Impact of different therapies on the survival of patients with stage I–IIA cervical cancer with intermediate risk factors

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Background: The aim of this study was to determine the effects of different therapies on patients with cervical cancer (CC) with intermediate risk factors.

Methods: Clinicopathological data of 596 patients diagnosed with stage I–IIA CC at the Obstetrics and Gynecology Hospital of Fudan University between January 2013 and November 2015 were retrospectively reviewed. Of the patients, 500 patients received adjuvant therapy including chemotherapy (CT), radiotherapy (RT), and sequential chemotherapy and radiotherapy (CT + RT). Patients who displayed at least one intermediate risk factor number were screened.

Results: The median follow-up was 62 months. The 5-year progression-free survival (PFS) and overall survival (OS) of the entire cohort were 90.4% and 90.9%, respectively. Univariate analysis showed that tumor stage, tumor size, pathological type, lymphovascular space invasion, and numbers of medium risk factors were not risk factors for early-stage CC. Compared with the control group, patients who received CT, RT, or CT + RT showed improved PFS and OS ($P<0.05$). The RT group had lower PFS and OS than the CT and CT + RT groups ($P<0.05$). Among the 318 patients with a single intermediate risk factor, 297 patients received CT, RT, and CT + RT benefit from adjuvant therapy ($P<0.05$). Of the 253 patients with high-risk factors, 220 patients received CT, RT and CT + RT get improved PFS and OS ($P<0.05$).

Conclusions: Patients who received adjuvant therapy had better postoperative outcomes than those who did not receive adjuvant therapy. Patients had CT alone or CT combined with RT had better efficacy than those had RT alone.

Keywords: Cervical cancer (CC); intermediate risk factors; progression-free survival (PFS); overall survival (OS)

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Introduction

Cervical cancer (CC) imposes a heavy burden on women worldwide, with 529000 new diagnoses annually (1). Despite the progress that has been made and the increased awareness of human papillomavirus over the last decade, 10–20% of CC patients go on to develop recurrence and metastasis after surgery, among which the lung is the most common site of metastasis (2). The recurrent CC remains challenging, especially in less developed regions. Currently, treatment options for recurrent CC include surgery, radiotherapy (RT), chemoradiotherapy, and chemotherapy (CT), depending on the stage and response of the tumor (3,4). Surgery or RT is recommended for patients with stage I–IIA disease. Surgery has the advantages of improving survival and the quality of life of patients. Intermediate risk factors for CC include lymphovascular space invasion,

depth of stromal invasion, and tumor size. The treatment guidance and options of patients with intermediate risk factors for CC remain unclear. Here, we conducted a long-term investigation into the survival rate of women with CC, assessed the possible independent risk factors for CC, and evaluated the optimal therapeutic method for CC patients with one or more intermediate risk factors.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-7679).

Methods

Study population

A total of 596 patients with a diagnosis of I–IIA CC in accordance with the International Federation of Gynecology and Obstetrics (FIGO) staging system (2018) were included in this study. The inclusion criteria for patients were: received radical hysterectomy and pelvic lymph node dissection; complete clinical data; and postoperative pathology showing one or more intermediate risk factors (LVSI+, DSI+, TS >4 cm). The exclusion criteria were: a history of malignancy or high-risk factors (positive nodes, positive margins, or positive parametria). A representative sample of the pathology slides, operative notes, and planning films for RT were reviewed for each patient. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived. The study protocol was approved by the ethics committee of Obstetrics and Gynecology Hospital of Fudan University (No. 2020-203).

Regimen for postoperative adjuvant therapy

Most patients with intermediate risk factors received CT, RT, or sequential CT and RT. The control group comprised patients who refused recommended postoperative complementary treatment and requested observation. Patients in the CT group received platinum-based combination CT every 3 weeks for four cycles with cisplatin/lobaplatin/carboplatin (AUC =5) + paclitaxel (135 mg/m^2)/docetaxel/paclitaxel liposomes. In the RT group, RT alone was administered approximately 4 weeks after the operation. The RT target area included the preoperative tumor site and the drainage area of the pelvic lymph nodes. A total dose of 45–50 Gy of RT was delivered in 25 fractions (in fractions of 1.8–2.0 Gy, Monday to Friday), using three-dimensional conformal RT or intensity-modulated RT. In the CT + RT group, CT was performed every 3 weeks for four cycles, with the first one or two cycles given before RT and the remaining cycles conducted after the completion of RT.

Follow-up

After treatment, all patients were followed up every 3 months for the first 2 years and every 6 months for the next 3 years. The follow-up methods included phone calls, questionnaires, and outpatient visits. Recurrence was diagnosed based on the results of computed tomography (CT) or positron emission tomography-CT (PET-CT). Overall survival (OS) was calculated from the time of the initial diagnosis of CC until the date of cancer-related death. Progression-Free-Survival was defined as the time from random to the first occurrence of disease progression or death of any cause.

Statistical analysis

Data analysis was performed using SPSS 17.0 (IBM Corp., New York, USA). Differences in the proportion were measured using the χ^2 test. For continuous data, Student's *t*-test was performed. Logistic regression models were used for univariate analysis. Survival curves were established using the Kaplan-Meier method. Statistical significance was set at $P<0.05$.

Results

Patient baseline characteristics

The follow-up rate was 95.8%, with 25 of the patients lost follow-up. The clinical characteristics of the 571 patients that met the inclusion criteria are shown in *Table 1*, including age, tumor stage, pathological type, tumor size, stromal invasion, lymphovascular space invasion, and postoperative complementary therapy. Of the 571 patients included, 318 cases had 1 intermediate risk factor and 253 cases had ≥2 intermediate risk factors. The number of intermediate risk factors is shown in *Figure 1*.

Survival analysis of CC patients

The survival curves of patients who received different adjuvant therapies are shown in *Figure 2*. The 5-year

Table 1 Clinical data of cervical cancer cases

Variables	Total	1 medium risk factors	≥2 medium risk factors	P value
Age				0.97196
≤45 years	232 (40.63%)	129 (40.57%)	103 (40.71%)	
>45 years	339 (59.37%)	189 (59.43%)	150 (59.29%)	
Tumor stage				4.0181e-10
IA	6 (1.05%)	3 (0.94%)	3 (1.19%)	
IB1	234 (40.98%)	157 (49.37%)	77 (30.43%)	
IB2	118 (20.67%)	71 (22.33%)	47 (18.58%)	
IB3	87 (15.24%)	24 (7.55%)	63 (24.9%)	
IIA1	95 (16.64%)	55 (17.3%)	40 (15.81%)	
IIA2	31 (5.43%)	8 (2.52%)	23 (9.09%)	
Pathological type				0.034515
Squamous ca.	485 (84.94%)	260 (81.76%)	225 (88.93%)	
Adenomatous ca.	59 (10.33%)	43 (13.52%)	16 (6.32%)	
Neuroendocrine ca.	4 (0.7%)	3 (0.94%)	1 (0.4%)	
Adenosquamous ca.	23 (4.03%)	12 (3.77%)	11 (4.35%)	
Tumor size				0
≤4 cm	440 (77.06%)	289 (90.88%)	151 (59.68%)	
>4 cm	131 (22.94%)	29 (9.12%)	102 (40.32%)	
Stromal invasion				0
Microscopic	11 (1.93%)	10 (3.14%)	1 (0.4%)	
Superficial 1/3	128 (22.42%)	118 (37.11%)	10 (3.95%)	
Middle and deep 1/3	432 (75.66%)	190 (59.75%)	242 (95.65%)	
Lymphovascular space invasion				0
Negative	272 (47.64%)	219 (68.87%)	53 (20.95%)	
Positive	299 (52.36%)	99 (31.13%)	200 (79.05%)	
Postoperative complementary therapy				9.806e-08
Control	71 (12.43%)	50 (15.72%)	21 (8.3%)	
Chemotherapy	164 (28.72%)	109 (34.28%)	55 (21.74%)	
Radiotherapy	61 (10.68%)	41 (12.89%)	20 (7.91%)	
Chemotherapy and radiotherapy	275 (48.16%)	118 (37.11%)	157 (62.06%)	

progression-free survival (PFS) rate for the entire cohort was 90.4% (*Figure 2A*). The 5-year PFS rate for the control group was 74.6%, and rates of 93.9%, 93.4%, and 91.6% for CT, RT, and CT + RT groups, respectively (*Figure 2B*). The OS rate for all patients was 90.9% (*Figure 2A*). The OS rate for the control group was 76.0%, and rates of 93.9%, 93.4%, and 92.4% for the CT, RT, and CT + RT groups, respectively (*Figure 2C*).

In terms of the number of intermediate risk factors, the PFS rates of low-risk patients with a single intermediate

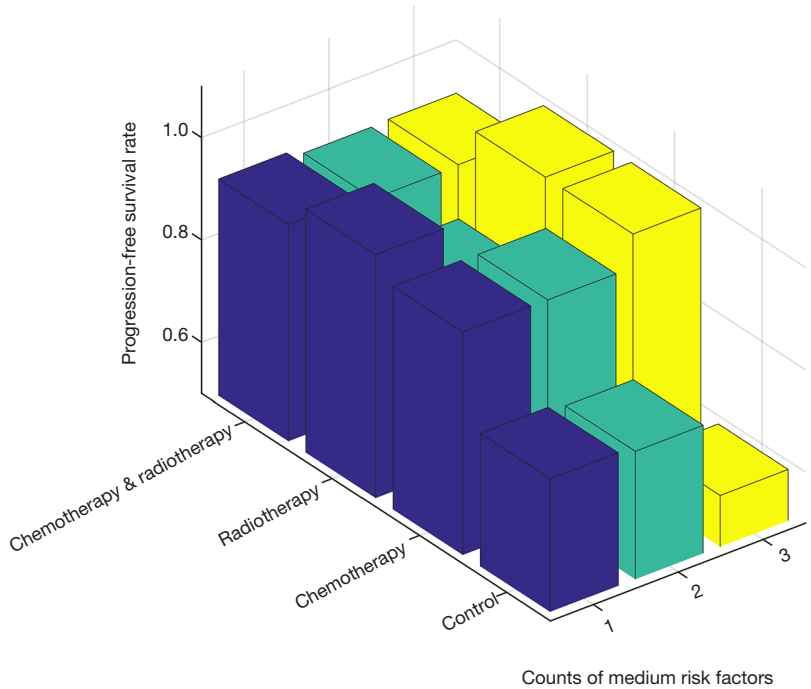

Figure 1 Bar chart showing the numbers of intermediate risk factors for the patients in each treatment group.

risk factor in the control, CT, RT, and CT + RT groups were 76.0%, 93.6%, 97.6%, and 92.4%, respectively (*Figure 2D*). The OS rates of the control, CT, RT, and CT + RT groups were 78.0%, 93.6%, 97.6%, and 93.2%, respectively (*Figure 2E*). For high-risk patients with ≥2 intermediate risk factors, the PFS rates of the control, CT, RT, and CT + RT groups were 71.4%, 94.5%, 85%, and 91.0%, respectively (*Figure 2F*). The OS rates of the control, CT, RT, and CT + RT groups were 71.4%, 94.5%, 85.0%, and 91.7%, respectively (*Figure 2G*). The PFS and OS rates in the RT group were significantly lower than those in the CT and CT + RT groups (P<0.05). These results indicated that patients who received adjuvant therapy had longer PFS and OS than those who did not receive adjuvant therapy, regardless of the number of intermediate risk factors (P<0.05). No significant difference was found in the PFS or OS rate between the various adjuvant therapies (P>0.05). The recurrence rates of the control, CT, RT, and CT + RT groups are shown in *Table 2*. Patients in the control group had a higher rate of recurrence than those in the CT, RT, and CT + RT groups (P>0.05). Patients who received RT had a higher rate of recurrence than those in the CT and CT + RT groups (P<0.05; *Figure 3*).

Prognostic factors for CC

Univariate analysis was performed to identify the possible prognostic factors. Tumor stage, tumor size, pathological type, lymphovascular space invasion, and numbers of intermediate risk factors were not found to be independent predictors of poor OS in early-stage CC (P>0.05; *Table 2*).

Discussion

Methods of adjuvant therapy have become a hotspot of CC management. The present study aimed to determine the survival benefit of adjuvant therapy in patients with early-stage CC. As reported, early-stage invasive disease accounts for 50–75% of all CC cases in the United States (5). Based on the FIGO system, early-stage CC refers to stages IA–IIA, and some oncologists consider stages IB3 and IIA2 to be advanced disease (6,7). Our data showed that early-stage CC patients who received postoperative adjuvant therapy had a relatively favorable prognosis compared those who didn't receive adjuvant therapy.

It is unclear whether the number of intermediate risk factors is an indication for adjuvant therapy, and different guidelines are inconsistent. In the AGO guidelines, for instance, RT or CT is recommended for patients with

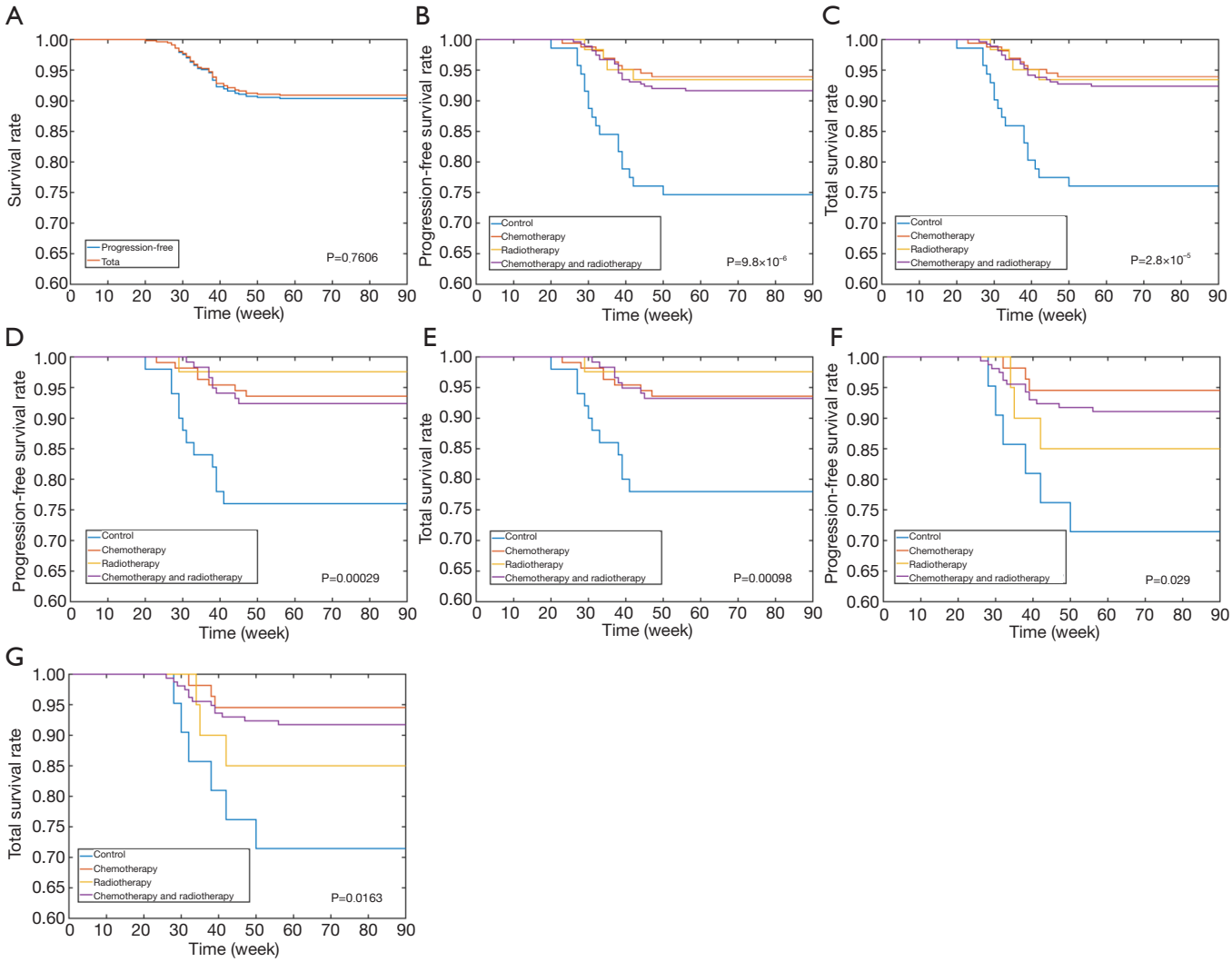

Figure 2 Comparison of different adjuvant therapy regimens [chemotherapy (CT), radiotherapy (RT), and sequential chemotherapy and radiotherapy (CT + RT)]. (A) Survival curve of the entire cohort; (B) Progression-free survival (PFS) of patients treated with various adjuvant therapies; (C) Overall survival (OS) of patients treated with various adjuvant therapies; (D) PFS of patients with a single intermediate risk factor; (E) OS of patients with a single intermediate risk factor; (F) PFS of patients with ≥2 intermediate risk factors; (G) OS of patients with ≥2 intermediate risk factors.

a single intermediate risk factor. Takeshima *et al.* (8) reported that after treatment with adjuvant CT alone, the rate of recurrence in patients with intermediate was 3.3% and the rate of recurrence in patients with high risk factors was8.6%. In this study, the patients did not receive preoperative neoadjuvant CT due to their early disease stage. According to our data, patients with ≥1 intermediate risk factor in the CT, RT, and CT + RT groups had increased survival rates compared to those in the control group. Notably, in the present study, the recurrence rate in patients with ≥2 intermediate risk factors who received RT was 15.8%, which is higher than that reported in a previous study (9). Furthermore, the PFS and OS in the RT group were significantly lower than those in the other groups. The influence of tumor stage on RT and even the guidelines for RT are still controversial. A meta-analysis revealed that concurrent RT and CT was effective than RT alone (10), which is consistent with the findings of the present study. It has been reported that relapse in patients treated with RT was on account of a higher risk of

Table 2 Univariate analysis of progression-free survival and clinical-pathological characteristics

Variables	N	Recurrence/death	χ^2	P value
Tumor stage			3.0824	0.68728
IA	6	0 (0%)		
IB1	234	23 (9.83%)		
IB2	118	10 (8.47%)		
IB3	87	12 (13.79%)		
IIA1	95	8 (8.42%)		
IIA2	31	2 (6.45%)		
Tumor size			1.3016	0.25393
≤4 cm	440	39 (8.86%)		
>4 cm	131	16 (12.21%)		
Pathological type			3.2547	0.354
Squamous ca.	485	48 (9.9%)		
Adenomatous ca.	59	7 (11.86%)		
Neuroendocrine ca.	4	0 (0%)		
Adenosquamous ca.	23	0 (0%)		
Lymphovascular space invasion			0.26144	0.60913
Negative	272	28 (10.29%)		
Positive	299	27 (9.03%)		
Counts of intermediate-risk factors			0.21676	0.64152
<1	318	29 (9.12%)		
≥2	253	26 (10.28%)		

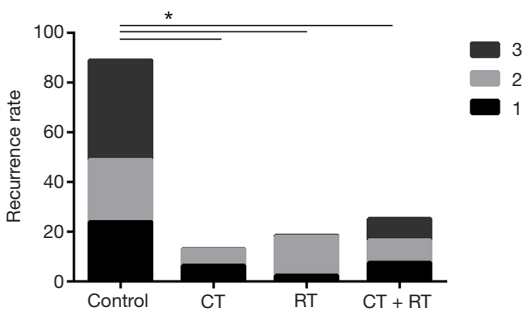

Figure 3 Recurrence rate of patients with different numbers of intermediate risk factors. Recurrence rates of patients had no adjuvant therapy or different adjuvant therapy regimens [chemotherapy (CT), radiotherapy (RT), and sequential chemotherapy and radiotherapy (CT + RT)] were calculated. *P<0.05.

complications (11), which may explain the higher recurrence rate in this study. Data on the use of CT in patients with stage IA–IIA CC is sufficient, including clinical outcome and follow-up research. A group study showed that the addition of paclitaxel to cisplatin, which was also applied in this study, contributed to rises in the response rate, PFS, and OS (12). Apparent evidence of the advantage of adjuvant therapy has been illustrated in other studies, as eradicates residual and microscopic disease (13-17). Generally, patients treated with postoperative adjuvant therapy who have ≥2 intermediate risk factors display a similar curative effect as those with a single intermediate risk factor.

Previous studies have identified stage, the number of pelvic lymph nodes, and histology as a strong prognosis factor of CC (18-23). The effects of pathological type,

lymphovascular space invasion, and numbers of intermediate risk factors on PFS and OS have not been determined. In the present study, tumor stage, tumor size, pathological type, lymphovascular space invasion, and numbers of intermediate risk factors were not found to be prognostic factors for early-stage CC patients who received CT, RT, or CT + RT as an adjuvant therapy.

In conclusion, we found that adjuvant therapy, especially CT and CT + RT, contributed to increased survival in patients with early-stage CC. This was a relatively large, population-based study of adjuvant therapy with a long-term follow-up. Based on the retrospective data analyzed in this study, CT or CT plus RT is recommended for patients with early-stage CC.

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Footnote

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Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-20-7679

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-7679). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived. The study protocol was approved by the ethics committee of Shanghai Obstetrics and Gynecology Hospital of Fudan University (No. 2020-203).

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