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Original Article

Survival analysis of Stage IIA1 and IIA2 cervical cancer patients

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Abstract

Objective: The aim of this study was to assess the benefits of the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system for survival of patients with Stage IIA1 and IIA2 cervical cancer (Cx Ca).
Materials and Methods: A study cohort of 51 patients with Stage IIA Cx Ca was retrospectively collected from the 2004–2009 hospital-based, long-form Cx Ca data registry at Mackay Memorial Hospital (Taipei, Taiwan). The survivorship and overall survival were compared between these two groups (Stages IIA1 and IIA2) using log-rank test.
Results: Thirty-six and 15 patients were classified into Stages IIA1 and IIA2, respectively. Stage IIA2 patients were younger than those with Stage IIA1 disease (mean age, 47.4 vs. 55.1 years, $p = 0.008$), but no significant difference was observed in confirmed pelvic lymph node status (21.4% vs. 38.5%, $p = 0.280$) between them. Although the 2-year and 5-year overall survival was better among Stage IIA1 patients, there was no significant difference in survival between Stage IIA1 and IIA2 groups (2-year, 90.6% vs. 77.8%; 5-year, 86.3% vs. 51.9%, $p = 0.218$).
Conclusion: Although there was a trend in survival difference between Stage IIA1 and IIA2 patients, the difference was not statistically significant. The revised FIGO 2009 staging system for Cx Ca defines a group of Stage IIA patients with bulky tumor (Stage IIA2) that are generally younger than Stage IIA1 patients. It is sensible to investigate an alternate or enhanced treatment scheme for Stage IIA2 patients. Ideally, the treatment scheme should prevent unnecessary radical surgery if a patient can be exposed to either chemotherapy or radiotherapy, alone or in combination.

Keywords: bulky tumor; Stage IIA; staging criteria; survival; tumor size

Introduction

The International Federation of Gynecology and Obstetrics (FIGO) staging system is used by gynecologic oncologists worldwide for therapeutic decision making for cervical cancer (Cx Ca). Although prognostic factors such as primary tumor size, pelvic lymph node (LN_P) metastasis, stromal invasion, and lymphovascular space invasion have been correlated with patient outcome in many studies [1–5], tumor size alone defines the FIGO staging of patients with Cx Ca [6]. The published experience on the clinical role of tumor size cutoff represents a collective effort of many clinicians over the past decade (Table 1). The tumor size cut-off value of 4 cm is an important criterion for both Stages 1B and IIA Cx Ca. Tumor extension >4 cm is often referred to as bulky tumor. The

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Table 1
Literature concerning the effect of different tumor sizes on the survival of stage IIA cervical cancer patients.

Author (y)	Study design	FIGO stage	Tumor size (cm)	Pts (*n*)	Treatment type	5-y OS	Recurrence rate	LN_P
Landoni et al (1997) [7]	RCT	IB-IIA	≤4	115	RH	87%		
			>4	55		70%		
			≤4	113	RT	90%		
			>4	54		72%		
Perez et al (1998) [14]	Retrospective (Hospital-based)	IIA	≤2	15	RT	93%[a]		
			2.1–4	50		63%[a]		
			4.1–5	29		39%[a]		
			>5	20		59%[a]		
Huang et al (2003) [8]	Prospective (Hospital-based)	IB-IIA	≥4	162	RH + Pre-NACT	69%		
Horn et al (2007) [31]	Retrospective (Hospital-based)	IIA-IIB	≤4	113	RH	67.7%	28.0%	42.4%
			>4	132		49.5%	40.2%	60.2%
Eifel et al (2009) [15]	Retrospective (Hospital-based)	IB-IIB	≤4	2386	(1) 12.2% RH	85%		
					(2) 2.6% RH+post-RT			
			>4, ≤6	1240	(3) 77.7% RT	69%		
			>6	593	(4) 7.5% RT+post-RH	52%		
Garg et al (2011) [16]	Retrospective (SEER national database)	IIA1	≤4	271	(1) 47.2% RT	65.8%		
					(2) 31.7% RH+post-RT			40.4%
					(3) 21.0% RH			
		IIA2	>4	289	(1) 64.7% RT	59.5%		46.0%
					(2) 27.3% RH+post-RT			
					(3) 8.0% RH			
Lai et al (2012) (Current study)	Retrospective (Hospital-based)	IIA1	≤4	36	(1) 47% RH	86.3%	2.8%	21.4%
					(2) 19.4% CCRT			
					(3) 16.7% RH+post-CCRT			
					(4) 8.3% RH+post-RT			
					(5) 5.6% BPLND+CCRT			
					(6) 2.8% RT			
		IIA2	>4	15	(1) 46.7% RH+post-CCRT	51.9%	6.7%	38.5%
					(2) 26.7% BPLND+CCRT			
					(3) 6.7% CCRT			
					(4) 13.3% RH			
					(5) 6.7% RH+pre-CT			

BPLND = bilateral pelvic lymphadenectomy; CT = chemotherapy; CCRT = concurrent chemo-radiation therapy; FIGO = International Federation of Gynecology and Obstetrics; LN_P = pelvic lymph node; NACT = neoadjuvant chemotherapy; OS = overall survival; post = postoperative; pre = preoperative; Pts = patients; RCT = randomized controlled study; RT = radiotherapy; RH = radical hysterectomy; SEER = Surveillance, Epidemiology, and End Results.
[a] 10-year disease-free survival.

prospective randomized trial by Landoni et al [7] and some other studies [8–10] have shown that the presence of bulky tumors significantly reduces the disease-free survival (DFS) and cumulative overall survival (OS) for patients with Stage IB disease regardless of the therapeutic modalities. Several multivariate analyses, nevertheless, have failed to observe similar correlation between bulky tumor size and survival for Stage IB patients [11–13]. The recently revised 2009 FIGO staging system for Cx Ca [6] also brings forth similar debates as we have seen in the past for Stage IB patients. Stage IIA disease is now further divided into Stages IIA1 and IIA2 using 4 cm as a discriminator. Although earlier studies have also supported the prognostic impact of substaging Stage IIA disease [14,15], the recent study by Garg et al [16] has concluded that the new FIGO 2009 staging criteria are not an independent predictor of survival for Stage IIA cervical cancer. The aim of the present study was to reassess the benefits of the 2009 FIGO staging system for the survival of patients with Stage IIA Cx Ca.

Materials and methods

Individual subject data of incident cases of Cx Ca under examination were retrospectively collected from the 2004–2009 hospital-based, long-form Cx Ca data registry at Mackay Memorial Hospital (MMH) (Taipei, Taiwan). The registry belonged to a subset of dataset submitted to the Taiwan National Cancer Registry Database, which is a population-based cancer registry founded in 2002 by the National Department of Health from the Executive Yuan [17]. The dataset was then linked with the medical records of the hospital to obtain patients' vital status at last follow-up. The long-form Cx Ca registry was received as de-identified patient data. The registry collects basic demographic data and

clinicopathological information on patients, including age, stage, primary tumor site, and tumor dimension at the time of diagnosis; regional lymph node status; initial course of treatment; and nature of the follow-up for vital status. Topography, morphology, and behavior coding of the primary cancer site is based on the third edition of the International Classification of Diseases for Oncology (ICD-O-3), published by the World Health Organization in 2000 [18]. All incident cases of Stages II, IIA, IIB Cx Ca patients with the ICD-O-3 primary site code of C53.9 were initially identified from the registry system between January 1, 2004 and December 31, 2009. A total of 2717 Cx Ca cases were identified during the study period, among whom 127 patients were staged as FIGO Stage IIA disease. Seventy-one patients who received an initial course of therapy at another hospital (16 cases); lacked microscopic confirmation of histology (1 case); lacked pathological tumor size information (40 cases); or died of uncertain causes or causes other than Cx Ca (14 cases) were initially excluded from the study to avoid survival bias. Patients were categorized into the following histological groups: squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, and all other histological groups. The latter group was excluded from the analysis due to histological heterogeneity, consisting mostly of rare histology. Three cases of rare histology (papillary squamous cell carcinoma; neuroendocrine cervical carcinoma; villous adenocarcinoma) and one histology inappropriate for Stage IIA disease (squamous intraepithelial neoplasia, grade III) were removed from the remaining cases. Another patient who was diagnosed with more than one type of primary cancer was not considered to be typical Stage IIA1, and was therefore precluded from this study. A total of 51 cases were therefore selected for the study. We believe that the selected patients were homogeneous with respect to prognosis and appropriate for this study.

All Stage IIA patients (based on 1989 FIGO recommendation) were reassigned to either FIGO Stage IIA1 or IIA2 groups in accordance with the current FIGO 2009 staging system for Cx Ca. Pathological staging is more accurate than clinical staging, especially in Stages IB2 and II (IIA and IIB) diseases [6,19–21]; therefore we favored the use of maximal tumor diameter resulting from the pathological assessment of the resection specimens in our study. The maximal tumor diameter is the largest tumor extension of either measurement, vertical or horizontal. All patients with pathological tumor size $\leq$40 mm or >40 mm were categorized as Stages IIA1 and IIA2, respectively. Tumor grade 1, 2, and 3 refer to well differentiated, moderately differentiated, and poorly differentiated/undifferentiated, respectively. The data concerning initial primary treatment were derived from procedure data codes. Data on LN_P status were derived from the confirmed number of regional lymph nodes. The OS was defined as the date from initial diagnosis to death or last follow-up in the intent-to-treat population. DFS was defined as the start of treatment until clinical or radiological evidence of recurrence. Patients were censored if they were still alive or lost to follow-up at last contact. Follow-up time was defined as the date of last follow-up or death from the date of initial treatment. The study was approved by the Institutional Review Boards and Ethical Committees at MMH on 2011/07/29 (Protocol #: 11MMHIS068).

Significance levels for association between continuous and categorical variables in different groups were computed by Student's t test and Pearson's χ^2 as appropriate. Mean (standard deviations), frequency (%), and 95% confidence interval (CI) were presented for continuous variable, categorical variable, and survival rates, respectively. Survival analysis was evaluated using the Kaplan–Meier product-limit method, and comparisons between survival curves were performed using a log-rank test. All statistical tests were performed with the use of SPSS for Windows (release R18) (SPSS Inc, Chicago, IL, USA). All reported p values corresponded to two-sided tests, and significance was set at an α of 0.05.

Results

The retrospective study included a study cohort of 51 Cx Ca patients who were treated at MMH between January 1, 2004 and December 31, 2009. The clinical profiles and related statistics of selected patients are listed in Table 2. All patients were adults with a mean age of 53.0 years (median, 53.0 years; range, 34–74 years) at initial diagnosis. Slightly over two-thirds (36/51, 71%) of these patients were classified into Stage IIA1 with a mean tumor diameter of 28.8 mm (median, 30 mm; range, 1–40 mm); and the remaining patients (15/51, 29%) were classified into Stage IIA2 with a mean tumor diameter of 54.0 mm (median, 50 mm; range, 45–75 mm). Stage IIA2 patients were younger than those with Stage IIA1 disease (mean age, 47.4 years vs. 55.1 years, $p = 0.008$). The majority of our patients were associated with squamous cell carcinoma histological pattern (90%) and tumor grade 2 (59%). Two-third of these patients was diagnosed with Cx Ca at another medical institute (34/51), but all patients received their initial treatment at least partially at our hospital. In addition, all selected patients were microscopically confirmed positive for Stage IIA disease.

LN_P status was available in 41 cases, and only 11 had LN_P metastases (11/41, 27%). The mean retrieved LN_P nodes number were 20.8 $\pm$ 17.9 (range, 0–96) and 27.1 $\pm$ 16.4 (range, 0–57) for Stage IIA1 and IIA2 patients, respectively. No significant difference was observed in retrieved LN_P number (20.8 vs. 27.1, $p = 0.240$) and confirmed LN_P status (21.4% vs. 38.5%, $p = 0.280$) between Stages IIA1 and IIA2 group.

The majority of these patients were treated initially with radical hysterectomy (RH) (36/51, 71%) plus bilateral pelvic lymph node dissection (BPLND), among whom only one patient also received para-aortic lymph node dissection. Nineteen of these patients received only RH (19/36), but other patients also had adjuvant treatments [1 preoperative chemotherapy, 3 postoperative radiotherapy, and 13 postoperative concurrent chemotherapy plus radiotherapy (CCRT)]. Non-RH surgery was performed in six patients (6/51), referring to those who were treated initially with BPLND followed by postoperative adjuvant CCRT. The remaining nine patients were

Table 2
Clinical profiles and related statistics of Stage IIA cervical cancer patients by stage ($n = 51$).

	Stage IIA1	Stage IIA2	p value	Stage IIA
n	36	15		51
Age (y)	55.1 ± 9.5	47.7 ± 6.3	0.008*	53.0 ± 9.3
Cell type				
SCC	32 (88.9%)	14 (93.3%)		46 (90.2%)
AC	3 (8.3%)	0 (0%)		3 (5.9%)
ASC	1 (2.8%)	1 (6.7%)		2 (3.9%)
Tumor grade[a]				
Grade 1	2 (5.6%)	1 (6.7%)		3 (5.9%)
Grade 2	21 (58.3%)	9 (60%)		30 (58.8%)
Grade 3	6 (16.7%)	1 (6.7%)		7 (13.7%)
Tumor size (mm)	28.8 ± 10.2	54.0 ± 8.5	<0.001**	36.2 ± 15.1
Retrieved LN_P mean no.	20.8 ± 17.9	27.1 ± 16.4	0.240	22.6 ± 17.5
LN_P status[b]				
LN_P meta (+)	6	5	0.280	11
LN_P meta (−)	22	8		30
Adjuvant treatment after non-RH surgery[c]				
CCRT	2	4		6
Non-surgical treatment				
RT	1	0		1
CCRT	7	1		8
Adjuvant treatment before RH[d]				
CT	0	1		1
Adjuvant treatment after RH				
No Tx	17	2		19
RT	3	0		3
CCRT	6	7		13
Survival status[e]				
NED	29 (82.9%)	8 (57.1%)		37 (75.5%)
AWD	2 (5.7%)	2 (14.3%)		4 (8.2%)
DOD	4 (11.4%)	4 (28.6%)		8 (16.3%)

Statistical significance ($p < 0.01$*; $p < 0.001$**).
AC = adenocarcinoma; ASC = adenosquamous carcinoma; AWD = alive with disease; BPLND = bilateral pelvic lymph node dissection; CCRT = concurrent chemo-radiation therapy; CT = chemotherapy; DOD = died of disease; LN_P = pelvic lymph node; NED = no evidence of disease; RH = radical hysterectomy; RT = radiotherapy; SCC = squamous cell carcinoma; Tx = treatment.
[a] Data of 11 cases were not available for the analysis of tumor grade.
[b] Data of 10 cases were not available for the analysis of LN_P status.
[c] Bilateral pelvic lymph node dissection.
[d] Radical hysterectomy plus lymph node dissection.
[e] Data of 2 cases were not available for the analysis of survival status.

managed by nonsurgical primary treatments, radiotherapy (1/9) or CCRT (8/9).

During the study period, eight patients died from Cx Ca. The median time from diagnosis to initial treatment was 29 days (95% CI: 26.1–31.9 days) and 41 days (95% CI: 24.6–57.4 days) for Stage IIA1 and IIA2 patients, respectively. Disease status after treatment was certain only in 49 cases. Within the time frame of this analysis, six patients (6/49, 12%) were never disease-free; among whom four (4/6, 67%) died of cancer progression at last follow-up. Only two of the 43 patients who recurred achieved complete tumor control after initial primary treatment, and continued to live without recurrence for 46.5 months (95% CI: 4.4–88.6 months). One patient (Stage IIA2) recurred locally and was treated by non-RH surgery plus postoperative adjuvant CCRT, whereas the other (Stage IIA1) with both local and distant recurrences was treated by RH alone.

The median survival was >5 years and the exact value was not calculable due to insufficient median follow-up time of 29 months (95% CI: 17.0–41.0 months) for the entire cohort. The 2-year and 5-year OS rates (2-year, 83.3%; 5-year, 75.8%) were similar to that of DFS rates (2-year, 86.6%; 5-year, 77.2%). Although the 2-year and 5-year OS rates were better among Stage IIA1 patients, there were no significant difference in survival between Stage IIA1 and IIA2 groups (2-year, 90.6% vs. 77.8%; 5-year, 86.3% vs. 51.9%, log-rank test, $p = 0.218$) (Fig. 1).

Survivorship analysis indicated no statistical significance in age, substage (IIA1 or IIA2), LN_P status, histological types, treatment types, tumor grade, surgical methods [RH with or without postoperative adjuvant therapies such as chemotherapy, radiotherapy, or CCRT], radiotherapy alone, and CCRT alone.

Discussion

The new FIGO 2009 staging criteria represent a major advancement that affects diagnostic and therapeutic decisions for pathologists and gynecologic oncologists, respectively. A total of 51 patients were retrospectively classified using the new FIGO 2009 staging system. Our experience shows that the revised FIGO 2009 staging system for Cx Ca defines a group of Stage IIA patients with bulky tumor (Stage IIA2) that are generally younger than those with nonbulky tumors (Stage IIA1).

Most authors would agree that the age of the patient is an important consideration when comparing clinical roles of reported results derived from literature available online. The respective mean patient age for Stage IIA1 and IIA2 patients at diagnosis were 54 and 49 years as reported by Garg et al [16] in their study of 560 cases. Landoni et al [7] described 52 and 46

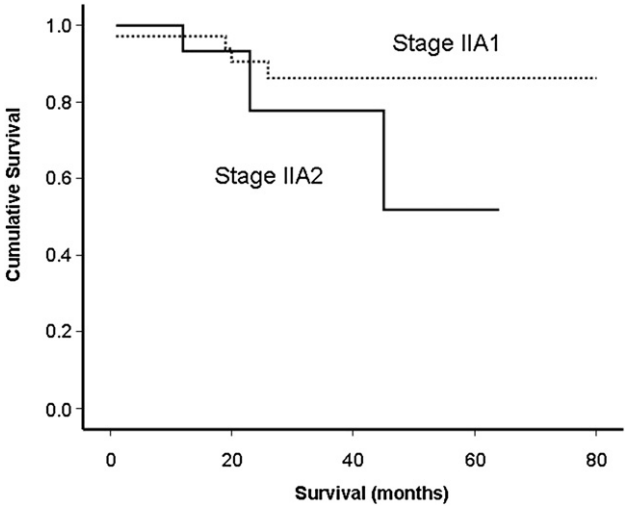

Fig. 1. Overall cumulative survival of patients with cervical cancer Stage IIA1 ($n = 36$) and IIA2 ($n = 15$). Differences were seen in overall survival between the two groups. The 2-year cumulative survival rates were 90.6% and 77.8% for Stage IIA1 and IIA2 patients, respectively; whereas the 5-year survival rates of these patients were 86.3% and 51.9%, respectively. Statistical analysis of survival curves were produced from the two groups of patients using log-rank test ($p = 0.218$).

years for patients with nonbulky and bulky tumors, respectively, in their RH group of 170 cases; and mean of 55 and 50 years for their radiotherapy group of 167 cases. In our study, the mean age was 55 and 48 years for Stage IIA1 and IIA2 patients, respectively. This finding concurs with other reported results in that patients with bulky tumor (Stage IIA2) are generally younger than those with nonbulky tumors (Stage IIA1).

The purpose of the new FIGO 2009 criteria is to determine the survival benefit for Stage IIA Cx Ca patients with bulky tumors (or Stage IIA2 patients). In the present study, a higher 5-year survival rate was observed in Stage IIA1 patients than in Stage IIA2 patients, which agreed with the published findings (Table 1). A equivalence 5-year OS rate was reported by Eifel et al [15] on 4219 patients ($\leq$40 mm, 86.3% vs. 85%; $>$60 mm, 51.9% vs. 52%). However, very few studies have been reported for Stage IIA patients alone. Most early staged Cx Ca studies have examined outcomes of both Stages IB and IIA patients, among whom Stage IB patients were the majority. The current study included a cohort that was composed entirely of Stage IIA patients. Although the study cohort reported by Garg et al [16] also consisted entirely of Stage IIA patients, they did not observe survival difference between the two stages. Those authors reported a much lower 5-year OS rate for the IIA1 group (86.3% vs. 65.8%), and a slightly higher 5-year OS rate for the IIA2 group (51.9% vs. 59.5%) than we did. The difference in sample size between the Surveillance, Epidemiology, and End Results (SEER) national database in their study and the hospital registry in our study was possibly the major reason explaining the expected discordant results between the two studies. However, a higher proportion of patients in our study were managed by radical surgery, which might also possibly explain the observed discrepancy with the findings by Garg et al [16].

Many would agree that the presence of lymph node metastases is an important prognostic factor that correlates with an unfavorable impact on the survival of both early and advanced Stage Cx Ca patients [7,22]. Traditionally, advanced-stage disease includes Stage IIB or higher; however, the National Comprehensive Cancer Network (NCCN) guidelines now categorize patients with Stage IIA1 into the early disease group, and those with Stage IIA2 into the advanced disease group [23]. Advanced patients are often considered to have a higher incidence of both para-aortic lymph node and LN_P metastasis than early stage patients. However, because the status of distant lymph node regions was not available in this registry, it is not possible to determine accurately the extent of disease spread for these patients. Nevertheless, although the difference in the incidence of LN_P metastasis was not statistically significant in our study (Table 2), the incidence of LN_P metastasis was more than twofold in patients with Stage IIA2 than those with IIA1 diseases, which corresponded well with the advanced stage classification of Stage IIA2 disease.

The majority of these patients in our study were treated initially with RH followed by postoperative CCRT (Table 2). Similar to other studies, adjuvant therapy (radiotherapy or CCRT) plays an important role in the postoperative adjuvant treatment of RH in the presence of increased tumor size and LN_P metastases [3,12,24,25]. However, the combined modality of RH and radiotherapy may lead to increased side effects and significant complications [26,27]. Alternatively, comparable cure rates have been reported for patients with early-stage Cx Ca treated with either RH or radiotherapy [7,28,29]. RH is a much more favorable alternative for young patients who desire to preserve ovarian and improved coital function. An additional advantage is accurate staging. Histological verification of tumor extent correlates better with the biological behavior of disease, therefore, surgical staging is superior to clinical staging. By contrast, the higher morbidity associated with RH has rendered radiotherapy a more suitable treatment option for older patients, as well as those who are physically unfit. Nevertheless, an important consideration is the association between increased local failure rate of primary radiotherapy and large tumor sizes [14,30]. The choice of therapy suitable for Stage IIA patients with bulky tumors must therefore be carefully selected based on the clinical and surgical assessments of the disease, as well as in consideration of patient and physician preferences.

The clinicians must bear in mind some of the limitations faced by the inherent nature of a retrospective study while interpreting the data reported herein. Our hospital had limited patients with bulky tumors (Stage IIA2), leading to unequal censoring rate when compared to those with nonbulky tumors. This weakened the univariate analysis for a hospital-based population. Moreover, there were insufficient data to assess the status of distant lymph node regions. Furthermore, we also lacked information on types of RH as well as types and dosages of chemotherapeutic agents.

Although the staging criteria divide the IIA patients into just two tumor groups, the current study finds that the revised FIGO 2009 staging system for Cx Ca defines a subgroup of Stage IIA patients with bulky tumor (Stage IIA2) who are generally younger than the remaining patients in Taiwan. The respective 2-year and 5-year OS rates for Stage IIA2 patients were 77.8% and 51.9%. Age groups, surgical methods, histological types, treatment types, tumor grade, and LN_P involvement do not appear to be associated with survival outcomes of Stage IIA patients. There was a trend of a difference in survival between the Stage IIA1 and IIA2 patients, therefore, it is sensible to investigate an alternate or enhanced treatment scheme for Stage IIA2 patients. Further prospective studies with large numbers of patients should be carried out to compare treatment protocols for Stage IIA2 patients. Ideally, the treatment scheme should prevent unnecessary RH if the patient can be exposed to either radiotherapy or CCRT alone. Despite the aforementioned limitations faced by this study, its significance lies in the fact that it is believed to be the first Asian study to date to report experiences with Stage IIA patients using the FIGO 2009 classification. Gynecologic oncologists in Asia perform a higher percentage of RH when treating patients with Stage IIA diseases, therefore, we hope that our 51-case experience with FIGO 2009 classification may serve as a basis of comparison for future studies on the Asian population.

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