

# Treatment and Outcomes of Early and Operable Recurrent Cervical Cancer: A Prospective Study

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ABSTRACT

**Objectives:** The aim of this study was to evaluate outcomes, survival, patterns of recurrence, and morbidity in both early and recurrent operable cervical cancer patients following radical hysterectomy, pelvic lymph node dissection, and adjuvant radiotherapy. **Materials and Methods:** This was a prospective analysis of 55 patients of stage IA–IIA and recurrent operable cervical cancer treated with radical hysterectomy, pelvic lymphadenectomy, and adjuvant radiotherapy from 2014 to 2017. Overall survival (OS), disease-free survival (DFS), morbidity, and mortality rates were the end points of this study. Survival analysis was performed using the Kaplan–Meir method. **Results:** The median age of the study group was 45 years (range 18–68 years). The most common presentation was stage IB2 disease in 34.5% of patients. Fifty (90%) patients had squamous histology, whereas 5 (9.1%) had adenocarcinoma. Upfront radical hysterectomy was performed in 90.9% of patients, whereas 9.1% underwent surgery for recurrent cervical cancer. The most common indication for adjuvant radiotherapy was lymph node involvement, followed by parametrium involvement in 20% and 13% patients, respectively. Median follow-up period was 48 months (range 6–60 months). The OS and DFS rates were 85.0% and 81.8%, respectively. The most frequent complication encountered was paralytic ileus in 4 (7.2%) patients. **Conclusion:** Radical hysterectomy with pelvic lymphadenectomy for early cervical cancer has a favorable survival outcome with acceptable long-term morbidity.

**KEYWORDS:** Cervical cancer, early stage, radical hysterectomy, survival

## INTRODUCTION

Cervical cancer is the fourth most common cancer among women. The treatment protocol for early-stage cervical cancer includes either radical hysterectomy with pelvic lymphadenectomy or radiation therapy, both of which have similar local control and survival. About 570,000 new cases of cervical cancer are detected yearly, and approximately 300,000 die each year.<sup>[1,2]</sup> According to the Indian council of Medical Research 2018, about 97,000 cases were detected in India in 2018. A total of 85% of the cases occur in developing countries.<sup>[1,3]</sup> Persistent human papillomavirus is the most important factor for the development of cancer.<sup>[4]</sup> Appropriate case selection is critical when considering the benefit of surgical therapy in a patient with cervical cancer. The cure rate

for surgically treated early cervical cancer is about 85%–90% and is comparable with patients treated with primary radiotherapy.<sup>[5]</sup> Squamous cell cancer accounts for 80%, whereas adenocarcinoma accounts for 20% of cases.

Adverse factors in patients with lymph node-negative disease are histology, size of tumor, lymphovascular space invasion, and depth of cervical invasion.<sup>[6,7]</sup> Adjuvant radiotherapy is considered in patients with high-risk criteria such as positive pelvic nodes, occult parametrial invasion, or positive surgical margins. According to

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Sedlis criteria (greater than one-third stromal invasion, lymphovascular space involvement, or cervical tumor size >4 cm), patients with intermediate-risk factors also require adjuvant treatment.<sup>[5]</sup>

This prospective study was carried out in operated cases of cervical carcinoma up to stage IIA disease to evaluate the management of the disease and its outcome, to study the prognostic factors for recurrence, and to increase treatment efficiency and minimize complications.

## MATERIALS AND METHODS

### Patient population

This prospective study consisted of 55 patients with cervical cancer up to stage IIA who underwent simple or modified radical hysterectomy with lymphadenectomy from October 2014 to August 2017, at Sri Aurobindo Institute of Medical Sciences. Pretreatment evaluation consisted of pelvic examination and a complete staging work-up including chest X-ray, Magnetic resonance imaging, and cystoscopy with proctoscopy when clinically indicated. A stage was assigned according to the International Federation of Gynecology and Obstetrics (FIGO) 2009 Clinical Staging System. Patients with good general condition and suitable for surgery, histologically confirmed operable cervical cancer clinically confined to the cervix and upper vagina (FIGO stage IA–IIA), cervical size <4 cm, and no lymph node metastases were eligible for this study. Magnetic resonance imaging of the pelvic region was done in 52 (94.5%) of patients.

### Radiotherapy

Patients with high-risk pathological factors such as lymph node metastasis, parametrial involvement, or positive surgical margins and some of the patients with intermediate-risk factors according to Sedlis criteria such as deep stromal and lymphovascular space invasion were advised to receive adjuvant concurrent cisplatin-based chemoradiotherapy. Adjuvant radiotherapy consisted of external beam irradiation of 40–50 Gy delivered to the whole pelvis, with a 10 MV X-ray by parallel opposed or four-field box beams with the daily fraction size being 1.8–2 Gy, 5 fractions per week. A boost of 5–10 Gy was delivered to the positive pelvic nodes. Para-aortic lymph nodes were treated with a dose of 45 Gy in 5 weeks with anteroposterior-shaped opposed fields.

### Follow-up

The median follow-up period was 48 months (range 6–60 months). Patients were followed up for every 3 months in the first 2 years, followed by every 4 months from the 3<sup>rd</sup> to 5<sup>th</sup> years and annually thereafter. Pelvic ultrasound scans and Pap smear were planned every 6

months along with an annual chest X-ray. Treatment failure was defined by histological proof of recurrence, imaging suggestive of recurrence, or enlargement of lymph nodes. The end points of the study were overall survival (OS), local recurrence, and morbidity of radical hysterectomy.

### Statistical analysis

OS was defined from the beginning of radical surgery to the time of death due to any cause or last follow-up. Disease-free survival (DFS) was defined from the beginning of radical surgery to the time of tumor progression or last follow-up. Continuous variables were assessed for normality (Kolmogorov–Smirnov test) and expressed as appropriate (median with range). Survival curves were constructed with the Kaplan–Meier method. The SPSS version 21.0 (IBM Co., Armonk, NY, USA) was used for analyses.

## RESULTS

### Patient characteristics

Over a span of 3 years, 55 patients with cervical cancer from stages IA–IIA underwent various types of hysterectomy with pelvic lymph node dissection. Out of these, 5 (9.1%) cases underwent salvage surgery postchemoradiotherapy for central recurrence. The median age of the patients was 45 years, with an age range of 18–68 years. Stage IB1 disease according to FIGO staging was seen in 29.1% of patients, whereas stage IB2 disease was seen in 34.5% of patients [Table 1].

**Table 1: Patient demographics (n=55)**

	n (%)
Stage	
IA1	3 (5.4)
IA2	8 (14.5)
IB1	16 (29.1)
IB2	19 (34.5)
IIA	9 (4.95)
Upfront surgery	50 (90.9)
Salvage surgery	5 (16.3)
Histology	
Squamous cell carcinoma	50 (90.9)
Adenocarcinoma	5 (9.1)
Type of Surgery performed	
Simple hysterectomy	3 (5.5)
Radical hysterectomy	52 (94.5)
Type 2	10 (18.1)
Type 3	42 (76.3)
Average lymph node yield	9 (6.22)
Indications of radiotherapy	
Lymph node involvement	11 (20.0)
Parametrium involvement	7 (12.7)
Positive vaginal margins	2 (3.6)

Squamous histology was observed in 50 (90.9%) patients, whereas adenocarcinoma was observed in 5 (9.1%) patients. The most common presentation in patients was irregular and postmenopausal bleeding in 27.3% and 23.7% of patients, respectively.

Simple hysterectomy was performed in 3 (5.4%) patients of stage IA1, whereas radical hysterectomy was performed in 52 (94.5%) patients. Pelvic lymphadenectomy was performed in all patients. The median lymph node yield in our study was 9 with a range of 6–22 [Table 1]. The median operative time taken for the surgery was 178 min (range 120–360 min). One-third of the patients received adjuvant radiotherapy. Lymph node involvement was observed in 20% of the patients. Most of the patients were discharged on the 7<sup>th</sup> postoperative day (range 6–21 days). The median blood loss during surgery was approximately 450 ml (range 250–900 ml). Adjuvant treatment was given to patients with either Parametrium involvement, vaginal margin positivity lymph node-positive disease or the risk factors according to Sedlis criteria. The most prevalent indication for radiotherapy was positive lymph node involvement, followed by parametrium involvement in 20% and 12.7% of patients, respectively [Table 1]. Type II radical hysterectomy was performed in 5 (9.1%) patients for central recurrence postradiotherapy. The median follow-up period was 48 months with a range of 6–60 months. Patients with lymph node involvement, parametrium involvement, and margin-positive disease had a high incidence of recurrence and lower survival rates.

**Morbidity and mortality**

The combined long- and short-term morbidity rate was 21.8%. The most frequent complication was paralytic ileus in 4 (7.2%), followed by wound infection in 3 (5.4%) patients [Table 2]. Lymphedema was observed in 2 (3.6%) patients of postradiotherapy salvage surgery. There was one mortality in our study. The patient developed deep venous thrombosis postsalvage surgery for carcinoma cervix postchemoradiotherapy. She developed acute onset dyspnea and was diagnosed to have pulmonary embolism. The patient expired due to Type 1 respiratory failure.

**Table 2: Complications of the operative procedure (n=12)**

Complication	n (%)
Paralytic ileus	4 (7.2)
Wound infection	3 (5.4)
Lymphedema	2 (3.6)
Urinary fistula	1 (1.8)
Deep vein thrombosis, pulmonary embolism, and death	2 (3.6)
Total	12 (21.8)

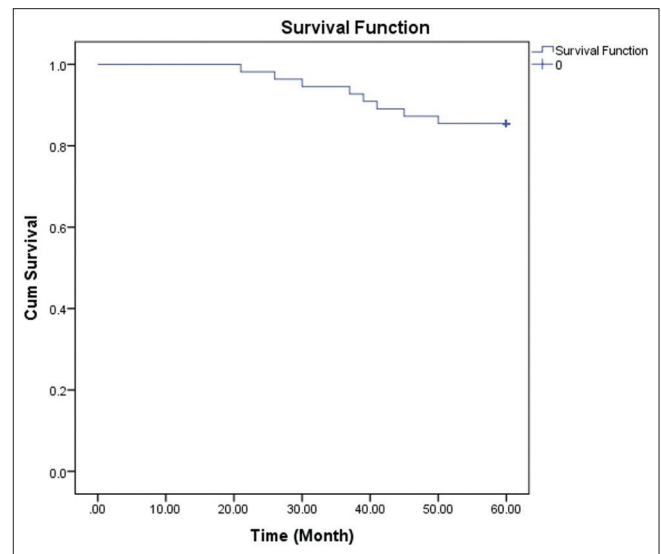
**Survival**

The OS and DFS rates were 85% and 81.8%, respectively [Figures 1 and 2]. During this period, one-fifth (6) of the patients developed local recurrence to vagina and pelvic sidewall. Distant recurrences to lung and para-aortic lymph nodes were observed in 4 (7.3%) patients. Most patients were in stage IIA category according to the FIGO staging.

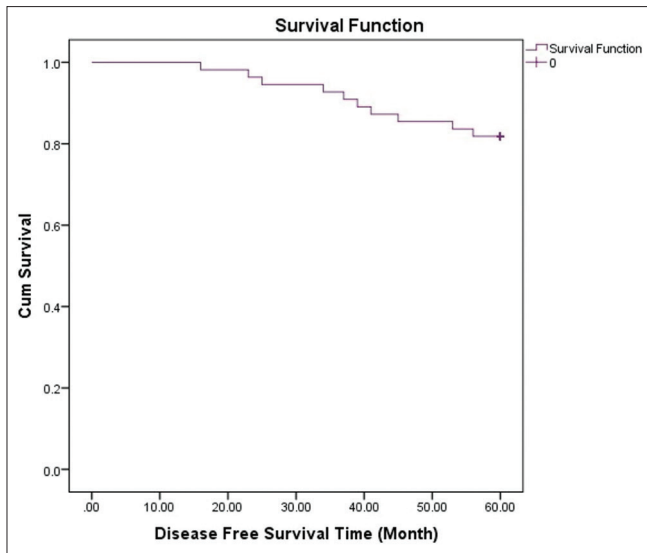
**DISCUSSION**

The present prospective study was conducted at a tertiary care referral center in 55 patients over a period of 3 years. Radical hysterectomy with pelvic lymphadenectomy is the treatment of choice for cervical cancer up to stage IIA. Type III radical hysterectomy was performed in 76.3% of cases including selected cases of recurrent cervical cancer as a salvage procedure. Radical hysterectomy is an option for localized central recurrence limited to cervix or vaginal orifices.<sup>[8,9]</sup> The present study was unique as it catered to patients with both early and recurrent operable cervical cancer, and survival data were calculated. Patients with early disease with no risk factors have better outcomes than patients with high-risk factors and recurrent cervical cancer.

Most recurrences of cervical cancer are observed in the pelvis.<sup>[10]</sup> The difference in OS with adjuvant radiotherapy in lymph node-negative disease is still questionable. In our study, OS with standard surgery and radiotherapy protocol was 85%. These values are comparable with studies conducted by Liu, Cai, Kodeira, and Ayhan *et al.*, who have reported outcomes in the range of 80%–91%.<sup>[7,11-13]</sup> The DFS in our study was 81.8%. DFS in the studies conducted by Arora



**Figure 1: Overall survival of patients who underwent radical surgical resection**



**Figure 2:** Disease-free survival of patients who underwent radical surgical resection

*et al.*, Suprasert *et al.*, Zhao *et al.*, and Sartori *et al.* was 85.7%, 90%, 84.5%, and 80%, respectively.<sup>[14-17]</sup>

Recurrence rates were slightly higher in our study as patients with recurrent cervical cancer were also included in the study. If these patients are excluded from the study, the recurrence rates would reduce drastically.

Lymph node metastases were observed in 20% of patients of our study. The studies conducted by Panici *et al.*, Raspagliesi *et al.*, and Rutledge *et al.* reported similar rates of lymph node metastases in the range of 15%–30%.<sup>[18-20]</sup> The rate of lymph node metastases increases as the stage of the disease progresses. Panici *et al.* reported lymph node metastases in about 3%–5% of patients with stage IA disease.<sup>[18]</sup>

In addition to lymph node involvement, other high-risk factors reported to have adverse outcomes are deep stromal invasion, lymphovascular invasion, tumor size, parametrium involvement, and positive vaginal margins. According to Sedlis criteria, these are also indications for adjuvant radiotherapy. Zhao *et al.* and Kridelka *et al.* followed the same radiotherapy protocol of 50 Gy radiation therapy and reported recurrence rates of about 8%.<sup>[16,21]</sup>

Short- and long-term complications were reported in 21.8% of patients. The most common complication in our group was paralytic ileus in 7.2% of patients and lymphedema in two patients. Both the patients of lymphedema were in the postradiotherapy salvage surgery group. Deep vein thrombosis followed by pulmonary embolism led to one mortality. Although we followed a protocol for the prophylaxis of deep venous thrombosis, we still had one mortality due to combined

multimodality treatment. Suprasert *et al.* and Bergmark *et al.* reported different phenomena of complications in their population which may be due to the difference in the study group and surgery protocol.<sup>[15,22]</sup>

## CONCLUSION

Early-stage cervical cancer from stages IA–IIA has a favorable survival outcome with surgery, with limited long-term morbidity after treatment. Adjuvant radiotherapy helps in decreasing the local recurrence in patients with high-risk features. Appropriate case selection, meticulous surgery, and proper postoperative care are critical in improving outcomes and increasing survival rates in patients with early-stage cervical cancer.

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## Conflicts of interest

There are no conflicts of interest.

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