Survival Analysis of Patients with Stage IB to IIA2 Cervical Cancer: A Five-Year Single Institution Review

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ABSTRACT

Objective: This study aims to determine the disease-free survival and overall survival outcome of patients with IB to IIA cervical cancer managed with surgery, chemoradiation, or a combination of both in a tertiary government training hospital.

Methodology: This is a retrospective study of patients diagnosed with stage IB-IIA2 cervical cancer from January 2013 to June 2017. Data were encoded using Microsoft Excel. Statistical analyses were computed using SPSS. Cox regression and Kaplan Meier analyses were used to predict survival outcomes.

Results: Out of 135 patients were included in the study, 111 received treatment. 61 had no evidence of disease. Median age is 46 years with stage IB1 disease. Majority of patients underwent surgery followed by adjuvant therapy. Tumor recurrence was highest in the surgery alone group, with median time to recurrence of 19 months. Median follow-up time was 10 months. Overall 5-year survival is 51.4%; 5-year disease-free survival is 54.8%.

Conclusions: Age is a statistically significant factor in survival. Surgery with adjuvant chemotherapy + radiation had the most favorable survival outcome. Neoadjuvant treatment gave the least number of recurrences. Despite a small sample size, this study provides baseline data into the survival outcome of patients with locally advanced cervical cancer in our institution given the different treatment recommendations.

Keywords: cervical cancer, early stage, disease-free survival, overall survival, hysterectomy, chemoradiation, adjuvant chemotherapy, neoadjuvant chemotherapy

INTRODUCTION

Cervical cancer is the second most common malignancy afflicting Filipino women belonging to the 15 to 44 years old age group. In the year 2017, worldwide cancer statistics tallied that 6,670 women were diagnosed with cervical cancer, with 2,832 succumbing to complications brought by the disease.[1] Owing to this high mortality rate is the late detection of cervical cancer, given that the majority of these cases are diagnosed during the advanced stages.

The term "locally invasive cervical cancer" is given to cases falling under stage IB up to stage IVA disease, and whose primary treatment is in the form of radiation therapy. Among patients belonging to Stage IB to IIA, surgery is performed as part of definitive treatment.[2] Studies have shown that in stage IB to IIA disease, surgery in the form of radical hysterectomy with pelvic lymph node dissection has equal efficacy with combination radiotherapy and chemotherapy, with five-year survival rates approaching 91%.[11] Our local clinical practice guidelines recommend either surgery, chemoradiation, or a combination of both for stages IB2 and IIA2; and chemoradiation for stages IIB-IVA.[3] However, the most recent guidelines recommend concurrent chemoradiation for stages IB2 to IIA2 cervical cancer, altogether omitting the option for surgery.[6]

General Objective

This study aims to determine the survival outcome of patients with IB – IIA cervical cancer managed with either surgery, chemoradiation, or a combination of both in a tertiary government training hospital.

Specific Objectives

The specific objectives are the following:

1. To determine the demographic characteristics of patients with stage IB to IIA2 cervical cancer

*Third Place, Society of Gynecologic Oncologists of the Philippines Foundation, Inc. (SGOP) 4th Dr. Luciano S.J. Sotto Research Paper Contest, November 13, 2018, Meeting Room 6 (A. Mabini), Philippine International Convention Center (PICC)

in a tertiary government training hospital;
2. To determine the treatment modalities used in this subset of patients;
3. To identify the patients' status given the administered treatment;
4. To determine the disease-free survival and overall survival rate of these patients;
5. To determine the association of age, disease stage, histology, and treatment modality on the survival of the patients;
6. To identify the sites of tumor recurrence and disease progression.

INTRODUCTION

The International Federation of Gynecology and Obstetrics (FIGO) staging system for cervical cancer states that Stage IB lesions are those which are clinically visible but confined to the cervix: IB1 has a size no greater than four centimeters, while IB2 are more than four centimeters. Stage IIA disease extends to the cervix but does not extend into the pelvic wall, with IIA1 and IIA2 exhibiting the same range of measurements as IB1 and IB2, respectively.[8]

For stage IB to stage IIA cervical cancer, surgery in the form of radical hysterectomy with pelvic lymph node dissection yield comparable survival rates with chemoradiation, thus are equivalently effective in the primary treatment of cervical cancer in its early stages.[11] On the other hand, radiotherapy alone or concurrent with systemic chemotherapy is offered and recommended for poor surgical risk patients.[5] For stage IB2 and IIA2 disease, or those called bulky tumors, the 2017 National Comprehensive Cancer Network guidelines recommend that the disease can first receive adjuvant chemotherapy and then undergo hysterectomy. This is due to the observation that the tumor volume could decrease after chemotherapy, affording better operability during surgery. Thence, radiotherapy or chemoradiotherapy can be administered depending on the pathology results after hysterectomy.[9]

However, there are some inconsistencies on the curative effects of surgery and radiotherapy in patients with stage IB2 and IIA2 cancer. Previous studies have proved that radical surgery and radiotherapy are equally effective in the treatment of stage IB2 and IIA, but the type and rate of complications and morbidity between them were different. While some studies found that early stage patients treated with primary surgery had improved outcomes than those treated with neoadjuvant radiation, other studies suggested that primary radical hysterectomy had better survival outcomes and lower treatment-related morbidities as compared to primary chemoradiation.[10]

The use of neoadjuvant chemotherapy followed by radical hysterectomy has become an attractive and acceptable approach to improve disease control and reduce toxicity. Due to the fact that cervical cancer is highly responsive to platinum-based and taxane-based agents, giving neoadjuvant chemotherapy can target micrometastases, thus reducing the probability of tumor recurrence after surgical treatment.[2] The systemic effect of chemotherapy likewise provides better survival rates than radiotherapy in the neoadjuvant setting.[12]

On the other hand, an important point against primary surgery in bulky cervical cancer is the fact that many women with stage IB2 disease have unfavorable prognostic factors necessitating the need for adjuvant chemotherapy with or without radiotherapy in 30– 84% of patients, resulting in increased morbidity for these women. Some use this argument to advocate primary chemoradiation for all women with stage IB2 disease. Unfortunately, there are not many studies that compared short-term and long-term morbidity of women treated by radical hysterectomy, followed by chemoradiation for a select group of high-risk women, with patients who had primary chemoradiation. Although some find morbidity to be higher in the surgical group, others refute this whereas quality of life did not differ in yet another study.[11]

METHODOLOGY

This is a retrospective study of all patients diagnosed with histology-proven cervical cancer with stages IB1 to IIA2 disease from January 2013 to June 2017 from a single Gynecologic Oncology fellowship training institution. These patients were referred to the institution seeking either primary or adjuvant treatment. Patients with concomitant malignancies were excluded from this study. Those patients who had cervical cancer but did not undergo radical hysterectomy with bilateral lymph node dissection were likewise excluded.

Medical records were reviewed and the following data were collected:

1. Age and gravidity
2. Stage of disease
3. Histology of cancer
4. Whether treatment was received
5. Treatment modality received
6. Date of last follow-up
7. Status at last follow-up
8. Site of tumor recurrence or progression

The collected data were encoded using Microsoft Excel. The number of samples to be collected will be computed using a 95% confidence interval.

In describing all categorical variables, frequency and

percentage will be used while all continuous data will be expressed in median. In testing associations among categorical variables, Chi square test was used with Fisher's Exact test. In evaluating for survival analysis, Kaplan-Meier test was used. Cox Regression Analysis was utilized to predict overall mortality. For all the tests' statistics, any associated p-values lesser than 0.05 will be considered statistically significant. All statistical analyses were performed using SPSS software.

RESULTS

The study cohort included a total of 135 patients. Mean age is 46 years old at initial diagnosis, with gravidity of three. Majority of patients were staged as IB1 disease, accounting for 40%. Seventy percent of the subjects were of squamous cell carcinoma histology. Table 1 shows the patients' demographics.

Out of the 135 subjects, only 111 received treatment. Twenty-four patients were not able to receive treatment: 21 of them were lost to follow-up after the first consultation, one had tumor progression and refused to undergo treatment, and two patients expired before the start of treatment. A diagram illustrating the summary of the results is in Figure 1.

A total of 80 patients underwent surgery. Sixty-seven of them underwent radical hysterectomy as primary treatment modality, and more than half received adjuvant chemoradiation. Thirteen received neoadjuvant therapy, while 31 patients received chemoradiation as primary mode of treatment. Table 2 shows the treatment modality received according to disease stage. The patients' status after receiving their treatment is tabulated in Table 3.

There were 12 episodes of tumor recurrence: half of them underwent primary hysterectomy only. Majority were central recurrences. There were four cases of extrapelvic

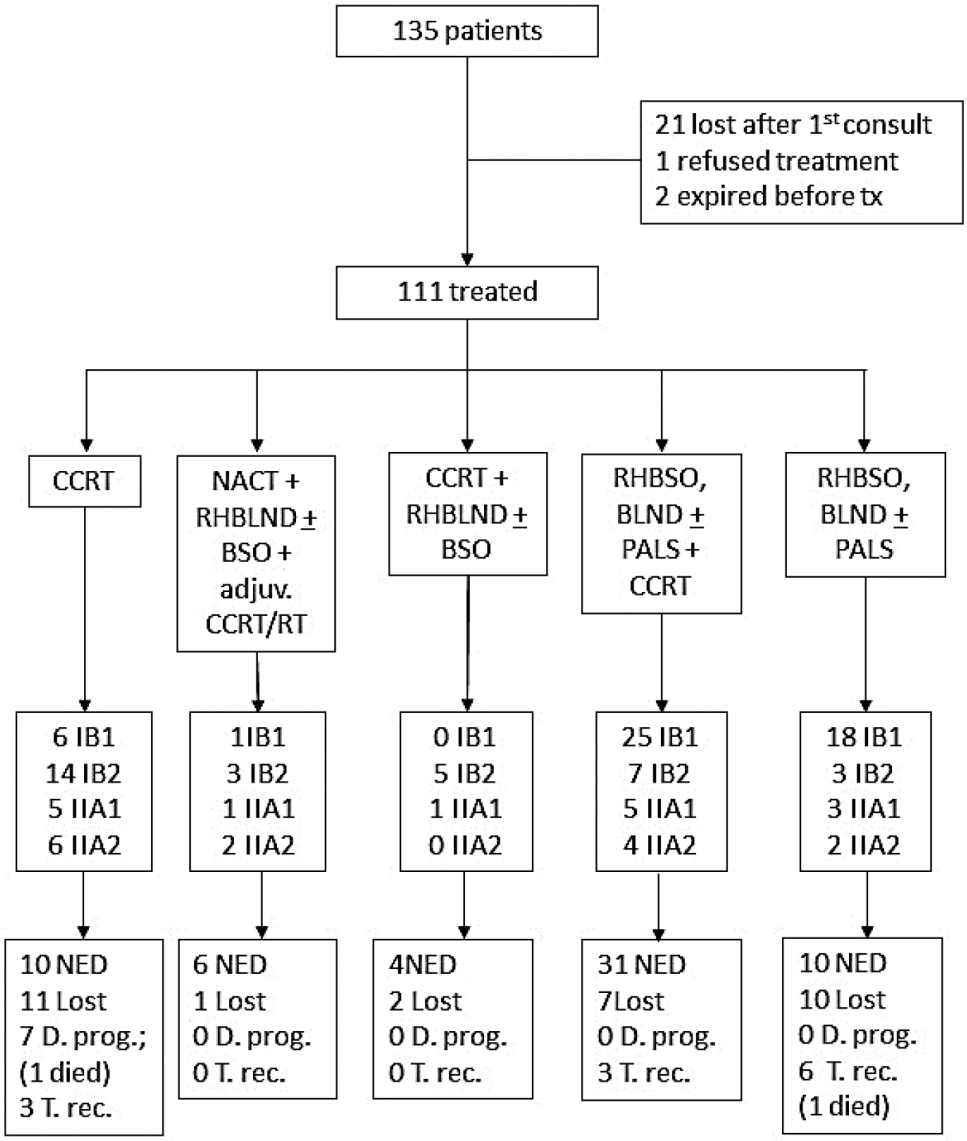

Figure 1. Diagram of Summary of Results

recurrence, specifically in the bone and liver. There were no reported recurrences in patients who underwent neoadjuvant therapy prior to radical hysterectomy (Table 4). Median time to tumor recurrence is 19 months (range 2 to 49 months).

Seven patients had tumor progression: two of which had positive aortocaval lymph nodes, while five had local progression. All of the patients received concurrent chemoradiation as primary mode of treatment, and they were given high dose chemotherapy (Table 5).

Median follow-up time is ten months. The overall 5-year survival rate for the cohort is 51.4%. The 5-year disease-free survival rate is at 54.8%.

Cox regression analysis shows that among the age groups, there is a higher rate of survival among patients aged 31 to 49 years old. However, the age group 40 – 49 years old alone shows statistical significance. When comparing survival by disease stage and histology, regression analyses show there is no significant difference between the groups (Table 6). Kaplan Meier plots for each group are illustrated in Figures 2, 3 and 4.

Analysis of survival based on the treatment modality showed that among the treatment modalities given to the cohort, there is greater survival among those who underwent primary surgery with adjuvant treatment, with median time of survival of 19 months which is the highest among the cohort and of statistical significance. (Table 7). Kaplan Meier estimates for survival is illustrated in Figure 5.

Table 1. Patient Demographics

Variables	n = 135	%
Age in years		
< 30	9	6.7
31 – 39	32	23.7
40 – 49	47	34.8
50 – 59	29	21.5
> 60	18	13.3
Gravidity		
< 3	66	48.9
4 – 6	56	41.5
> 7	13	9.6
Clinical stage		
IB1	54	40.0
IB2	40	29.6
IIA1	20	14.8
IIA2	21	15.6
Histology		
Squamous Cell Carcinoma	95	70.4
Adenocarcinoma	31	23.0
Adenosquamous Carcinoma	3	2.2
Poorly differentiated Carcinoma	6	4.4

DISCUSSION

In this study, we analyzed the clinical features of patients with stage IB to IIA cervical cancer and how the given treatment modalities affected their survival. The study likewise determined whether independent variables such as age, histology, and stage of disease affected the patients' survival.

Our results showed that among the different independent variables, only the age presented with a statistically significant outcome. This is in congruence with the reports of Ruslim et al. that the highest incidence of stage IB-IIA cervical cancer is among the 33-49 years old age group, and the dominant histology being squamous cell carcinoma.[14]

Table 2. Treatment Given According to Stage of Disease

Treatment Received	Stage of Disease (n=111)			
	IB1	IB2	IIA1	IIA2
Primary RHBSO, BLND ± PALS + adjuvant chemoradiation	25 *(22.5%)*	7 *(6.3%)*	5 *(4.5%)*	4 *(3.6%)*
Concurrent chemoradiation followed by RHBLND ± BSO + lymph node dissection	0	5 *(4.5%)*	1 *(0.9%)*	0
Neoadjuvant chemotherapy followed by RHBLND ± BSO + adjuvant postoperative radiation or chemoradiation	1 *(0.9%)*	3 *(2.7%)*	1 *(0.9%)*	2 *(1.8%)*
Concurrent chemoradiation	6 *(5.4%)*	14 *(12.6%)*	5 *(4.5%)*	6 *(5.4%)*
Primary RHBSO, BLND ± PALS only	18 *(16.2%)*	3 *(2.7%)*	3 *(2.7%)*	2 *(1.8%)*

The study showed increased survival in the patients who underwent primary surgery followed by adjuvant therapy compared to the other treatment modalities. The results of our study showed similar data with the report of Landoni, et al where they found that for stage IB to IIA cervical cancer, survival rate of patients who underwent radical hysterectomy is equal to those who received radiation therapy.[19] We also yielded comparable results in the study of Doll, et al, who showed that radical hysterectomy decreased the recurrence rate and lowered the number of disease complications among cases of stage IB1 cervical cancer when compared with radiation therapy (with or without chemotherapy).[20]

Our results showed that neoadjuvant chemotherapy followed by hysterectomy provided better survival than concurrent chemoradiation alone, despite the wide difference in the number of subjects in each group. The positive impact of neoadjuvant therapy is likewise reflected in the lack of tumor recurrences in this subgroup of patients in our study.

Table 3. Patient Status and Primary Treatment Received

Treatment Received	Patient Status (n=111)			
	No Evidence of Disease	Lost to Follow Up	Tumor Recurrence	Tumor Progression
Primary RHBSO, BLND + PALS + adjuvant chemoradiation	31 *(27.9%)*	7 *(6.3%)*	3 *(2.7%)*	0
Concurrent chemoradiation followed by RHBLND + BSO + lymph node dissection	4 *(3.6%)*	2 *(1.8%)*	0	0
Neoadjuvant chemotherapy followed by RHBLND + BSO + adjuvant postoperative radiation or chemoradiation	6 *(5.4%)*	1 *(0.9%)*	0	0
Concurrent chemoradiation	10 *(9.0%)*	11 *(9.9%)*	3 *(2.7%)*	7 *(6.3%)*
Primary RHBSO, BLND + PALS only	10 *(9.0%)*	10 *(9.0%)*	6 *(5.4%)*	0

Table 4. Tumor Recurrence (n=12)

	Number of cases	Site/s of recurrence
Primary RHBSO, BLND + PALS + adjuvant chemoradiation	3	Central
Concurrent chemoradiation followed by RHBLND + BSO + lymph node dissection	0	N/A
Neoadjuvant chemotherapy followed by RHBLND + BSO + adjuvant postoperative radiation or chemoradiation	0	N/A
Concurrent chemoradiation	3	Central (1) Bone (1) Liver (1)
Primary RHBSO, BLND + PALS only	6	Central (4) Bone (1) Liver (1)

Table 5. Tumor Progression (n=7)

	N cases	Site/s of progression
Primary RHBSO, BLND + PALS + adjuvant chemoradiation	0	0
Concurrent chemoradiation followed by RHBLND + BSO + lymph node dissection	0	0
Neoadjuvant chemotherapy followed by RHBLND + BSO + adjuvant postoperative radiation or chemoradiation	0	0
Concurrent chemoradiation	7	Aortocaval LN (2) Pelvic (5)
Primary RHBSO, BLND + PALS only	0	0

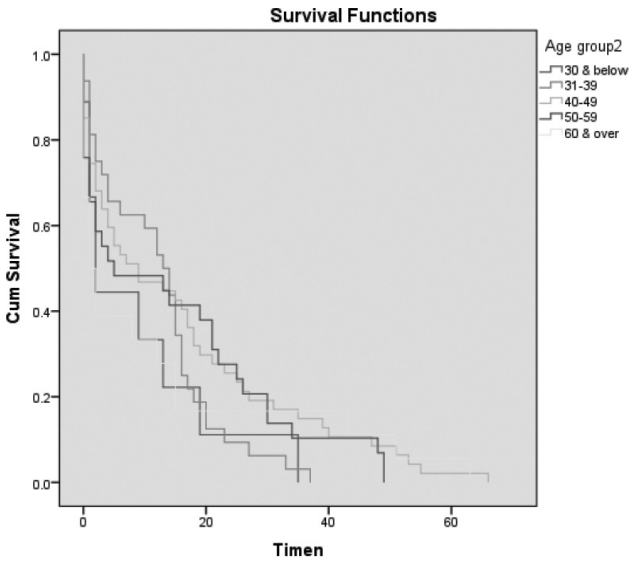

Figure 2. Kaplan Meier Plot for Age

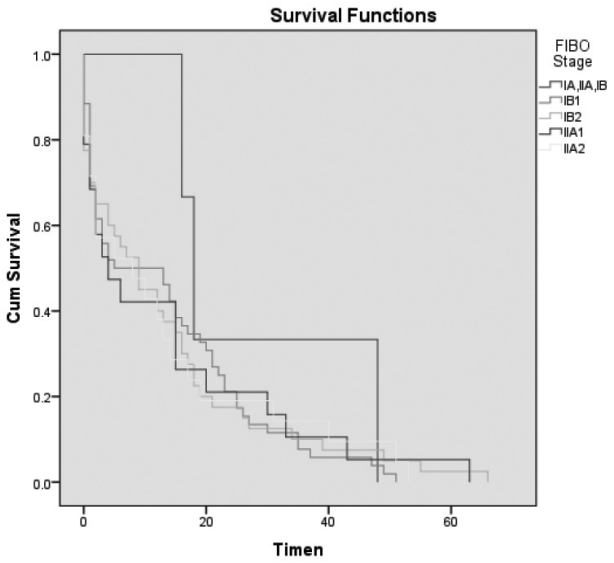

Figure 3. Kaplan Meier Plot for Stage

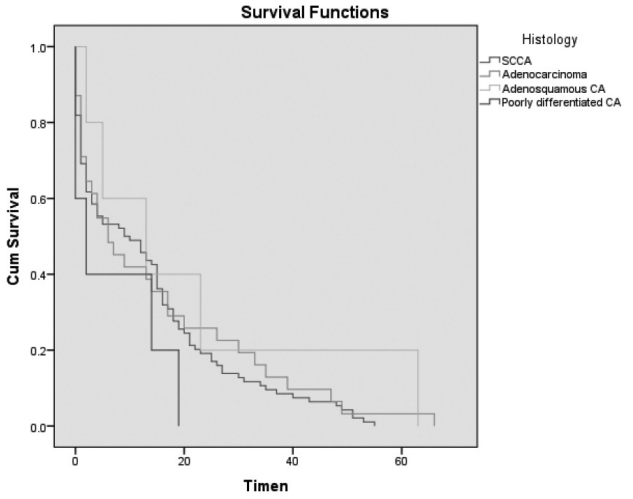

Figure 4. Kaplan Meier Plot for Histology

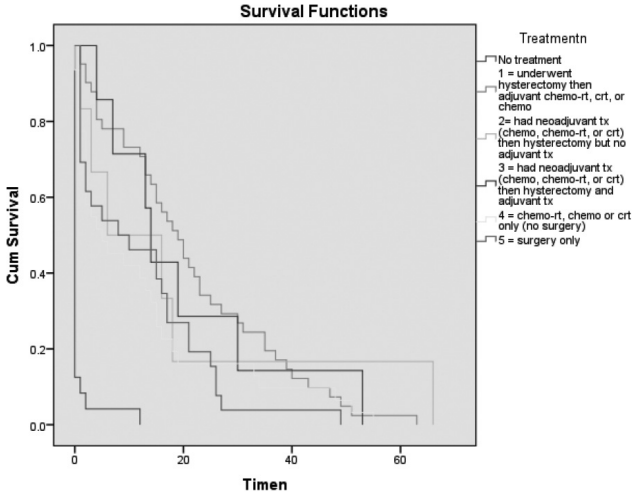

Figure 5. Kaplan Meier Plot for Treatment

Table 6. Survival and Hazard Functions By Age, Stage and Histology

Variable	Coefficient	p-value	Exp (B)	Median Time of Survival (months)
Age				
≤ 30 years	0.383	0.592	1.193	2.0
31 – 39 years	1.163	0.092	3.199	9.0
40 – 49 years	1.148	0.033	3.152	13.0
50 – 59 years	0.631	0.197	1.880	5.0
> 60 years	0.561	0.296	1.752	1.0
FIGO Stage				
IB1	-0.443	0.567	0.642	5.0
IB2	0.131	0.716	1.140	9.0
IIA1	0.012	0.976	1.012	4.0
IIA2	-0.555	0.280	0.574	8.0
Histology				
SCCA	-0.696	0.340	0.498	9.0
Adenocarcinoma	-0.904	0.238	0.405	6.0
Adenosquamous CA	-0.980	0.273	0.375	13.0
Poorly differentiated CA	-0.903	0.256	0.389	2.0

Table 7. Survival and Hazard Functions By Treatment

Variable	Coefficient	p-value	Exp (B)	Median Time of Survival (months)
Primary RHBSO, BLND + PALS + adjuvant chemoradiation	3.952	.006	52.049	19.0
Concurrent chemoradiation followed by RHBLND + BSO + lymph node dissection Concurrent chemoradiation followed by RHBLND + BSO + lymph node dissection	-0.074	.865	.929	6.0
Neoadjuvant chemotherapy followed by RHBLND + BSO + adjuvant postoperative radiation or chemoradiation	-0.738	.379	.478	14.0
Concurrent chemoradiation	-0.379	.591	.685	5.0
Primary RHBSO, BLND + PALS only	-0.572	.315	.564	8.0

Zhang et al. postulated that the rate of intrapelvic lymph node metastasis was significantly decreased in patients treated with neoadjuvant chemotherapy followed by surgery, compared to those who underwent primary surgery. This may be due to the role of neoadjuvant systemic chemotherapy causing lymph node apoptosis.[16] Unfortunately, one patient who received neoadjuvant chemotherapy died while ongoing preoperative workup. Despite the cause of death being renal failure, it was not established whether the cause of renal failure was chemotherapy-induced. Singh, et al in 2013 reported no incidence of renal toxicity in patients who received neoadjuvant chemotherapy.[18]

It can be noted that there is a lower overall survival rate and disease-free survival rate in this study compared to published data. Gupta, et al reported an average disease-free survival rate of 73%,2 While Wu, et al. reported an overall survival rate of 71.2%.[5] Factors affecting survival that have been analyzed in this study were not found to be statistically significant, except for the age, which is the most commonly occurring age group in early stage cervical cancer.[14] Treatment variables, as discussed above, have a contributing factor in the survival rate. Probable reasons behind this finding may include having poor compliance to treatment, with patients being lost to follow-up after surgery, only to return with tumor recurrence, or being completely lost to follow-up altogether. A considerable number of patients have likewise dropped out of treatment at different stages in the regimen. Determining the quality of life of these patients, including reasons for poor compliance during the treatment course are important in the spectrum of cancer treatment, and its investigation is highly recommended.

The rates of tumor recurrence are highest in the surgery only group. The main purpose of adjuvant chemotherapy after radical surgery is to reduce extrapelvic recurrence, and adjuvant radiotherapy serves to reduce local recurrence[17], which was not given in the surgery alone group. This study, however, did not include the toxicities and complications related to chemotherapy.

On the other hand, there is a high incidence of tumor progression in the chemoradiation group. Several hypotheses may lead to the cause of this outcome, including the inability to deliver high dose in the pelvis due to critical organs i.e. the urinary bladder and rectum, in proximity of cervix, thereby giving suboptimal doses of radiation to the diseased cervix[16], and the inadequate cycles of chemotherapy that should augment the effects of radiation by inhibiting the repair of radiation-induced sub lethal damage and by sensitizing hypoxic cells to radiation. Further studies on the effect of adequacy of chemotherapy cycles in order to produce the least risk of progression is recommended in this group of patients, as this study did not evaluate on this correlation.

This study has several limitations. Foremost, it is a retrospective study, which is an inherent limitation in itself. The sample size is small compared to the wide duration of study period. Likewise, the high dropout rate of subjects and censored data have greatly contributed to the low survival outcome. Other information for determining treatment outcomes such as complications and toxicities, that can provide a better understanding of the survival rate in our institution, were also not elicited in this study.

SUMMARY

In summary, this study investigated the survival outcome of cervical cancer patients with stage IB to IIA2 disease over the course of five years in a single institution. We were able to gather 135 patients, 111 of which received treatment. Age, among other independent variables, had a significant impact on the survival of patients. Primary surgery followed by adjuvant therapy obtained the most favorable of survival outcomes, while neoadjuvant therapy prior to surgery contributed to zero recurrence and progression. Despite a small sample size that could have yielded a comparatively lower

survival rate than published data, this study provides a baseline reference for future researches. It is therefore recommended that similar studies be done prospectively to have better follow-up of the involved cohort. ■

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