

Stadium IB – IIA cervical cancer patient's survival rate after receiving definitive radiation and radical operation therapy followed by adjuvant radiation therapy along with analysis of factors affecting the patient's survival rate

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Abstract. To evaluate the characteristics and overall survival rates of early stage cervical cancer (FIGO IB–IIA) patients who receive definitive radiation therapy and those who are prescribed adjuvant postoperative radiation and to conduct a factors analysis of the variables that affect the overall survival rates in both groups of therapy. The medical records of 85 patients with cervical cancer FIGO stages IB–IIA who were treated at the Department of Radiotherapy of Cipto Mangunkusumo Hospital were reviewed and analyzed to determine their overall survival and the factors that affected it between a definitive radiation group and an adjuvant postoperative radiation group. There were 25 patients in the definitive radiation and 60 patients in the adjuvant radiation group. The overall survival rates in the adjuvant radiation group at years one, two, and three were 96.7%, 95%, and 93.3%, respectively. Negative lymph node metastasis had an average association with overall survival ($p < 0.2$). In the definitive radiation group, overall survival at years one, two, and three were 96%, 92%, and 92%, respectively. A hemoglobin (Hb) level >12 g/dl was a factor with an average association with the overall survival ($p < 0.2$). The differences between both groups of therapy were not statistically significant (92% vs. 93.3%; $p = 0.138$). This study did not show any statistically significant overall survival for cervical cancer FIGO stage IB–IIA patients who received definitive radiation or adjuvant postoperative radiation. Negative lymph node metastasis had an effect on the overall survival rate in the adjuvant postoperative radiation group, while a pre-radiation Hb level >12 g/dl tended to affect the overall survival in the definitive radiation group patients.

1. Introduction

Cervical cancer is the second leading cause of mortality in the world after breast cancer, with approximately 500,000 new cases being diagnosed each year and 233,000 of these leading to mortality [1-3]. In 2015, the World Health Organization estimated that cervical cancer caused 260,000 deaths each year; almost 80% of these cases occurred in developing countries, and about 10% of all cancers in women were new cases of invasive cervical cancer [4-6]. Among an Asian population of 100,000, there were 54.5 incidences of cervical cancer that led to 28.9% mortality cases. About 24.6% cases occurred in



Central and South Asia and caused 14.1% deaths; 15.8% cases were identified in Southeast Asia and produced 8.3% deaths, while 9.6% mortality cases were reported in East Asia and led to 3.9% mortality cases. Finally, 4.5% cases occurred in West Asia and caused 2.1% mortality cases [7]. Cervical cancer is the most prevalent gynecologic cancer and makes up about 75% of all diagnosed gynecological cancers; the five-year survival rates for cervical carcinoma stages II, III, and IV are 40%, 20%, and 0%, respectively [8].

According to the published literature, the treatments of choice for early stage cervical cancer are surgery, radiation, and a combination of both [1-3,5,6,8-10]. Several studies have found that early stage cervical cancer cases can be effectively treated with radical hysterectomy or definitive radiation therapy, which have roughly the same survival rates [11-15]. Although adjuvant radiation significantly lowers the chances of local relapse, the improvement in patient survival rates is still controversial [16]. MacLeod and Vinod observed that the survival rate was better in the adjuvant radiation group than in the definitive radiation group (86% vs. 58%, respectively), but their study was flawed due to its unbalanced selection of research participants. Okada reported that the survival rate of a surgery group was better than that of the group that underwent surgery followed by adjuvant radiation (97.6% vs. 82.7%, respectively) [16].

There are currently no data about the survival rates of patients with stage IB–IIA cervical cancer who receive either definitive radiation therapy or both radical surgery and adjuvant radiation in Indonesia. In addition, there are still no guidelines for stage IB–IIA cervical cancer treatment sequences in Indonesia. The Indonesian Obstetrics and gynecology Association guideline is still insufficient to use as an appropriate reference, so all decision-making in the management of stage IB–IIA cervical cancer is based on the physician's personal judgment and typically refers to the National Comprehensive Cancer Network (NCCN) guidelines and International Federation of Gynecology and Obstetrics (FIGO). This study aimed to observe the survival rate of stage IB–IIA cervical cancer patients receiving definitive radiation and adjuvant radiation therapy after radical hysterectomy and any factors that affected the results.

2. Materials and Methods

This study was a retrospective cohort study that used the secondary data of patients who underwent surgery followed by adjuvant and definitive radiation therapy from 1 January 2007–31 December 2009. All data were collected and sorted using the inclusion and exclusion criteria. Patient data that met both criteria were searched to observe the output assessed with a telephone interview. The last known condition of the patient was assessed as well as whether the patient was still living. All collected data were processed and presented in Tables prior to our analysis. The inclusion criteria for adjuvant radiation patients were those with stage IB–IIA cervical cancer who had received adjuvant radiation therapy after radical hysterectomy from January 2007–December 2009 and were between 18–65 years old with all types of histopathologies who completed the adjuvant radiation program with a 45 Gy minimum external radiation dose. When brachytherapy was performed as indicated, patients received an additional dose of at least 2 x 8.5 Gy or equivalent, which was confirmed by the doctor's written instructions on the finished radiation therapy sheet or the letter of patient return inside the patient's status. The maximum external radiation overall treatment time (OTT) was 49 days or about 63 days maximum OTT when brachytherapy was added.

The inclusion criteria for definitive radiation patients were those with stage IB–IIA cervical cancer who received definitive radiation therapy from January 2007–December 2009 and aged 18–65 years with all types of histopathologies who completed the definitive radiation program with a 45-Gy minimum external radiation dose. When brachytherapy was performed as indicated, the patients received an additional dose of at least 3 x 7 Gy, which was reinforced by a doctor's written instructions on the finished radiation therapy sheet or the letter of patient return inside the patient's status; the maximum OTT was 63 days. The exclusion criteria for adjuvant radiation patients omitted those who did not receive a radical hysterectomy, who did not complete the adjuvant radiation program at the minimal doses according to the inclusion criteria, those for whom the maximum OTT did not fit the inclusion

criteria, and those for whom the Hb was not checked during the radiation treatment. The exclusion criteria for definitive radiation patients were patients who did not complete the adjuvant radiation program at minimal doses according to the inclusion criteria, for whom the maximum OTT did not fit the inclusion criteria, and for whom the Hb was not checked during radiation therapy.

3. Results and Discussion

3.1 Results

The number of patients with stage IB–IIA cervical cancer registered to receive radiation therapy at the Cipto Mangunkusumo Radiotherapy Department were 157. Of these, 85 patients were selected as research participants (Table 1). These patients were followed-up by telephone; however, 52 (61.7%) were lost to follow-up because they moved or the phone number they provided could not be used to contact them (Table 2).

Table 1. Patient survival rates

Survival rates based on therapy	Number of patients (N = 85) n (%)
Definitive radiation	
Survived	5 (20%)
Died	2 (8%)
Lost to follow-up	18 (72%)
Surgery and adjuvant radiation	
Survived	22 (36.7%)
Died	4 (6.7%)
Lost to follow-up	34 (56.7%)

Table 2. Research participant characteristic distribution

Variables	n	%
Age		
<50 years	52	61.2
≥50 years	33	38.3
FIGO stage		
IB1	24	28.2
IB2	21	24.7
IIA	40	47.1
Therapy		
Definitive radiation	25	29.4
Surgery and adjuvant radiation	60	70.6
Histopathologic		
Squamous cell carcinoma	50	58.8
Adenocarcinoma	17	20
Adenosquamous	16	18.8
Other	2	2.4

In the definitive radiation therapy patient group, most patients were less than 50 years of age (72%) and were classified as FIGO stage IB1 (48%) (Table 3). The histopathological type was dominated by squamous cell carcinoma (64%), while the degree of tumor differentiation frequency was distributed equally over three levels. The most common tumor size was a maximum of 4 cm in size (75%), and a majority of the participants showed positive lympho-vascular invasion (58.3%). In the definitive

radiation patient group, the pre-radiation hemoglobin (Hb) levels were dominated by the group with Hb levels >12 g/dl (42.8%), while the most prominent Hb levels during radiation therapy ranged from of 10–12 g/dl (60%). In the post-operative adjuvant radiation patient group, most patients were less than 50 years (56.7%) of age and had a FIGO stage of IIA (53.3%). The most frequent histopathological type was squamous cell carcinoma (56.7%), while half (50%) of participants demonstrated a medium degree of differentiation. The most common tumor size was the highest at 4 cm (59.2%), and most participants showed positive lympho-vascular invasion (58.3%). In the postoperative adjuvant radiation patient group, the pre-radiation Hb levels were dominated by the group with Hb levels of 10–12 g/dl (64.9%). During radiation, Hb levels were most likely to remain at 10–12 g/dl (54.4%).

Table 3. The distribution of participants' demographic and risk factors based on therapy type

Variable	Operation + Adjuvant Radiation (N = 60) N (%)	Definitive Radiation (N = 25) N (%)
Age		
Mean	48.28 years	47.48 years
Minimum age	28.0 years	29.00 years
Maximum age	62.0 years	65.00 years
33–49 years	34.0 (56.7%)	18.00 (72%)
50–65 years	26.0 (43.3%)	7.00 (28%)
FIGO stage		
IB1	12 (20%)	12 (48%)
IB2	16 (26.7%)	5 (20%)
IIA	32 (53.3%)	8 (32%)
Histopathologic type		
Squamous cell carcinoma	34 (56.7%)	16 (64%)
Adenocarcinoma	12 (20.0%)	5 (20%)
Adenosquamous	13 (21.7%)	3 (12%)
Other	1 (1.7%)	1 (4%)
Degree of differentiation		
Good	8 (15.4%)	5 (33.3%)
Moderate	26 (50.0%)	5 (33.3%)
Bad	18 (34.6%)	5 (33.3%)
Tumor size:		
0–4 cm	31 (59.6%)	18 (75%)
>4 cm	21 (40.4%)	6 (25%)
LVSI:		
Positive	39 (73.6%)	11 (64.7%)
Negative	14 (26.4%)	6 (35.3%)
Pre-radiation Hb levels		
<10 g/dl	1 (2.7%)	3 (21.4%)
10–12 g/dl	24 (64.9%)	5 (35.7%)
>12 g/dl	12 (32.4%)	6 (42.9%)
Hb levels during radiation therapy		
<10 g/dl	2 (3.5%)	0 (0%)
10–12 g/dl	31 (54.4%)	15 (60%)
>12 g/dl	24 (42.1%)	10 (40%)

Based on the postoperative histopathological characteristics, 20 patients (39.2%) in the adjuvant radiation group had positive incision limits/a closed margin (Table 4). About 14 patients (70%) were referred from the Obstetrics Department of the Cipto Mangunkusumo Hospital, while 6 (30%) were referred from

private hospitals. The one-, two-, and three-year cervical cancer patient survival rates for those who received definitive radiation therapy were 96%, 92%, and 92%, respectively, while those of patients who received postoperative adjuvant radiation therapy were 96.7%, 95%, and 93.3%, respectively (Figure 1).

Table 4. Postoperative histopathological characteristics distribution

Postoperative histopathological characteristics	Operation + Adjuvant Radiation (N = 60) n (%)
Incision margin	
Positive	20 (39.2%)
Negative	31 (60.8%)
Parametrial invasion	
Positive	9 (16.1%)
Negative	47 (83.9%)
Lymph node metastasis	
Positive	8 (13.8%)
Negative	50 (86.2%)

Table 5. Univariate associations between the predictor variables and patient survival rates in the surgical followed by adjuvant radiation group

Variables	B	Sig	OR	95% CI	
Age	0.47	0.27	1.6	0.69	3.70
FIGO stage	-0.14	0.74	0.87	0.38	2
Histopathologic type	-0.37	0.93	0.96	0.41	2.25
Tumor differentiation	-0.44	0.39	0.64	0.24	1.74
Tumor size	-0.14	0.76	0.87	0.37	2.08
LVSI	0.15	0.76	1.16	0.45	2.96
Pre-radiation Hb levels	0.065	0.88	1.07	0.45	2.54
Hb levels during radiation	-0.37	0.93	0.96	0.41	2.25
Incision margin	-0.29	0.49	0.75	0.32	1.72
Parametrial invasion	-0.48	0.34	0.62	0.23	1.68
Lymph node metastasis	-0.68	0.18	0.51	0.19	1.37

Based on the results of the univariate analysis (Table 5), only one variable in the postoperative adjuvant radiation group had a moderate association ($p < 0.2$) with the patient survival rate: negative lymph node metastasis. In the definitive radiation therapy group (Table 6), a pre-radiation Hb level >12 g/dl was the only variable that had a moderate association ($p < 0.2$) with the patient survival rate.

Table 6. Univariate associations between predictor variables and the patient survival rate in the radiation therapy group

Variables	B	p-value	OR	95% CI	
Age	0.42	0.64	1.52	0.26	9.12
FIGO stage	1.03	0.26	2.81	0.47	16.83
Histopathologic type	-3.58	0.38	0.28	0.00	84.93
Tumor differentiation	4.18	0.26	65.29	0.49	58.56
Tumor size	-3.31	0.51	0.37	0.00	65.26
LVSI	-0.69	0.54	0.50	0.56	4.47
Pre-radiation Hb levels	1.54	0.17	4.67	0.52	41.75
Hb levels during radiation	0.67	0.46	1.95	0.33	11.67

In this study, the three-year survival rate of the definitive radiation therapy group was compared with that of the posthysterectomy adjuvant radiation therapy group. There was no significant difference in patient survival rate in both treatment groups (93.3% vs. 92%, $p = 0.138$). Furthermore, high risk factors for both treatment groups were the tumor stage ($p = 1.000$), histopathologic type ($p = 0.378$), tumor size ($p = 1.000$), and Lymphovascular space invasion (LVSI) ($p = 1.000$). The degree of differentiation (0.084) was also compared, but there were no significant differences between these two groups (Table 7).

Table 7. A comparison of the prognostic factor distribution based on therapy type

Variable	Operation + Adjuvant Radiation (n = 26) n (%)	Definitive Radiation (n = 7) n (%)	p-value
FIGO stage			
IB	13 (50%)	4 (57.1%)	1.000
IIA	13 (50%)	3 (42.9%)	
Histopathologic type			
Squamous cell carcinoma	16 (61.5%)	6 (85.7%)	0.378
Non-squamous cell carcinoma	10 (38.5%)	1 (14.3%)	
Degrees of differentiation			
Good-moderate	18 (69.2%)	2 (28.6%)	0.084
Bad	8 (30.8%)	5 (71.4%)	
Tumor size			
0–4 cm	16 (61.5%)	5 (71.4%)	1.000
>4 cm	10 (38.5%)	2 (28.6%)	
LVSI			
Positive	18 (69.2%)	5 (71.4%)	1.000
Negative	8 (30.8%)	2 (28.6%)	

3.2 Discussion

This study included 85 patients with early stage cervical cancer (stages IB–IIA), and 61.2% of these patients were younger than 50 years of age. This finding is in agreement with the literature, which states that the highest prevalence of cervical cancer occurs between the ages of 25–49 years [7]. In 2002, Aziz examined secondary data of Cipto Mangunkusumo Hospital and reported the highest age incidence of cervical cancer in Indonesia occurred in two age groups: 45–54 and 35–44 years. According to the distribution of histopathologic type, most patients were diagnosed with squamous cell carcinoma (55.8%) and adenocarcinoma (20%). This finding is also in agreement with the literature, which indicates that cervical cancer histopathology is dominated by squamous cell carcinoma and adenocarcinoma [1,2,5,6]. Regarding the postoperative histopathologic characteristics of the adjuvant radiation therapy patients, 20 (39.2%) had a positive/closed margin incision, 14 (70%) had been referred from the Obstetrics Division at Cipto Mangunkusumo Hospital, and 6 (30%) were referred from private hospitals. The incision margin indicates the diagnostic and surgical ability of the physician. Our results indicate that the RSCM, which is a national referral center and teaching hospital, should improve its standard of services, especially when making a diagnosis and evaluating the ability of the surgeon.

The one-, two-, and three-year cervical cancer patient survival rates of those who received definitive radiation therapy were 96%, 92%, and 92%, respectively. In the postoperative adjuvant radiation therapy group, 96.7%, 95%, and 93.3% survived for one, two, and three years, respectively. These results did not vary widely from those of previous studies. According to the literature, the five-year early stage cervical cancer patient survival rate of those who receive definitive radiation ranges from 74–91%. Research conducted by Landoni (83%), Morley and Sesky (83%), and Newtons (74%) also found a similar patient survival rate [11–15]. The five-year early stage cervical cancer patient survival rate in

this study for participants who received adjuvant postoperative radiation was similar to those reported by the research investigations of Macleod and Vinod (86%) and Okada (82.7%) [16].

In this study, 12 patients (48%) with stage-IB1 cervical cancer received definitive radiation therapy alone, while 12 patients were given adjuvant radiation therapy after undergoing a radical hysterectomy. IB1-stage cervical cancer patients with tumors <4 cm who received definitive radiation were eligible for a radical hysterectomy. The indications for IB1 cervical cancer patients to receive definitive radiation instead of a radical hysterectomy were not listed and therefore remained unclear. Possible reasons may include the selection criteria used for therapy in patients who refused surgery or had contraindications for surgery. Furthermore, when the three-year survival rates of both groups were assessed, only 2 of the 12 patients who received definitive radiation therapy were available; the remaining 10 patients were lost to follow-up. In the adjuvant radiation group, 4 patients survived, 1 patient died, and the remaining 7 of the original 12 patients were lost to follow-up. These results do not reflect the success of these two types of therapy due to the high number of patients who failed to follow-up.

Statistical tests were performed to examine factors that might have affected the survival rates of the postoperative adjuvant radiation therapy group and the definitive radiation therapy group. The negative lymph node metastasis variable was the only variable in the adjuvant radiation therapy after surgery group that had a moderate association with the patient survival rate ($p < 0.2$; OR = 0.51; 95% CI = 0.19 to 1.37). There was also a moderate association between negative lymph node metastases and patient survival rates statistically. This study concluded that patients with negative lymph node metastasis had a better survival rate. A pre-radiation Hb level >12 g/dl was the only variable in the definitive radiation therapy group that had a moderate association with the patient survival rate ($p < 0.2$; OR = 4.67; 95% CI = 0.52 to 41.75). This result was relevant because a major prior study conducted in Canada reported that patients with pre-radiation Hb levels ≥ 12 g/dl had a 12% higher five-year survival rate. Therefore, it was hypothesized that pre-radiation Hb levels ≥ 12 g/dl may improve the patient response to radiotherapy [17,18]. There is also an association between anemia and poor outcomes, which may reflect a more aggressive and extensive tumor load rather than the direct effects of anemia. However, evidence also exists that hypoxic tumor cells can influence radiosensitivity and potentially aggravate anemia with hypoxia [19-22].

The results of this study indicated that the survival rates of stage IB–IIA cervical cancer patients who received postoperative adjuvant radiation therapy or definitive radiation therapy did not differ significantly until the third year (93.3% vs. 92%, respectively; $p = 0.138$). Perez *et al.* also calculated the 5- and 10-year patient survival rates and the numbers of disease-free stage IB–IIA cervical cancer patients who received definitive radiation or postoperative adjuvant radiation therapy [23]. Gray *et al.* reported that high stage and high risk cervical cancer patients who received definitive radiation therapy alone did not differ significantly compared with those who received surgery and adjuvant radiation therapy (73% vs. 80%, respectively; $p = 0.772$) [24].

Because the survival rates were not significantly different, it remains to be determined whether definitive radiation therapy offers more than an alternative therapy in the management of IB–IIA cervical cancer patients with contraindications for surgery or who refuse surgery. Therefore, further research will be needed to identify the factors that influence the selection of treatment between radical hysterectomy with adjuvant radiation therapy or definitive radiation therapy. These factors should be used to create a guideline for use in Indonesia along with cervical cancer stage IB–IIA treatment by considering the post-treatment side effects as well as costs that influence the selection of therapy, which can affect patients' quality of life. This study also compared the high risk factors that were present in both treatment groups, including tumor stage ($p = 1.000$), histopathologic type ($p = 0.378$), tumor size ($p = 1.000$), LVSI ($p = 1.000$), and the degree of differentiation (0.084). There were no significant differences between the two groups, which may be due to the small number of patients who completed the follow-up. Some limitations were encountered during the implementation of this study. This investigation was a retrospective study conducted using secondary data from patient medical records. Many obstacles were also encountered in the data collection; the data regarding patient status were often incomplete or missing entirely.

At the time of follow-up by telephone, it was discovered that many phone numbers were no longer active, especially when the patient had provided a temporary phone number or residence (boarding house/rental home) that had been used during treatment. As a result, patient loss to follow-up affected the results of our research due to the overestimation of the survival rate and was therefore a weakness. Ideally, research follow-up visits should be carried out in person at patients' homes instead of over the telephone; however, limited funding and time constraints often necessitate the use of telephone follow-up. This study found that surgical treatment was an inadequate factor, which can be seen in a positive incision margin variable. This inadequate therapy was associated with the ability of the surgeon's diagnosis and expertise during the operation. Most of these patients were referred from the obstetric and gynecologic oncology division at the RSCM. This study can serve as an evaluation to offer feedback intended to improve the quality of services and treatment at the RSCM, a national referral center and teaching hospital.

4. Conclusion

Patients with negative lymph node metastasis had a better survival tendency than those with positive lymph node metastasis. Other factors had no association with the patient survival rate. Patients with pre-radiation Hb levels >12 g/dl had a better survival tendency than patients with pre-radiation Hb levels <12 g/dl. No other factors were associated with the survival rate of the patients. There were also no significant differences between the high-risk factors identified in the definitive radiation therapy or adjuvant radiation after radical hysterectomy groups.

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