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Original Research

Non-squamous histology but not adjuvant therapy affects survival in stage IB–IIA cervical cancer patients with intermediate risk following radical hysterectomy

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Objective: Radiotherapy is usually recommended following radical hysterectomy (RH) in early-stage cervical cancer with intermediate risk. However, adjuvant radiotherapy only decreases recurrence but not overall survival. This study aimed to compare different adjuvant modalities's efficacy and to identify prognostic factors among these patients. *Methods*: A single-center retrospective study was conducted between 2001 and 2015 on FIGO stage IB–IIA cervical cancer patients with intermediate risk following RH. 97 patients were enrolled for analysis. The patients underwent either RH and chemotherapy (n = 24), RH and radiotherapy (n = 21), or RH and close surveillance (n = 52). Prognostic factors that affected disease-free survival (DFS) and overall survival (OS), were compared by Kaplan-Meier analysis. Cox regression was used for univariate and multivariate analyses. *Results*: The median follow-up period was 117.7 months. There was no statistical difference between 5-year DFS and OS among patients receiving different adjuvant treatments, but patients with non-squamous histology had a lower 5-year DFS (p = 0.014). Multivariate analysis demonstrated no factors but only non-squamous histology significantly predicted DFS (HR = 3.565, 95% CI 1.334–9.531). *Conclusions*: Non-squamous histology, but not different adjuvant treatment, affects DFS in patients with stage IB–IIA cervical cancer with intermediate pathological risk following RH.

Keywords

Cervical cancer; Intermediate risk; Adjuvant treatment

1. Introduction

Cervical cancer is the fourth most common cancer in women worldwide [1]. Owing to the promotion of cervical smear screening since 1995, the age-standardized incidence rate of cervical cancer in Taiwan has decreased from 12.8 per 100,000 women in 2008, to 8.1 per 100,000 in 2016 [2]. Although the 3-year Pap smear screening rate among Taiwanese women aged $\geq$30 was 50.9% in 2017, cervical cancer is still the seventh leading cause of cancer-related deaths in this population [2, 3].

The Taiwan Clinical Practice Guidelines for Cervical Cancer [4] and the National Comprehensive Cancer Network guidelines [5] both recommend radical hysterectomy (RH) for patients with early-stage cervical cancer, with the administration of adjuvant treatment if final pathological characteristics indicate risk of recurrent disease [4, 5]. The presentation of positive surgical margins, parametrium involvement, or confirmed pelvic lymph node metastasis after RH indicate a high risk of recurrence, for which adjuvant concurrent chemoradiation therapy (CCRT) is recommended [6]. Adjuvant radiotherapy is typically recommended for patients with an intermediate risk of recurrence, which is defined by pathological features which meet the Sedlis criteria, including the presence of lymph-vascular space invasion (LVSI), deep stromal invasion (SI), and large tumor size [7].

The Gynecologic Oncology Group (GOG) randomized trial #92 [7] noted that, in patients with an intermediate risk, adjuvant radiotherapy (RT) led to a 47% reduction in recurrence; however, follow-up of the same cohort demonstrated that adjuvant RT only reduced the risk of recurrence, but created no significant improvement in overall survival (OS) [8]. Therefore, this study aimed to identify potential prognostic factors, including modalities of adjuvant treatment, that contribute to oncologic outcomes among patients with stage IB–IIA cervical cancer with intermediate risk following RH.

2. Materials and methods

2.1 Patients

This retrospective cohort study was performed at the Department of Obstetrics and Gynecology, Kaohsiung Chang Gung Memorial Hospital (KCGMH), and was approved by the Ethics Committee and the Institutional Review Board of KCGMH (IRB201902292B0). Between January 2001 and December 2015, a total of 424 patients with cervical cancer, staged at IB–IIA according to the 2009 International Federa-

Table 1. Demographics of the study cohort.

Variable	Total	Treatment			*p*-value
		RH+CT	RH+RT	RH only	
All cases	97	24	21	52	
Mean age (range)	50.7 (30–72)	47.0 (30–66)	50.7 (36–69)	52.4 (31–72)	0.079
Histology					0.638
SCC	68 (70.1)	15 (62.5)	15 (71.4)	38 (73.1)	
Non-SCC	29 (29.9)	9 (37.5)	6 (28.6)	14 (26.9)	
2009 FIGO stage					>0.99
IB	96 (99.0)	24 (100)	21 (100)	51 (98.1)	
IIA1	1 (1.0)	0 (0)	0 (0)	1 (1.9)	
Tumor size (cm)					0.015
≤4	81 (83.5)	21 (87.5)	13 (61.9)	47 (90.4)	
>4	16 (16.5)	3 (12.5)	8 (38.1)	5 (9.6)	
Stromal invasion					0.711
<50%	12 (12.4)	2 (8.3)	2 (9.5)	8 (15.4)	
≥50%	85 (87.6)	22 (91.7)	19 (90.5)	44 (84.6)	
LVSI (%)					0.029
No	12 (12.4)	0 (0.0)	5 (23.8)	7 (13.5)	
Yes	85 (87.6)	24 (100.0)	16 (76.2)	45 (86.5)	

FIGO, International Federation of Gynecology and Obstetrics; RH+CT, radical hysterectomy followed by adjuvant chemotherapy; RH+RT, radical hysterectomy followed by adjuvant radiotherapy; RH only, radical hysterectomy followed by close surveillance; SCC, squamous cell carcinoma; non-SCC, non-squamous cell carcinoma, such as adenocarcinoma or adenosquamous cell carcinoma; LVSI, lymph-vascular space invasion. Values are presented as the number of cases and percentages in brackets.

Statistics: Kruskal-Wallis one-way ANOVA; Chi-squared test/Fisher's exact test; Kaplan-Meier analysis and Cox regression.

tion of Gynecology and Obstetrics (FIGO) staging system and who received standard RH and pelvic lymphadenectomy by laparotomy as primary treatment, were identified. Experienced pathologists performed the pathological reviews of patients' surgical specimens to evaluate the risk of recurrence. The diagnosis was defined as intermediate risk if any of the Sedlis criteria from GOG protocol #92 [7] were met: (1) positive LVSI and involvement of deep one-third SI; (2) positive LVSI, middle one-third SI, tumor size ≥2 cm; (3) positive LVSI, superficial one-third SI, tumor size ≥5 cm; (4) negative LVSI, deep one-third SI, tumor size ≥4 cm. Intermediate risk patients were identified and categorized into three groups according to the modalities of adjuvant management that they received, as follows: adjuvant RT (RH+RT), adjuvant chemotherapy (RH+CT), and close surveillance (RH only).

2.2 Post-operative modalities of adjuvant treatment

2.2.1 Adjuvant chemotherapy (RH+CT)

All patients who received adjuvant chemotherapy (CT) underwent 3–6 cycles of one of the following cisplatin-based combination chemotherapy regimens: (1) 50 mg/m^2 cisplatin, followed by four consecutive daily infusions of 5-fluorouracil (1000 mg/day), repeated every 28 days (PF regimen) [9]; (2) 50 mg/m^2 cisplatin and 6 mg/m^2 mitomycin-C, followed by four consecutive daily infusions of 5-fluorouracil (1000 mg/day), repeated every 28 days (FMP regimen) [10]; (3) 25 mg/m^2 cisplatin, followed by three consecutive daily infusions of 75 mg/m^2 etoposide and 1 g/m^2 ifosfamide (VIP regimen) [11]; or (4) 50 mg/m^2 cisplatin and 1 mg/m^2 vincristine, followed by three consecutive daily infusions of 25 mg/m^2 bleomycin (POB regimen) [12].

2.2.2 Adjuvant radiotherapy (RH+RT)

Patients in the adjuvant RT group received whole-pelvic RT, which was administered using either the four-field box technique [7] or intensity-modulated radiation therapy (IMRT) [13]; the latter of which replaced the four-field box technique at our institute from 2006 onwards. The dose of external-beam RT was administered with a daily fraction of 1.8 Gy for five fractions per week. Based on the radiologists' preference, some patients also received additional intravaginal brachytherapy at a total dose of 800 cGy administered by two fractions.

2.2.3 Follow-up

Patients were regularly followed up every three months for three years, and then every six months thereafter, starting from the commencement of close surveillance after RH (i.e., the RH only group) or after completion of adjuvant therapy. The performed surveillance modalities included symptom review, pelvic examination, vaginal cuff cytology, and chest

radiographs. If symptoms or suspicion of recurrence, computed tomography or magnetic resonance imaging were performed for surveillance following RH. Any recurrence noted during follow-up was categorized as either local recurrence (involving the pelvis), distant failure (outside the pelvis), or a combination of both.

2.3 Statistical analysis

Descriptive statistics were reported as the mean and range. Mann-Whitney U tests or Kruskal-Wallis one-way ANOVAs were used to compare continuous variables. Chi-squared tests or Fisher's exact tests were used to compare categorical variables. Disease-free survival (DFS) and overall survival were defined as the interval between the date of surgery and the date of first evidence of recurrence or disease-specific death, respectively. Patients who died of intercurrent diseases without recurrence, or who were lost to follow-up, were censored at the time of last known follow-up. Actuarial rates of survival were estimated using the Kaplan-Meier method, and statistical differences between groups were examined using the log-rank test. A Cox regression model was used to determine the independent factors associated with survival. Data management and analysis were performed using the SPSS software for Windows (version 22.0) (IBM, Armonk, NY, USA). p-values < 0.05 were considered statistically significant.

3. Results

Detailed pathological review revealed 113 patients with stage IB–IIA cervical cancer who met the criteria of intermediate risk following RH. Sixteen patients were excluded for treatment heterogeneity, rare histologic type, or loss to follow-up; therefore, 97 patients were enrolled in this study cohort. These patients all received standard RH and pelvic lymphadenectomy by laparotomy, and there was an average of 37.5 lymph nodes harvested in each patient. Demographic characteristics of the study cohort are listed according to the different treatment modalities in Table 1. The mean age of patients at diagnosis was 50.7 years (range, 30–72 years). Twenty-one patients (21.6%) underwent RH and radiotherapy, 24 patients (24.7%) underwent RH and chemotherapy, and 52 patients (53.6%) received RH and close surveillance. Sixty-eight patients (70.1%) were diagnosed with squamous cell carcinoma (SCC), while the 29 patients (29.9%) with non-SCC histology were either diagnosed with adenosquamous carcinoma (ASC) (n = 14) or adenocarcinoma (AC) (n = 15). Regarding intermediate risk factors, 16.5% of patients presented with >4 cm-sized tumors, 87.6% of patients presented with SI $\geq 50\%$, and 87.6% patients presented with LVSI. A statistically significant difference was found between distribution of tumor size and LVSI among groups receiving different treatment modalities. Approximately 90% of patients in the RH only group had ≤ 4 cm tumors; which were otherwise only observed in 61.9% of the RH+RT group. In addition, LSVI was observed in all patients in the RH+CT group.

Table 2. Patterns of recurrence in groups receiving different adjuvant modalities.

Treatment	Total	Recurrence	Local recurrence
RH+CT	24	5 (20.8)	3 (60.0)
RH+RT	21	6 (28.6)	4 (66.7)
RH only	52	9 (17.3)	6 (66.7)
Overall	97	20 (20.6)	13 (65.0)
p-value		0.560	0.964

RH+CT, radical hysterectomy followed by adjuvant chemotherapy; RH+RT, radical hysterectomy followed by adjuvant radiotherapy; RH only, radical hysterectomy followed by close surveillance. Values are presented as the number of cases and percentages in brackets. Statistics: Chi-squared test/Fisher's exact test.

The median duration of follow-up was 117.7 months (range, 6.9–218.3 months). The Kaplan-Meier DFS and OS survival curves of the 97 patients receiving different modalities of adjuvant treatments are shown in Fig. 1A,B. There were no statistically significant differences in 5-year DFS (RH+CT: 82.6%, RH+RT: 70.8%, RH only: 88.1%, $p = 0.350$) and OS (RH+CT: 91.3%, RH+RT: 85.4%, RH only: 95.8%, $p = 0.343$) between the different modalities of adjuvant treatment. The overall recurrence rate was 20.6%, with local and distant recurrence accounting for 65% and 35%, respectively (Table 2). There were no obvious differences in local or distant recurrence rates between adjuvant treatment modalities ($p = 0.964$). In addition, the deaths of two patients in RH+RT group, two patients in RH+CT group, and three patients in RH only group were related to recurrent disease.

The Kaplan-Meier curves for DFS and OS of the 97 patients, grouped by histological type, are shown in Fig. 2A,B. Univariate analysis showed that patients with SCC-type histology had a better DFS compared to patients with non-SCC histology ($p = 0.014$). However, no differences in OS were observed between histology types ($p = 0.489$). In addition, the overall rate of recurrence was higher in patients with non-SCC histology than those with SCC histology (35.5% vs. 14.7%, $P = 0.028$) (Table 3). Multivariate analysis showed that non-SCC histology was the only significant variable that predicted DFS. The hazard ratio and 95% confidence interval for predicting recurrence was 3.565 (1.334–9.531; $p = 0.011$) (Table 4). Age, histological type, depth of SI, presence of LVSI, tumor size, and different modalities of adjuvant management were not significant factors predicting OS in either univariate or multivariate analyses.

4. Discussion

Our study revealed a significant difference in DFS between SCC and non-SCC histological types in stage IB–IIA cervical cancer patients with intermediate risk following RH. Univariate and multivariate analyses both showed that histological type, but not adjuvant treatment modality, was a significant prognostic factor for recurrence. The main controversy of dual-modality treatments (RH+RT) is that they may be related to the risk of long-term morbidities, which include

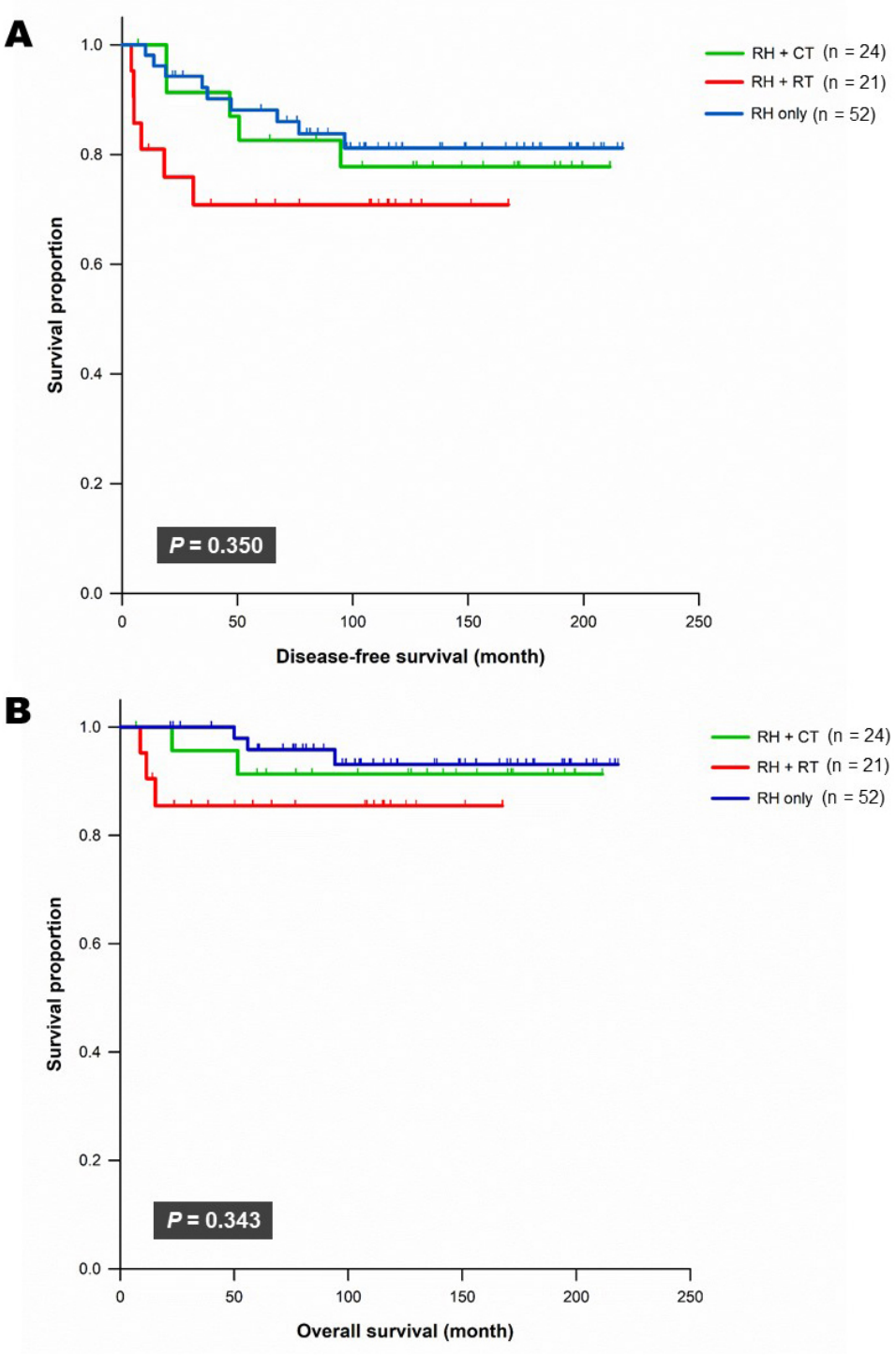

Fig. 1. Comparing the efficacy between different adjuvant management. (A) Comparison of DFS between the different modalities of adjuvant management. (B) Comparison of OS between the different modalities of adjuvant management. RH+CT, radical hysterectomy followed by adjuvant chemotherapy; RH+RT, radical hysterectomy followed by adjuvant radiotherapy; RH only, radical hysterectomy followed by close surveillance.

lower limb lymphedema and ureteral and gastrointestinal obstruction [8, 14]. Considering the increased long-term morbidity associated with adjuvant RT, and its uncertain prognostic outcome [8, 15, 16], the gynecologic oncologists at our institute also provided adjuvant CT or close surveillance for intermediate-risk patients. Interestingly, we found that close surveillance following RH also yielded a similar survival outcome when compared to adjuvant RT or CT.

The impact of histological type on the prognosis of cervical cancer has been extensively investigated [17–19]. Shingleton *et al.* [17] analyzed the cancer register database in United States between 1984 and 1990. They found no sig-

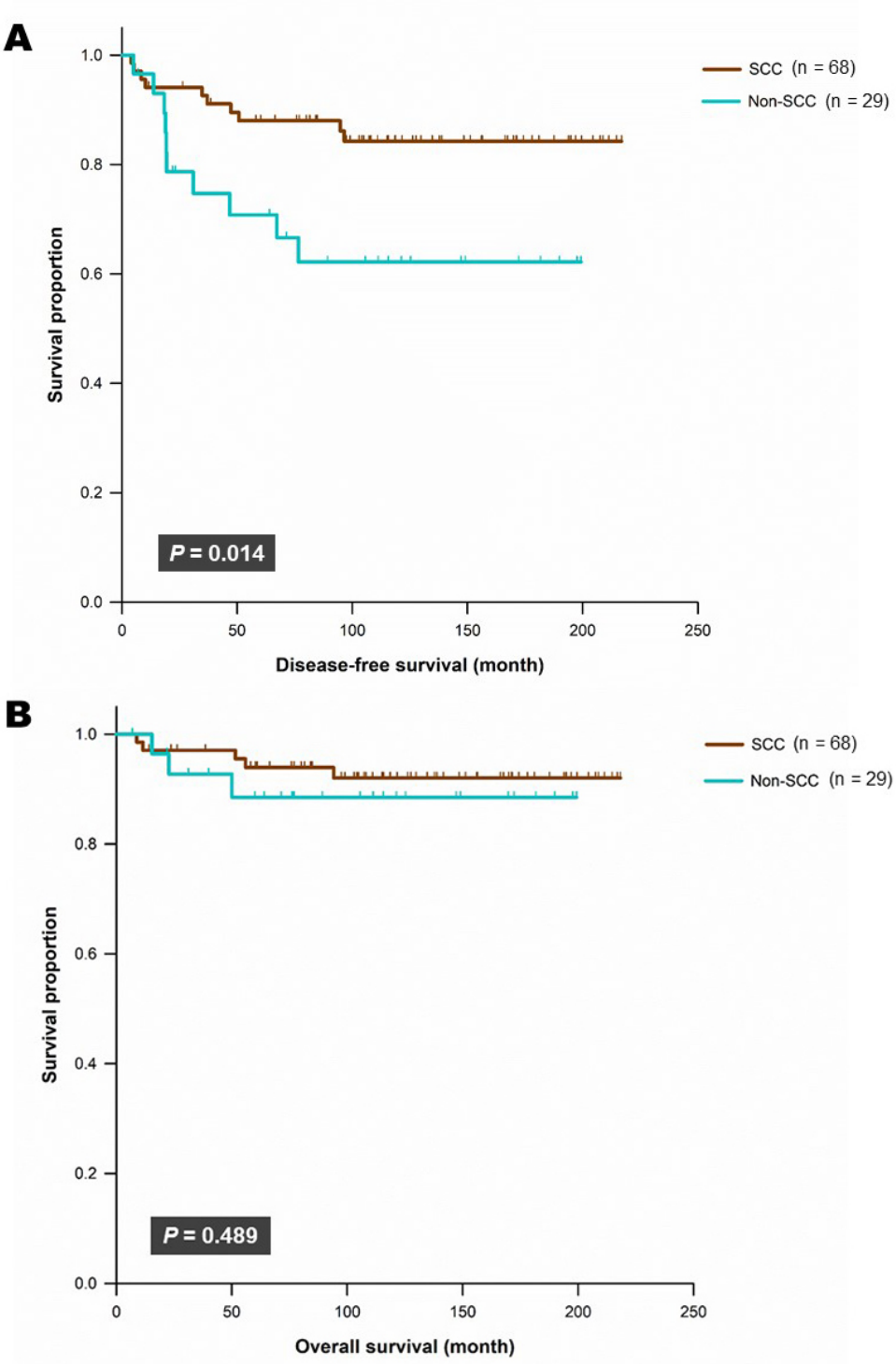

Fig. 2. Comparing the prognosis between different histologic types. (A) Comparison of DFS between SCC and non-SCC histological types. (B) Comparison of OS between SCC and non-SCC histological types. SCC, Squamous cell carcinoma; Non-SCC, Non-squamous cell carcinoma, such as adenocarcinoma or adenosquamous cell carcinoma.

nificant difference in 5-year survival when comparing SCC, AC, and ASC types; however, the enrolled cohort involved patients from a wide spectrum of clinical stage and treatment heterogeneity. A 1995 GOG study [17], that focused primarily on surgically-staged stage IB cervical cancer, demonstrated that histology had a significant impact on survival (p = 0.02), but not recurrence (p = 0.29), after adjusting for LVSI status, SI depth, and tumor size, poor survival was remain noted in patients with ASC. Grisaru *et al.* [19] grouped patients with similar features such as in the aforementioned

Table 3. Pattern of recurrence between the SCC and non-SCC histological types.

Histology	Total	Recurrence	Local recurrence
SCC	68	10 (14.7)	6 (60.0)
Non-SCC	29	10 (35.5)	7 (70.0)
Overall	97	20 (20.6)	13 (65)
p-value		0.028	0.639

SCC, Squamous cell carcinoma; Non-SCC, Non-squamous cell carcinoma, such as adenocarcinoma or adenosquamous cell carcinoma. Values are presented as the number of cases and percentages in brackets.

Statistics: Chi-squared test/Fisher's exact test.

GOG study, and also reported a poorer 5-year DFS among patients with ASC ($p < 0.03$). Accordingly, a prospective study conducted by Ryu *et al.* [20] created different criteria for defining intermediate risk, to predict recurrence and survival more effectively. In addition to the Sedlis criteria (i.e., LVSI status, SI depth, and tumor size), this new risk assessment model included the AC and ASC histological types, and the intermediate-risk group was defined by the presence of any two of four risk variables [20]. Our results corroborate the observations of Ryu *et al.* [20] and highlight the importance of non-SCC histology in assessing clinical outcomes in patients with stage IB–IIA cervical cancer and intermediate pathological risk following RH.

The GOG #92 trial [7] was pivotal in creating support for the role of adjuvant RT in intermediate-risk patients, although the follow-up study indicated that the impact of adjuvant RT on OS was inconclusive [8]. The major limitation of GOG trial #92 was that the inclusion criterion for tumor size were assessed by visual inspection and palpation during pelvic examination rather than by more quantitative/homogenous methods. Moreover, the extent of surgery was not standardized in the study protocol. Several retrospective studies also investigating the role of adjuvant RT in intermediate-risk patients following surgery. Although retrospective in nature, unique surgical protocols were used in these studies, and imaging or pathological assessment of tumor size was adopted, which reflected the clinical staging of the modern era. For example, Cibula *et al.* [21] reported a recurrence rate of 6.3% in the RH only group, of which one-fourth were categorized as local pelvic recurrence. This extremely low local failure rate was thought to be associated with the extensive nature of surgery undergone by the RH only group, which involved with a greater degree of lymph node retrieval and higher proportion of radical parametrectomies when compared to the RH+RT group. They further indicated that the only independent factor found to predict recurrence was tumor size $\geq$4 cm. The study conducted by Yahata *et al.* [22] also illustrated that adjuvant therapy for deep SI, LVSI, or bulky tumor after open radical hysterectomy might not be necessary with an exception of patients with complete SI. In their study, only six patients (7%) experienced recurrence during a median follow-up period of 84 months. The study conducted by Akilli *et al.* [23] also demonstrated that RH followed by close surveillance was sufficient; i.e., local recurrence rates in the close surveillance and RT groups were around 12–13%, indicating that adjuvant RT did not decrease local failure. The retrospective GOTIC study conducted by Nakamura *et al.* [15] suggested that RT and CCRT after RH are not beneficial in patients with intermediate risk factors but increase the incidence of lymphedema after they made a comparison among patients receiving different adjuvant modality, such as close surveillance, RT, CCRT or CT. In our study, the finding that two-thirds of local recurrent cases in the group receiving only close surveillance were categorized as local pelvic recurrence, is consistent with the findings of Akilli *et al.* [23]. The inefficacy of adjuvant RT in decreasing recurrence rates might be associated with the fact that the RT group comprised a significantly higher proportion of patients with $\geq$4 cm tumors.

The efficacy of adjuvant CT has been validated in some retrospective studies [24–26]. A nationwide retrospective study in Japan, which enrolled 555 women with stage IB cervical cancer in the intermediate-risk group, demonstrated that adjuvant chemotherapy was not associated with a significant difference in 5-year DFS ($p = 0.90$) and 5-year cause-specific survival ($p = 0.99$) when compared to adjuvant RT or adjuvant CCRT [25]. Similarly, a meta-analysis published in 2018 also demonstrated no statistical difference in disease recurrence between patients with early-stage cervical cancer and those who received adjuvant CT, compared to adjuvant RT after RH [27]. In our study, intermediate-risk patients managed with adjuvant CT after RH achieved comparable oncologic outcomes to those who received adjuvant RT.

Our study specifically focused on stage IB–IIA cervical cancer patients at intermediate risk of recurrence following radical hysterectomy, who were enrolled after pathological review. The results presented here are subject to some limitations. For example, our study was a retrospective, single-center design, across the long study period. Besides, only limited case number enrolled in this study. There were also some uneven distributions in certain pathological features among the three treatment groups; such as, tumor size, LVSI, and the heterogeneity in the adjuvant chemotherapy regimen that the patients received. Despite these limitations, we identified that non-SCC histology, but not adjuvant treatment modalities, had an influence on DFS in stage IB–IIA cervical cancer patients with intermediate pathological risk following RH. Therefore, close surveillance after RH may be a viable option for patients with SCC-type histology. A prospective study evaluating the efficacy of more aggressive adjuvant management to reduce the recurrence rate for intermediate-risk patients with non-SCC histology may be warranted.

5. Conclusions

Non-squamous histology, but not modes of adjuvant treatment, affects DFS in patients with stage IB–IIA cervical cancer with intermediate pathological risk following RH.

Table 4. Univariate and multivariate analyses of potential prognostic factors for recurrence.

		Univariate		Multivariate	
Variable	5-year DFS (%)	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age			0.601		0.222
<50	87.4	Ref			
≥50	78.4	1.265 (0.524–3.054)			
Histology			0.019		0.011
SCC	88.0	Ref		Ref	
Non-SCC	70.8	2.866 (1.189–6.908)		3.565 (1.334–9.531)	
Stromal invasion			0.765		0.915
<50%	82.5	Ref			
≥50%	83.0	1.250 (0.290–5.389)			
LVSI			0.784		0.466
No	81.8	Ref			
Yes	83.1	1.226 (0.284–5.287)			
Tumor size			0.132		0.228
≤4 cm	86.1	Ref			
>4 cm	76.0	1.968 (0.815–4.752)			
Treatment			0.364		0.367
RH+CT	82.6	1.201 (0.402–3.584)			
RH+RT	70.8	2.098 (0.746–0.899)			
RH only	88.1	Ref			

SCC, Squamous cell carcinoma; Non-SCC, Non-squamous cell carcinoma, such as adenocarcinoma or adenosquamous cell carcinoma; LVSI, lymph-vascular space invasion; RH+CT, radical hysterectomy followed by adjuvant chemotherapy; RH+RT, radical hysterectomy followed by adjuvant radiotherapy; RH only, radical hysterectomy followed by close surveillance.

Statistics: Kaplan-Meier method for survival analysis; Cox regression for univariate and multivariate analyses.

Author contributions

Y-WW, HL, H-CF, C-CCC, Y-CO, and C-HW were responsible substantial contributions to the conception or design of the work. Y-WW, HL, H-CF, Y-CO, P-HL, C-CH, and C-HW were responsible for the acquisition, analysis, or interpretation of data. YW, HL, CW were responsible for drafting the work and revising it critically for important intellectual content. Y-WW, HL, H-CF, C-CCC, Y-CO, P-HL, C-CH, and C-HW were responsible for final approval of the version to be published, and all of them agreed to be 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.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee and the Institutional Review Board of KCGMH (IRB201902292B0). Due to the retrospective nature of the study, informed consent were not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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