Early stage cervical cancer with negative pelvic lymph nodes: morbidity and survival patterns following radical hysterectomy and postoperative adjuvant radiotherapy

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ABSTRACT

Background: The objective of the present study was to optimize the role of adjuvant radiotherapy in lymph node negative cervical cancer treated with radical hysterectomy and pelvic lymph node dissection, and to analyse patterns of failure and complication following surgery and radiotherapy in same patients.

Methods: This is retrospective analysis of 98 patients of cancer cervix FIGO Stage IB; IIA treated with radical hysterectomy with bilateral lymphadenectomy and adjuvant radiotherapy between the years 2000 and 2007at our hospital. Among all node negative patients who were operated during this period 97 patients were high risk. [High risk-Two or more of following risk factors: primary tumor size >4 cm, cervical stromal invasion ≥1/2, lymph-vascular space invasion, Unfavorable histology,≥].

Results: Median follow up: 79 months [6 months to 109 months], Recurrence rate: 13.26% [2 Pelvic and 11 distant recurrence] Pelvic control rate: 98 %Radiotherapy Complications: 4 % [Grade 3-4].

Conclusions: Adjuvant radiotherapy following radical hysterectomy in high risk node negative early cervical cancer is effective treatment. It reduces pelvic recurrence with acceptable morbidity.

Keywords: Cervical cancer, Negative lymph nodes, Prognostic factors, Radiotherapy, Survival

INTRODUCTION

Cervical cancer is one of the common malignancies in women worldwide with more than 500,000 new cases diagnosed annually and approximate 250,000 related deaths each year.1 Patients with invasive cervical carcinoma limited to the cervix alone [stage IB] and cervix plus upper vagina [stage 2A] are candidates for radical hysterectomy and pelvic lymphadenectomy. Patients with lymph node metastases have historically been considered high risk, and it is considered strongest predictor of pelvic failure.2,3 Patients without lymph node metastases individually have a lower risk of disease recurrence, but still account for half of total early stage cervical cancer recurrence.4 Histological type and grade, pathologic tumor size, lymph vascular space invasion and depth of cervical invasion have been identified as poor prognostic factors in patients with negative lymph nodes.4,6 The indications for postoperative radiotherapy have varied over the years. Various studies conducted by the American Gynecology Oncology Group (GOG) have provided some clarity regarding the prognostic factors which portend an increased risk of pelvic relapse. The high-risk criteria are positive pelvic nodes, occult parametrial invasion or positive resection lines, for which adjuvant chemoradiation is now a standard
recommendation. Patients without these criteria but with combinations of ‘intermediate’ criteria have varying degrees of risk. The grouping of intermediate-risk factors were done using two criteria (the classic and GOG).

According to the Classic criteria, the intermediate-risk group is defined by the presence of any two factors among three variables (tumour size or equal to 2 cm, more than one-third stromal invasion, and Lymphovascular space invasion (LVSI)).

In contrast, the GOG criteria define the intermediate-risk group more strictly than the Classic criteria, as they include various combinations of the three factors (LVSI, stromal invasion, and tumour size); however, these criteria are too complex and inconvenient, and they demonstrate low sensitivity and are poor predictors of recurrence and survival.

The Gynecologic Oncology Group Study (GOG) has conducted a prospective randomized study of adjuvant pelvic radiation for patients with these intracervical risk factors.

The study showed the benefit of postoperative radiation in these patients by reducing the recurrence from 28% in patients who underwent surgery alone to 15% in patients who received adjuvant radiation.

This retrospective study of lymph node-negative high-risk stage 1B and 2A cervical cancer patients was undertaken to identify poor prognostic factors and evaluate the effectiveness and sequelae of adjuvant pelvic radiotherapy following radical hysterectomy.

METHODS

Patient selection

From January 2000 to December 2007, patients with uterine cervical cancer who completed post-operative adjuvant radiotherapy in at our Institute were taken. 98 patients with negative lymph node metastases but with pathologic prognostic factors predictive of poor outcome [High risk-Two or more of following risk factors: primary tumor size >4 cm, cervical stromal invasion ≥1/2, lymph-vascular space invasion. Unfavorable histology] were evaluated in the study to compare treatment outcome and prognostic factors.

Follow-up

After completion of radiotherapy patients received regular follow up every 3 months for the first three years with radiological assessment every 6 months and then follow up every 6 months subsequently.

Treatment failure was defined by pathological proof of recurrence or was defined by image study showing regrowth of tumor or enlargement of lymph nodes. A pelvic examination was performed during each follow up. Radiological and/or laboratory investigations were performed when indicated. Patients having blood in stools underwent sigmoidoscopy to identify the cause of bleeding.

Complication analysis

Rectal and bladder complications and non-rectal gastrointestinal sequelae [small bowel complications] were scored according to RTOG (radiation therapy oncology group) grading scale. Grade 3-4 complications were categorized as major complications.

Statistical analysis

Patient survival was measured from the date of radiotherapy initiation to that of last follow up examination. Survival rate was determined using the Kaplan Meier method.

Long rank tests were used for univariate analysis. Logistic regression analysis was performed for assessment of patient and treatment factors associated with late complications.

RESULTS

Patient characteristics are

- Mean age - 42±9.2 years
- FIGO stage-
  - 1B-90
  - 2A-8
  - Histological type
    - Squamous cell carcinoma-93
    - Adenocarcinoma-5
- Tumour size
  - ≤4 cm -71
  - 4 cm-27
- Pathology
  - Lymph vascular permeation-14
  - Vaginal invasion-8
  - More than half thickness-74

Median follow-up-79 months

The five-year disease-free survival [DFS] and overall survival rates [OS] were 85.7% and 98% respectively. After 6 months to 109 months of follow up, [median-79 months] 85 patients were alive without evidence of disease, 13 patients died of disease [11 distant and 2 central recurrences]. Median interval from surgery to recurrence was 34 months. The pattern of failure is listed in Table 1. The common site of distant metastasis were Liver [n=2], Spine[n=2], Lung[n=2], Para aortic[n=2], followed by Vulval [n=1], scar [n=1]and umbilical[n=1]. None of the enrolled patients died of other concurrent diseases.
Overall radiotherapy complication rate was 24%. Grade 1-2 gastrointestinal complications was 6.1%. Patients presented with abdominal discomfort, increased frequency of motion (5-8 times per day), and intermittent bleeding in stool. Grade 3-4 complication rate involving the gastrointestinal tract was 4%.

**Table 1: Pattern of failure.**

| No. of patients | Risk factors | Site of recurrence |
|-----------------|--------------|-------------------|
| Pelvic recurrence: 2 | • Full thickness disease  
• Moderately differentiated  
• Nuclear grade 2  
• Adenocarcinoma | Parametrium |
| Distant recurrence: 11 | | |
| 1 | • 4 cm disease  
• Full thickness  
• Nuclear grade 3  
• LV +ve | Spine |
| 1 | • Full thickness  
• Nuclear grade 2  
• Adenocarcinoma | Lungs |
| 1 | • > 4cm disease  
• Full thickness  
• Nuclear grade 2 | Paraaortic |
| 1 | • Full thickness  
• Moderately differentiated  
• LV+ | Spine |
| 1 | • Full thickness  
• Poorly differentiated  
• >4cm disease | Paraaortic |
| 2 | • Full thickness  
• Nuclear grade 3  
• LV +ve  
• Vagina positive | Liver |
| 1 | • Full thickness  
• Nuclear grade 2  
• >4cm disease | Scar |
| 1 | • Nuclear grade 2  
• Moderately differentiated  
• Vagina positive  
• >4cm disease  
• Adenocarcinoma | Vulval |
| 1 | • Nuclear grade 3  
• Greater than half thickness  
• >4cm disease | Umbilical |

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**Table 2: Radiotherapy related complications.**

| Complications | No. of patients | % |
|---------------|-----------------|---|
| Overall complications rate | 24/98 | 24.4 |
| Percentage needing operation | 1.0 |
| Small/large Intestine | |
| Grade 1-2 | 6 | 6.1 |
| Grade 3-4 | 4 | 4.0 |
| Bladder | |
| Grade 1-2 | 4 | 4.0 |
| Grade 3-4 | - |
| Skin Reaction | 4 | 4.0 |
| Lower leg edema | 3 | 3.0 |
| Obstructive uropathy | 3 | 3.0 |

Grade 1-2 urinary tract complications was seen in 4% of patients. Patients presented with either increase frequency of urine or intermittent hematuria. Obstructive uropathy was seen in 3% of patients. On univariate analysis of prognostic factors age, tumour size, histological type, depth of invasion, grade, vascular permeation, lymphatic permeation and vagina only vascular permeation was found to be significant. (p value-0.000).

**DISCUSSION**

There is increasing evidence that some subgroups of the patients with Stage 1B-2A lymph node negative cervical carcinoma are at a high risk of recurrence and that the recurrences occur predominantly in the pelvis.\(^5\)\(^6\) Although the survival benefit of adjuvant radiotherapy for lymph node negative cervical cancer is still controversial, optimization of the strategies of adjuvant therapy of these patients should be done. In the current study, all enrolled patients received the same mode of surgical resection and uniform irradiation doses. In present study vascular permeation was independent prognostic factor (Table 3). Previous investigators have identified the independent prognostic value of LVS1 in early stage cervical cancer. Burke et al. noted that the presence of LVS1 was three times more common in stage 1B cervical carcinoma with negative lymph nodes and clear margins that developed recurrence than in those who did not.\(^5\) A multicentre GOG study of patients with negative lymph node stage 1B squamous cell cervical carcinoma found the disease-free interval to be significantly lower for patients with LVS1.\(^6\) Vavra et al. reviewed 54 lymph nodes negative stage 1B patients with LVS1 who underwent radical surgery. Recurrence-free interval was prolonged in those patients with LVS1 who received adjuvant radiation, but there was no difference in 5-year survival.\(^10\) In present study large tumor size, lymph space invasion, deep stromal invasion, worsening differentiation and vaginal involvement were not adverse variable for DFS and OS.
Table 3: Univariate analysis of prognostic factors.

| Variable                              | n (%)     | 5 years overall survival % | p      | 5 years disease free survival % | p      |
|---------------------------------------|-----------|----------------------------|--------|--------------------------------|--------|
| Age                                   |           |                            |        |                                |        |
| ≤40                                   | 47 (47.96)| 97.9                       | 0.873  | 85.1                           | 0.950  |
| >40                                   | 51 (52.04)| 98                         |        | 86.3                           |        |
| Histological type                     |           |                            |        |                                |        |
| Squamous cell carcinoma               | 93 (94.89)| 97.8                       | 0.730  | 84.9                           | 0.202  |
| Adeno Carcinoma*                      | 5 (5.11)  | 100                        |        | 100                            |        |
| Tumor size                            |           |                            |        |                                |        |
| ≤4cm                                  | 71 (72.45)| 98.6                       | 0.514  | 83.1                           | 0.430  |
| >4cm                                  | 27 (27.55)| 96.3                       |        | 92.6                           |        |
| Depth of invasion                     |           |                            |        |                                |        |
| ≤1/2                                  | 24 (24.49)| 95.8                       | 0.411  | 91.7                           | 0.332  |
| >1/2                                  | 74 (75.51)| 98.6                       |        | 83.8                           |        |
| Nuclear grade                         |           |                            |        |                                |        |
| 1                                     | 6 (6.12)  | 100                        | 0.639  | 100                            | 0.537  |
| 2                                     | 74 (75.51)| 98.6                       |        | 86.5                           |        |
| 3                                     | 17 (17.34)| 94.1                       |        | 76.5                           |        |
| LP (Lymphatic permeation)             |           |                            |        |                                |        |
| -                                     | 85 (86.73)| 97.6                       | 0.545  | 85.9                           | 0.997  |
| +                                     | 13 (13.27)| 100                        |        | 84.6                           |        |
| VP (Vascular permeation)              |           |                            |        |                                |        |
| -                                     | 97 (98.98)| 99                         | 0.000  | 86.6                           | 0.000  |
| +                                     | 1 (1.02)  | 0.0                        |        | 0.0                            |        |
| Vagina                                |           |                            |        |                                |        |
| -                                     | 90 (91.83)| 97.8                       | 0.640  | 86.5                           | 0.675  |
| +                                     | 8 (8.17)  | 100                        |        | 75                             |        |

In addition to nodal involvement, a number of other tumour associated characteristics have been reported to be predictive of outcome by several retrospective studies. Increasing tumor size, deep stromal invasion, lymph vascular space involvement, worsening differentiation, FIGO stage, adverse histology and extension to parametria are all associated with lower 5-year survival rates.3,13

Takeshi Kodaira et al in their study reported large tumor size and histology of adenocarcinoma as adverse prognostic factors for DFS and OS. Age, stage, deep stromal invasion, nuclear grade were not adverse prognostic factors.14 In present study, bulky disease, full thickness disease, lymphovascular invasion and nuclear grade were surgico-pathological factors present in patients with distant metastasis but were not proved on analysis (Table 1,3).

Takamura et al, reported that 70 patients with lymph node negative, Stage I and II cervical cancer with histologically confirmed parametrial extension received adjuvant standard whole pelvic irradiation to a total dose 50 Gy. Local control was achieved in 66 of 70 patients. However, 28 complications requiring medical treatment occurred and 6 of the 66 patients developed major complications requiring further surgery.15 Kriedelka et al, reported 25 patients with negative lymph nodes receiving 50.4 Gy of adjuvant small field irradiation to the pelvis. There was one recurrence recorded at 16 months. No major radiation morbidity was reported. 16 Failures in node negative patients usually develop within pelvis but rarely at distant sites.11,12,16 Our experiences with adjuvant radiotherapy for patients with lymph node negative cervical cancer achieve compatible pelvic control as with other series. In present study there were 11 distant recurrences and 2 pelvic recurrences [Recurrence rate 13.2%].

In studies by Schorge et al and Sartori et al recurrence rate were 20% and 17% respectively.11,12 Adjuvant radiotherapy probably reduced locoregional recurrences in our series However, since nearly 13.2% of the patients died of disease; it is justified to intensify the strategy for adjuvant treatment for some subgroups of the patients. Because failures occurred at distant sites, the most feasible approach for the improvement of treatment outcome is a combination of systemic chemotherapy.

In present study Five-year disease-free survival [DFS] and overall survival rates [OS] were 85.7% and 98% respectively. Pelvic control rate was 98%. This is comparable with other studies. Similar conclusions were reported by other studies. DFS / OS in study by Takeshi
Kodaira et al and A Ayan et al were 85.3%/89.7% and 87.6%/91% respectively.\textsuperscript{13,14} Similar Study was done by Sang-Young Ryu et al. Records of 172 patients with any of intermediate factors were taken for analysis. Among 172, 137 patients had two or more intermediate risk factors. There were 12 recurrences, six in the pelvis and six in the distant sites. The classic criteria detected all 12 recurrences; however, GOG criteria could detect only six recurrences.

Although no prognostic factor was significant on multivariate analysis, the difference in the 3-year recurrence-free survival was significant among no further treatment, Radiotherapy and chemoradiotherapy groups.\textsuperscript{17} As has been suggested in recent studies concurrent chemotherapy and radiotherapy may be more effective than radiation alone in terms of distant metastasis and survival. Therefore, introduction of randomized studies is suggested to elucidate the role of chemotherapy for the subgroups of patients. In present study overall radiotherapy complication rate was 24%.Grade 3-4 complication rate involving the gastrointestinal tract was 4% (Table-2). Only in one patient ileal resection and anastomosis was done after perforation. Sedlis et al in the GOG 92 trial reported a 2.3% Grade 3-4 involving the gastrointestinal tract and 3.1% involving the genitourinary tract.\textsuperscript{9}

The development of distant metastasis could not be reduced through the use of the whole pelvic field: therefore, the benefit of a standard field for this subgroup is doubtful. As radiation morbidity is highly associated with irradiation volume, for the patients with lymph node negative and lymphovascular invasion positive early cervical cancer, authors suggest using a lower pelvic field to minimize gastrointestinal complications. Moreover, Authors advocate the introduction of randomized studies to elucidate the role of chemotherapy for this group of patients.

\textbf{CONCLUSION}

Postoperative radiotherapy in node-negative stage IB-IIA cervical cancer patients with intermediate risk factors reduced only the incidence of locoregional recurrence. Distant recurrence was the major pattern of treatment failure after adjuvant radiotherapy. In high risk node negative cervical cancer patients most, feasible approach for the improvement of treatment outcome is a combination of systemic chemotherapy.

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