Original Article

# Pattern of Care of Recurrent Cervical Cancer in Low-resource Settings: Challenges and Patient-initiated Follow-up as a Novel Opportunity

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**Abstract**

**Introduction:** The availability of optimum diagnostic strategies remains a major problem in resource-constraint countries. This technique of patient-initiated follow-up (PIFU) has been recently adopted in the UK for gynecological cancers and has proven cost benefits. However, no study from the Indian subcontinent has ever been reported. **Aims and Objectives:** The primary objective was to study the pattern of care of recurrent cervical cancer in low-resource settings. The secondary objective was to compare the reliability of symptomatology/clinical evaluation and imaging methods on follow-up to detect recurrence and thus explore the feasibility of symptom-based PIFU. **Materials and Methods:** This was a single-institutional retrospective analysis of recurrent cervical cancer cases for a period of 3 years from January 2019 to January 2022. Patients who followed up for minimum of 6 months were included in the study. **Results:** In 57 of the total 69 patients, symptoms alone were the index diagnostic method. Interestingly, neither of the methods of recurrence detection had impact on overall survival (OS). Cox regression analysis revealed adverse impact of erratic/lost to follow-up (hazard ratio [HR] = 3.8) and pelvic side wall disease (HR = 1.33) on survival. Patients with positive para-aortic nodes had significantly shorter disease-free interval of 11 months, so adding systemic therapy to adjuvant treatment in this cohort needs to be further investigated. **Conclusion:** Our analysis showed that patients with recurrence who were diagnosed with clinical manifestations alone vis-à-vis the ones who were diagnosed primarily on routine follow-up visit by some imaging or diagnostic test had comparable oncologic outcomes. PIFU can be a "practice changing modality" in patient management system, especially in low-resource settings. It will prove to be a simple cost-effective method to detect recurrence and prevent fallouts. Our study points to the feasibility of PIFU in Indian scenario.

**Keywords:** *Cost benefit, patient-initiated follow-up, recurrent cervical cancer*

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## Synopsis

The availability of optimum diagnostic strategies remains a major problem in resource-constraint countries. This technique of "PIFU" – patient-initiated follow-up has been recently adopted in the UK for gynecological cancers and has proven cost benefits. However, no study from the Indian subcontinent has ever been reported. Our analysis showed that, among the two groups of recurrence detection, ones who were diagnosed with clinical manifestations alone and the ones who were diagnosed primarily by some imaging or diagnostic test had comparable oncologic outcomes. Emphasizing on simple and cost-effective follow-up methods such as regular patient-initiated follow-up (PIFU) by counseling and educating them regarding symptoms of relapse can help to detect recurrences early and optimize survival.

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## Introduction

According to the GLOBOCAN 2020, there were 604,100 new cases of cervical cancer found worldwide, with 341,831 reported deaths. Cervical cancer led to 18.3% (123,907) of new cases and 9.4% of all cancer cases in India, in 2020. It is one of the most prevalent malignancies in India with North East India reporting the highest age-adjusted ratio.[1,2] With chemoradiation as the standard of therapy, the 5-year recurrence-free survival rate for Stage IB, Stage IIA, and Stage III/IVA, is about 79%, 59%, and 36.7%, respectively. Despite this, local failure in central pelvis occurs in about 36.7% of cases.[3] Furthermore, 50% and 75% of cervical cancer recurrences occur within the initial 1 and 2 years following treatment, respectively.[4]

Financial toxicity is an emerging issue in cancer care, as patient financial burden has been associated with worse quality of life, lower patient satisfaction, and delaying or avoiding care. Patient-initiated follow-up (PIFU) is increasingly being recognized as a more suitable and effective alternative to hospital-based consultations, as health-care facilities struggle to keep up with demand.[5] The Society of Gynecologic Oncology advises that reducing unnecessary tests and frequent hospital visits may result in significant cost savings while maintaining the quality of care for these patients. Counseling patients about signs and symptoms is still a crucial part of survivorship care for patients with cervical cancer.[4] Research on the best practices for surveillance after patients have achieved complete response, however, is sparse. Different nations and institutions have different follow-up schedules and durations. The availability of the best diagnostic approach also continues to be a significant issue in countries with limited resources.

When hospital-based consultations were cancelled due to the COVID-19 epidemic, there was a rising reliance on alternate methods, which gave additional insight into patient-led follow-up strategies.[6] Such surveillance techniques, however, need to be confirmed and validated in cohorts with greater sample sizes. The TOTEM study, which compares routine hospital visits with a more rigorous follow-up program in patients with endometrial cancer, is one of the several ongoing trials examining minimalistic follow up procedures for gynecological malignancies.[7] The role of PIFU as a surveillance technique in various malignancies has recently been indicated in studies.[8] In PIFU technique, patients are asked to contact the unit when they develop symptoms rather than undergoing routine follow-up visit to the hospital. This may result in significant appointment and expense savings. PIFU is widely practiced in the UK-based settings for follow-up of cancer patients. This approach can be practice changing surveillance strategy in low-resource settings.[9] As of now, its impact has not been widely validated. PIFU may offer a potential avenue to administer care while reducing patient burden.

To our knowledge, there is no available data from North-Eastern India on the pattern of care of recurrent cervical cancer cases. In our setting, where locally advanced cervical cancer cases form the major bulk, we observed that many patients are lost to follow-up and adherence to stringent surveillance recommendations is not followed. Hence, we tried to explore the outcomes of recurrence detection in symptomatic patients who came to the hospital with clinical manifestations as opposed to asymptomatic patients who were diagnosed with recurrence based on imaging and thus provide indirect evidence to suggest the feasibility of PIFU as means of cost-effective follow-up strategy. Furthermore, in this study, we aim to analyze the factors associated with recurrence which will provide insight to tailor treatment protocols in future.

### Aims and objectives

Our primary objective was to study the pattern of care of recurrent cervical cancer in low-resource settings. The secondary objective was to compare reliability of symptomatology/clinical evaluation as opposed to imaging methods on follow-up to detect recurrence and thus explore the feasibility of symptom-based PIFU.

## Materials and Methods

Ours is a single-institutional retrospective analysis of treated patients with biopsy-proven cancer cervix, FIGO Stage IB1 to IIIB who presented with recurrence during a span of 3 years from January 2019 to January 2022 [Figure 1].

Patients included were those with histopathologically proven diagnosis and complete medical records of stage, grade of disease at initial treatment, first radical treatment regimen, and subsequent recurrence details.

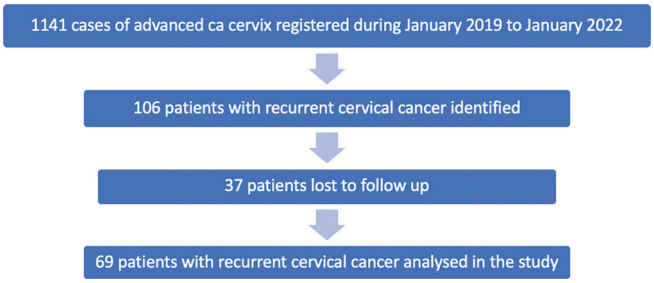


**Figure 1:** Flow diagram

We excluded patients with FIGO Stage IV disease, uncommon histology, and ones without adequate hospital records. Patients with progressive disease on treatment and those with disease-free interval of <6 months after completion of the primary treatment were excluded from this analysis. Clinical details of patients with recurrent cervical cancer who were treated at Dr. B Borooah Cancer Institute from January 2019 to January 2022 were collected from electronic records. Their demographic details, clinical profile, and the treatment details were studied. The follow-up protocol at our institute involves thorough physical examination and imaging 3 monthly for the first 2 years, then every 6 months for the next 3 years, and annually for the next 10 years. Although there are no specific recommendations for follow-up imaging, it may be performed to assess treatment response or when a recurrence is suspected. Routine follow-up imaging is not recommended; however, the practice varies across different centers in India.

We recorded the index method of diagnosis in recurrent cases, whether they were diagnosed based on symptomatology and clinical examination or whether they were solely detected on imaging. The imaging methods included either ultrasonography abdomen pelvis, chest X-ray, magnetic resonance imaging, or contrast-enhanced computed tomography. The primary method of recurrence detection, the mode of therapy for recurrence, the date of death or the last visit, the presence or absence of symptoms, the site of the relapse, and the treatment received for recurrence were all noted. Different clinicopathological characteristics of patients were recorded, and the diagnostic techniques for recurrence detection and their association with survival outcomes were compared. Furthermore, we compared outcomes for patients who followed up regularly versus those who were lost to follow-up. Univariate and multivariate analyses of prognostic factors for survival were performed using Cox proportional hazards regression analysis. Recurrence has been defined as the presence of disease after a disease-free survival (DFS) of more than 6 months after the end of primary treatment. DFS has been defined as the time from the end of primary treatment until the detection of recurrence.

Recurrences were considered asymptomatic in patients who had no relevant complaints before the routine follow-up and were purely diagnosed on imaging. Conversely, recurrences were considered symptomatic if the patient reported with symptoms before examination. Local recurrence was considered if disease was detected centrally or in the parametrium within the pelvis (in field). Recurrences were defined as distant if they occurred in the para-aortic lymph nodes or elsewhere outside the pelvis. Postrecurrence survival (PRS) was calculated from the date of detection of recurrence to the date of death or the last follow-up.

**Table 1: Patient characteristics and recurrence sites**

| Patient characteristics | *n* (%) |
|---|---|
| Median age | 54 (49–62) |
| SCC | 84.1% |
| Early stage (IB1) | 4.3% (3) |
| LACC (IB2–IIB) (locally advanced) | 58% (40) |
| Advanced (III) | 37.6% (26) |
| Prior surgery | 10.1% |
| Prior CTRT | 85.5% |
| Prior RT only | 4.3% |
| Recurrence in 2 years | 57.9% |
| Pelvic site recurrence | 36.2% |
| Single/isolated metastases | 71% |

LACC: Locally advanced cervical cancer, CTRT: Consolidative thoracic radiation therapy, RT: Radiotherapy, SCC: Squamous cell cancer

### Statistical analysis

By comparing the Kaplan–Meier curves of the subgroups with log-rank test, a survival analysis was conducted. The Cox proportional hazards regression analysis was used to analyse prognostic factors. Statistical significance was determined by $p$ value < 0.05.

## Results

### Patient characteristics and recurrence sites

Sixty-nine patients were included in this analysis with a median follow-up of 24 months [Table 1]. Overall, 27.53% (19) of cases recurred within 1 year. Majority (58, 84.1%) were squamous cell cancers, whereas only 11 (15.9%) belonged to other histologies. Of these, 3 (4.3%) were early-stage cervical cancer (FIGO Stage IB1), 40 (58%) belonged to locally advanced disease (FIGO Stage IB2–IIB), and 26 (37.6%) to advanced-stage disease (FIGO Stage III).

### Diagnostic efficacy of different methods

In our study, 82.6% of recurrences were detected based on clinical symptomatology and physical examination alone, whereas only 1.4% were solely detected based on imaging. In 19 (27.53%) cases, symptoms or suspicion of recurrence prompted an unscheduled evaluation. The symptoms included pain abdomen in 26 cases. Eight patients presented with bleeding per vaginum, five with cough and/or hemoptysis, two with bowel obstruction, and two with swelling in the leg. Fever was the presenting complaint in two cases, urinary frequency in one patient, fatigue in one patient, hemoptysis in one patient, and self-detection of supraclavicular lymph node swelling in one patient. There was no statistically significant difference seen in the diagnostic role of

imaging and clinical examination in detecting recurrence in various groups of patients, stratified as per their stage, site of relapse whether local or distant, and mode of initial treatment received ($P = 0.33$).

Compared with patients of recurrent carcinoma cervix diagnosed using imaging methods, patients presenting with clinical manifestations alone had comparable PFS (progression-free survival) ($p = 0.084$) and OS ($p = 0.162$) as depicted in the Kaplan–Meier curves [Figure 2].

### Predictors of failure and oncologic outcomes

The median DFS was 22 months in our cohort. DFS in patients with para-aortic node involvement was 11 months as opposed to 24 months in women without nodal involvement. The median PRS was 11 months (3-36 months). Para-aortic node involvement significantly decreased DFS in our cohort ($p = 0.001$). Furthermore, our study revealed that para-aortic node involvement was an independent predictor of distant metastasis ($P = 0.03$). Of the 11 patients belonging to Stage IIIC2 cervical cancer, just one patient had recurrence limited to pelvis and the rest ten had distant failures. Erratic follow-up/lost to follow-up (HR = 3.9) and pelvic side wall fixation (HR = 1.3) had adverse impact on OS in our study, as revealed by Cox regression analysis [Figures 3 and 4]. None of the treatment modalities were associated with improved survival. For 28 patients in whom we were able to evaluate outcome post-treatment for recurrence, 10 showed complete response, 1 had partial response, 5 had stable disease, while 12 of them progressed.

In our cohort, 11 patients (15.9%) defaulted and did not receive any treatment, 1 patient received stereotactic RT to node, 11 patients received palliative chemotherapy and hemostatic/palliative radiotherapy. Two underwent surgical procedures in the form of salvage hysterectomy and hepatic segmentectomy. Thirty-one patients (nearly ½) completed six cycles of palliative chemotherapy. Fifteen among these were not able to continue six cycles due to chemotherapy-related side effects such as myelosuppression, neuropathy, thrombosis, neutropenia, and sepsis. Only one patient could afford bevacizumab.

## Discussion

Despite extensive therapy, the prognosis for patients with recurrent cervical cancer is still dismal, with a 5-year OS rate of <5%.[10] The treatment of recurrent cervical cancer remains challenging. This study explores the major shortcomings in the management of recurrent cases in resource-constraint settings.

In our study, the median PRS was 11 months. Our study's findings are consistent with other research that

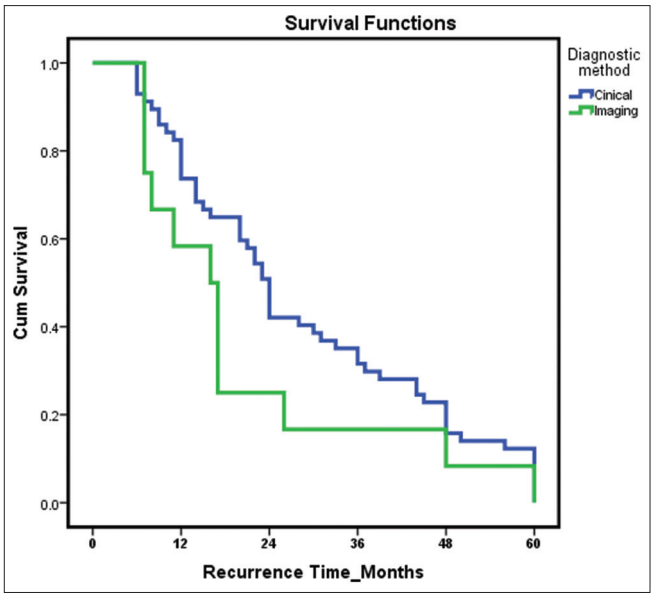


**Figure 2:** Oncologic outcomes of various surveillance strategies

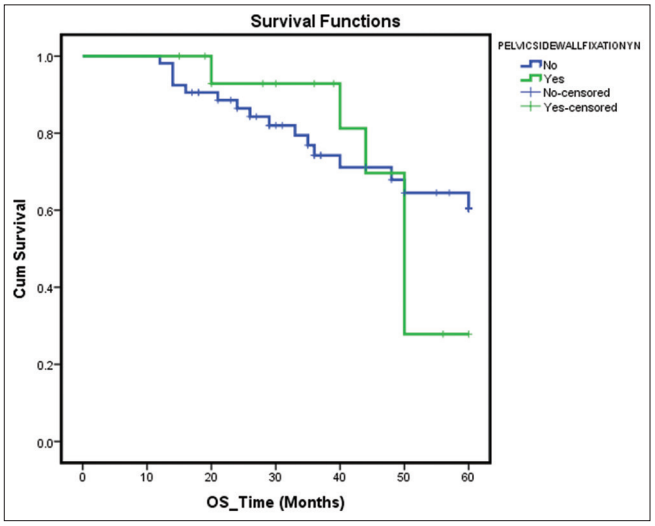


**Figure 3:** Survival curves for patients with pelvic side wall fixation

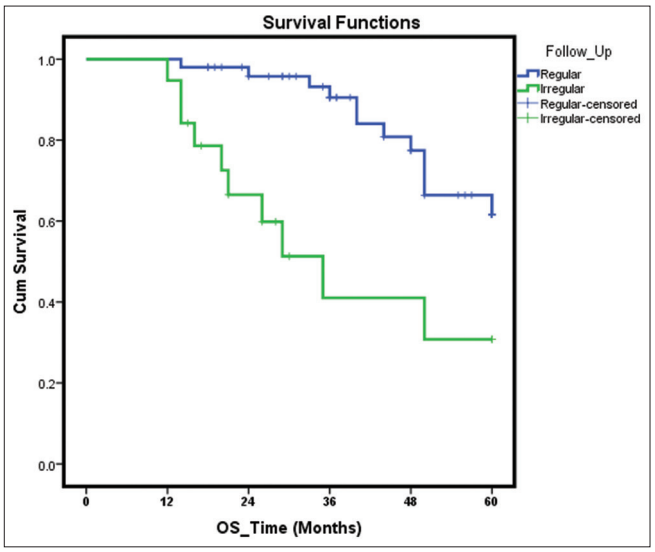


**Figure 4:** Survival curves for patients with irregular follow-up

have demonstrated that locally advanced cervical cancer has diverse patterns of failure.[11] Some patients may have a higher chance of locoregional relapse, whereas other patients may have a higher risk of distant relapse. Cervical cancer in India is rurally predominant; hence, cost-effective strategies for treatment and follow-up will reduce out-of-pocket expenditures and enhance patient compliance.[12] Following their initial diagnosis and treatment for cancer, patients are monitored in hospitals for 5–10 years, principally to detect recurrence early and improve survival.[13] There is not much proof that this strategy increases survival, though. In addition, there is evidence that hospital follow-up does not address the medical, psychological, and social requirements of cancer survivors over long term.[14] There is growing literature from developed nations focusing on nonhospital-based follow-up.[15]

In PIFU, patients are asked pay follow-up visits to the hospital whenever they experience symptoms rather than receiving standard follow-up sessions. The use of PIFU has increased, especially in gynecological oncology.[16]

The availability of optimum diagnostic strategies remains a major problem in resource-constraint countries.[17] In our study, survival outcomes were not influenced by diagnostic method of recurrence detection. This supports the feasibility of PIFU as a surveillance strategy.

Studying the prognostic factors and outcomes of recurrent cervical cancer cases can help to stratify patients who need intensive hospital-based follow-up while those who can undergo PIFU. This will help us in optimal utilization of resources and thus turn our challenges into our opportunities. Our study's findings are consistent with earlier retrospective research[18] on numerous prognostic variables in predicting recurrence. On multivariate analysis, comparing age >55 years, stage, and mode of treatment at initial diagnosis with chances of distant failures, only para-aortic node involvement was independently found to increase the chances of distant metastasis ($p$ value = 0.003).

Interestingly, we observed that all patients who had pelvic side wall involvement at recurrence had initial tumor size of more than 4 cm. Large lesions frequently have insufficient blood supply in their centers, which leads to the recruitment of hypoxic cells and increased radiation therapy resistance. This is one likely reason for the phenomenon. Our study implies that we need to explore treatment escalation in tumors of larger size. A retrospective analysis of several GOG trials has shown that FIGO stage and tumor size are the two most important factors related to pelvic recurrence.[19] Furthermore, a study by Queiroz *et al.* showed that tumor size was a key factor related to locoregional recurrence.[20] Para-aortic lymph nodal (PALN) involvement adversely affects OS of cervical cancer patients.[21] As was also seen in our study, para-aortic node involvement was associated with poor DFS and more distant recurrences. More research is ongoing on the diagnostic evaluation of PALN and subsequent alteration in treatment plan in case of their involvement.[22,23]

DFS is an important prognostic factor in patients with cervical cancer. DFS varies across studies. In Duyn *et al.*'s[24] study, it was 18 months. Lim *et al.*[25] reported DFS of 17.6 months.

The median DFS of recurrent cases was 22 months in our study, which is quite dismal. Furthermore, the poor PRS of 11 months in our study points toward the huge unmet need for the treatment of recurrent cases. While, on the one hand, we are heading toward an era of precision medicine, a huge gap exists in the availability of affordable standard of care treatment modalities in India. As shown in the GOG 240 study, for recurrent cases, the addition of bevacizumab provides an OS benefit of 5 months and PFS benefit of 3 months, but unfortunately, owing to its high cost, only one of our patients could afford it.[26] Surgical therapy, especially for oligometastatic disease, has shown good results, like in our study, the patient who underwent hepatic segmentectomy is doing well with PFS approaching 12 months.

Although literature mentions pelvic exenteration as a mode of treatment with OS benefit ranging up to 40%, by and large, it is not acceptable to most patients.[27] One patient with rectovaginal fistula in our cohort refused for same and instead received best supportive care.

### Strengths and limitations

Although retrospective nature and small single-institute sample size was the limitation in our study, it does provide hope to set in PIFU as an opportunity for follow-up in carcinoma cervix patients.

It will help prevent fallouts, by reducing pocket crippling expenditures incurred with multiple hospital visits.

## Conclusion

Our study depicts the real-world scenario of challenges in the detection and treatment of recurrent cervical cancer cases from the largest cancer referral center in Northeast India. It portrays the fact that, in low-resource settings, there is a lack of follow-up post primary treatment. This can be attributed to difficult terrain, long distances, and pocket crippling expenditure associated with same.

PIFU can be a "practice changing modality" in patient management system, especially in low-resource settings.

It will be a simple cost-effective method to detect recurrence timely and prevent fallouts.

## Future implications

Nonhospital-based follow-up regimens are increasingly prevalent in the UK following gynecological malignancy, and they have demonstrated cost benefits. There have been no studies on PIFU in Indian subcontinent till date. Future randomized control trials (RCTs) for impact of PIFU on OS in India are strongly recommended. Further studies needed to precisely identify subsets of carcinoma cervix patients with higher chances of recurrence, for tailored upfront treatment escalation like adding systemic chemotherapy for para-aortic node involvement (IIIC2). Future studies are required to evaluate tumor size as a predictor of recurrence.

## What this research adds

The intensity of follow-up regimens after the treatment of cervical cancer is highly variable in clinical practice. This study shows equivalent oncologic outcomes in patients in whom recurrence is diagnosed clinically and based on symptoms versus those with routine follow-up imaging. It highlights the importance of symptoms of recurrence and their awareness among patients. This study paves way for future RCTs to explore the feasibility of patient-led follow-up in cervical cancer cases in low-resource settings.

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## Conflicts of interest

There are no conflicts of interest.

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