, Tang X, Li J, Li X, Zhang Y. Neoadjuvant Chemotherapy Followed by Radical Surgery versus Radiotherapy (with or without Chemotherapy) in Patients with Stage IB2, IIA, or IIB Cervical Cancer: A Systematic Review and Meta-Analysis. Disease Markers. 2020; 2020: 7415056.

[41] Hu T, Li S, Chen Y, Shen J, Li X, Huang K, *et al*. Matched-case comparison of neoadjuvant chemotherapy in patients with FIGO stage IB1-IIB cervical cancer to establish selection criteria. European Journal of Cancer. 2012; 48: 2353–2360.

[42] Rydzewska L, Tierney J, Vale CL, Symonds PR. Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer. The Cochrane Database of Systematic Reviews. 2010; CD007406.

[43] Katsumata N, Yoshikawa H, Kobayashi H, Saito T, Kuzuya K, Nakanishi T, *et al*. Phase III randomised controlled trial of neoadjuvant chemotherapy plus radical surgery vs radical surgery alone for stages IB2, IIA2, and IIB cervical cancer: a Japan Clinical Oncology Group trial (JCOG 0102). British Journal of Cancer. 2013; 108: 1957–1963.

[44] Duenas-Gonzalez A, Lopez-Graniel C, Gonzalez-Enciso A, Mo-

har A, Rivera L, Mota A, *et al*. Concomitant chemoradiation versus neoadjuvant chemotherapy in locally advanced cervical carcinoma: results from two consecutive phase II studies. Annals of Oncology. 2002; 13: 1212–1219.

[45] Nwankwo TO, Umeh UA, Aniebue UU, Onu JU, Umeh CR. Impact of neoadjuvant chemotherapy in improving operative intervention in the management of cervical cancer in low resource setting: a preliminary report. The Pan African Medical Journal. 2020; 36: 210.

[46] Giannini A, D'Oria O, Bogani G, Di Donato V, Vizza E, Chiantera V, *et al*. Hysterectomy: Let's Step Up the Ladder of Evidence to Look Over the Horizon. Journal of Clinical Medicine. 2022; 11: 6940.

[47] Ramirez PT, Frumovitz M, Pareja R, Lopez A, Vieira M, Ribeiro R, *et al*. Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer. The New England Journal of Medicine. 2018; 379: 1895–1904.