

## Recurrence of cancer cervix in patients treated by radical hysterectomy followed by adjuvant external beam radiotherapy

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### Abstract

One hundred and twenty patients with FIGO stage Ib-IIa cervical cancer who had radical hysterectomy prior to January 2003 in different hospitals of Bangladesh and thereafter received external beam pelvic radiotherapy (RT) at National Institute of Cancer Research and Hospital, Dhaka were studied. Until December 2007, 50 (42%) patients developed recurrence. Thirty-four (70%) patients experienced local recurrence, 13 (26%) distant recurrence and 2 (4%) both local and distant recurrence. Of 15 patients with distant metastasis, 6 (40%) experienced it in extra-pelvic lymph nodes. The median time to recurrence was 19 months (range 6-120 months) for local failure, 33 months (range 12-108 months) for distant failure and 25 months (range 13-36 months) for those with both local and distant failure. Eighty percent recurrences occurred within 36 months. There was significant correlation between lymph node metastasis and recurrence. All 5 (100%) patients with adenocarcinoma who had positive nodes experienced local recurrence compared with 18 of 49 (37%) squamous cell carcinoma patients with positive nodes. Recurrence more than 5 years after treatment developed in 5 (4%) patients. Mentionable, 4 (80%) out of 5 patients with late recurrence had squamous cell carcinoma with negative pelvic nodes.

### Introduction

Worldwide, cervical cancer is the third most common malignancy and second most common cancer in women<sup>1</sup>. Early stage cervical cancer can be treated by radical hysterectomy or radiotherapy (RT) with similar effectiveness. The choice of treatment depends upon a number of considerations, such as, age of the patient, medical status, experience of the gynaecologist and availability of institutional facilities. When surgery is chosen as the primary therapy, it is supplemented with adjuvant RT if adverse clinicopathological factors are present. These adverse factors are positive lymph nodes, involvement of the parametrium, close or positive surgical margins, and presence of large or deeply invasive tumours. The aim of postoperative RT is to prevent recurrence and improve survival, since recurrence is invariably associated with poor prognosis. The 5-year survival rates for early stage cervical cancer treated by radical surgery are in the 80% to 85% range; these figures drop to 3.2% to 13% when there is recurrence<sup>2-5</sup>.

Cervical cancer is the leading gynaecological malignancy among females in Bangladesh<sup>6</sup>.

Hospital-based studies show that it constitutes 22-35% of all female cancers<sup>6,7</sup>. The usual practice in Bangladesh is to do surgery for disease up to stage IIa. However, since most patients present with locally advanced disease and surgery is done by general gynaecologists rather than trained gynaec-oncologists, there are concerns regarding the adequacy of surgery performed. A recent study has shown that in Bangladesh, dissection in radical surgery is often not carried out as extensively as is the norm in developed countries of the world.<sup>8</sup> Pelvic lymphadenectomy – an integral part of radical surgery is incomplete in majority (93%) of cases and insecure vaginal margins are present in about a third of patients<sup>8</sup>. Considering the ground realities, all surgically treated patients in Bangladesh are considered high-risk and routinely offered adjuvant RT. Whether such an integrated treatment policy is beneficial or not is an issue that has not yet been addressed.

We carried out this study to evaluate the clinical outcome of cervical cancer patients treated by radical hysterectomy and postoperative RT. The endpoints of measurement were the rate and patterns of recurrence.

## Materials & Methods

This study was done at Gynae Out Patient Department of National Institute of Cancer Research & Hospital (NICR&H) Dhaka from July 2001 to December 2007. Patients who underwent pelvic lymphadenectomy during radical hysterectomy and whose stage at the time of operation was specifically mentioned in the records were included in the study. Patients whose records did not clearly elaborate the extent of surgery done were excluded. Thereafter 120 patients with stage Ib and Iia cervical cancer who had undergone radical hysterectomy in different hospitals/clinics of Bangladesh prior to the year 2003 and subsequently attended NICR&H for postoperative RT and follow-up were enrolled as the study population. The discharge certificates, operation notes, histopathology reports were studied to obtain the following information: age, stage of cervical cancer, pathological type and grade of tumour, status of removed lymph nodes and excised vaginal margins. All patients received 50c Gy external beam RT to the pelvis at NICR&H in 25 fractions over a period of 5 weeks. Radiotherapy was commenced within 42 days of surgery and given by Cobalt<sup>60</sup> machine. Upon completion of RT patients were asked to report for follow-up at 2 months interval in the 1<sup>st</sup> year, 3 months interval in the 2<sup>nd</sup> year, 6 months interval in the 3<sup>rd</sup> year and yearly thereafter. At each visit, thorough clinical examination was done and Pap smear taken. Recurrence when detected was confirmed by biopsy, FNAC (Fine Needle Aspiration Cytology) and imaging studies in relevant cases.

The association between recurrence and prognostic factors was analyzed by chi-square test.

## Results

The median age of the patients was 42 years (range 26-65 years). Median follow-up was 35 months (range 6-144 months). Majority (83%) of patients presented with stage Iia cervical cancer. Histologically confirmed positive nodes were found in 54 (45%) patients (Table I). Squamous cell carcinoma was the predominant tumour type comprising 91% of cases. Sixty-five percent of squamous carcinoma and 73% of adenocarcinoma were moderately differentiated (Table II).

Recurrent cancer was detected in 50 (42%) patients. Thirty-four (70%) patients experienced local recurrence, 13 (26%) distant metastasis and 2 (4%) both local and distant recurrence. The median time of recurrence was 19 months (range 6 – 120 months) for local recurrence, 33 months for distant

metastasis (range 12–108 months), and 25 months (range 13–36 months) for those with both local and distant recurrence. Distant recurrences most often involved the lymph nodes, followed by lungs and bones (Table III).

The associations between different prognostic factors and recurrence are shown in Table IV. Amongst the prognostic factors, only lymph node status significantly correlated with recurrence.

Analysis of patterns of recurrence according to cell type and node status shows that local recurrence was twice as common in adenocarcinoma as in squamous cell carcinoma (55% versus 27%). All 5 (100%) patients with node positive adenocarcinoma suffered local recurrence (Table V).

Among the 50 patients who had recurrence, 10 (20%) experienced it within the 1<sup>st</sup> year, 30 (66%) within 2 years, 40 within 3 years (80%), 44 (88%) within 4 years, 45 (90%) within 5 years. Of the 5 recurrences that occurred more than five years after completion of treatment, two were evident at the 6<sup>th</sup> year, and one each at the 8<sup>th</sup>, 9<sup>th</sup> and 10<sup>th</sup> years. Four of the late recurrence occurred in patients with node-negative squamous cell carcinoma, while one late recurrence was evident in a patient with node-positive adenocarcinoma.

**Table I** Clinico-pathologic characteristic

Characteristic	Number	Percentage
All cases	120	
Age (years)	42	
Median (range)	26-65	
FIGO stage		
Ib	21	17.5
Iia	99	82.5
Pelvic nodes		
Positive	54	45
Negative	66	55
Vaginal resection margins		
Positive	27	40
Negative	41	60
Not stated*	52	

\* 'Not stated' category not included in the calculation of %

**Table II:** Histotype and grade according to stage of tumor

Stage Ib <b>21</b>					
Squamous Cell Carcinoma <b>18</b>			Adenocarcinoma <b>3</b>		
Grade			Grade		
I	II	III	I	II	III
4	11	3	1	1	1
Stage Iia <b>99</b>					
Squamous Cell Carcinoma <b>91</b>			Adenocarcinoma <b>8</b>		
Grade			Grade		
I	II	III	I	II	III
20	60	11	1	7	0

**Table III:** Sites of distant metastasis

Site	No.
Lung	5
Bone	3
Inguinal nodes	3
Supraclavicular node	2
Supraclavicular and axillary nodes	1
Abdominal wall	1
Total	15

**Table IV:** Association of recurrence with prognostic factors

Prognostic Factors	No. of Recurrence	Local	Site Distant	Local + Distant
Lymph node status (n)				
Positive (54)	31 (57%)	23	7	1
Negative (66)	19 (29%)	12	6	1
	p < 0.01			
Histotype (n)				
Squamous (109)	43 (39%)	29	12	2
Adeno (11)	7 (63%)	6	1	0
	p > 0.05			
Stage (n)				
Ib (21)	8 (38%)	6	3	0
IIa (99)	42 (42%)	29	11	2
	p > 0.05			

**Table V:** Site of recurrence according to histotype and pelvic node status

	Positive nodes		Negative nodes	
	Squamous (n = 49)	Adeno (n = 5)	Squamous (n = 60)	Adeno (n = 6)
Local	18	5	11	1
Distant	7	0	5	1
Local and Distant	1	0	1	0
Total	26	5	17	2

## Discussion

Recurrence rates ranging from 19% to 36% have been reported in various series following treatment of cervical cancer by radical surgery and postoperative RT.<sup>9, 10, 11</sup> The above recurrence rates were found in study populations with early-stage cervical cancer who had risk factors identified at surgery and consequently received adjuvant RT. The frequency of recurrence in this series is 42%, and it is higher than the above quoted figures. Mentionable, this rate was observed in a heterogeneous study sample comprising both patients with low-risk as well as high-risk factors. It can, therefore, be assumed that most of the surgically treated patients in this series had high-risk clinico-pathological factors, which were either under-reported or else not detected due to inadequate surgery.

Local recurrence rates of 61% to 74% have been mentioned in the literature indicating that local relapse accounts for maximal cases of failure in cervical cancer.<sup>9, 11, 12</sup> Over two-thirds of the recurrence in this series are local; this distribution is in accord with the general trend of treatment failure in cervical cancer.

In this series, distant metastasis was more frequently observed in lymph nodes. Some workers have identified the lung as the commonest site of distant failure<sup>11, 13</sup>. Whether incomplete pelvic node resection, as is common in radical hysterectomy in Bangladesh, has any bearing on involvement of distant lymph nodes is not certain.

The median time to local recurrence was shorter than that for distant recurrence. Similar observations have been made by other workers<sup>9, 13, 14</sup>

Metastasis to pelvic lymph nodes is considered to be the dominant prognostic factor in cervical cancer.<sup>15</sup> In this study, a significantly higher proportion of patients with pelvic node metastasis experienced recurrence than did patients without metastasis. While comprising 45% of the study population, patients with node metastasis accounted for 68% of recurrence.

The prognostic relevance of adenocarcinoma is arguable. Some workers have noted higher incidence of lymph node metastasis and increased recurrence rates in adenocarcinoma, while other have not.<sup>9, 12, 16, 17</sup> The frequency of recurrence in patients with adenocarcinoma and squamous carcinoma in this series (63% versus 39%) is not statistically significant. What is however, noteworthy, is that all 5 (100%) patients with adenocarcinoma who had lymph node metastasis experienced local recurrence compared to 37% (18 of 49) patients with squamous carcinoma who had positive nodes. This finding reinforces the view that lymph node metastasis portends a worse prognosis for adenocarcinoma than for squamous carcinoma.

In the first year of follow-up after radical hysterectomy, recurrence rates ranging from 35% to 63% have been mentioned in various series.<sup>5, 13, 18</sup> Twenty percent recurrences were diagnosed within the first 12 months in this study. Adjuvant RT given invariably to all patients after surgery probably had a role in delaying the process of recurrence.

There are few published reports on recurrence of cervical cancer more than 5 years after primary therapy. Studies indicate that late recurrence is more common in patients treated by primary radiotherapy than those who had surgery as initial

treatment<sup>19,20</sup>. Late recurrence rate of cervical cancer in this study is 4%; it is higher than 2.5% relapse rate mentioned by Takehara et al<sup>20</sup>. Late recurrence was mostly seen in patients with node-negative squamous carcinoma. Whether node-negative patients have a propensity for late recurrence cannot be stated with conclusivity since the number of patients is small. However, the tendency of squamous cell carcinoma to recur after a long period of dormancy has also been noted by other workers<sup>20, 21</sup>.

From the available data, it is obvious that quite a large number of cervical cancer patients in Bangladesh have recurrence of the disease after being treated with radical hysterectomy and postoperative RT. Local control is not satisfactory in majority of cases despite adjuvant RT. Several studies have suggested that there is a benefit to cisplatin-based chemotherapy (CT) given either alone or before RT for high-risk surgical patients<sup>22-24</sup>. Peter et al.<sup>25</sup> carried out a study where high-risk post surgical patients were randomized into two groups-one group receiving concurrent cisplatin-based CT along with RT after radical surgery, and another group receiving only adjuvant RT. Analysis of treatment results showed that there was a 60% reduction in the rate of local failure and 34% reduction in distant spread in the group receiving both CT and RT compared to the group receiving only pelvic RT after surgery. In Bangladesh, where women will continue to suffer from cervical cancer until sustainable screening programs are initiated, consideration should be given to concurrent chemoradiation in high-risk surgical patients to improve disease control and survival.

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