Early stage cervical cancer with negative pelvic lymph nodes: Pattern of failure and complication following radical hysterectomy and adjuvant radiotherapy

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Summary

Purpose of investigation: The objective was to optimize the adjuvant treatment for patients with lymph node negative cervical cancer by analyzing patterns of failure and complications following radical hysterectomy and adjuvant radiotherapy.

Methods: From September 1992 to December 1998, 67 patients with lymph node negative uterine cervical cancer (FIGO stage distribution: 50 Ib, 17 IIa), who had undergone radical hysterectomy and postoperative adjuvant radiotherapy with a minimum of three years of follow-up were evaluated. All patients received 50-58 Gy of external radiation to the lower pelvis followed by two sessions of intravaginal brachytherapy with a prescribed dose of 7.5 Gy to the vaginal mucosa. For 21 patients with lymphovascular invasion, the initial irradiation field included the whole pelvis for 44 Gy. The data were analyzed for actuarial survival (AS), pelvic relapse-free survival (PRFS), distant metastasis-free survival (DMFS), and treatment-related complications. Multivariate analysis was performed to assess the prognostic factors.

Results: The respective five-year AS, PRFS, and DMFS for the 67 patients were 79%, 93% and 87%. Multivariate analysis identified two prognostic factors for AS: bulky tumor vs non-bulky tumor ($p = 0.003$), positive resection margin ($p = 0.03$). The independent prognostic factors for DMFS was bulky tumor ($p = 0.003$), while lymphatic permeation showed marginal impact to DMFS ($p = 0.08$). The incidence of RTOG grade 1-4 rectal and non-rectal gastrointestinal complication rates were 20.9% and 19.4%, respectively. The independent prognostic factor for gastrointestinal complication was age over 60 years ($p = 0.047$, relative risk 4.1, 95% CI 1.2~11.7). The incidence of non-rectal gastrointestinal injury for the patients receiving whole pelvic radiation and lower pelvic radiation was 28.5% and 15.2%, respectively ($p = 0.25$).

Conclusion: For patients with lymph node negative cervical cancer following radical hysterectomy, adjuvant lower pelvic radiation appears to be effective for pelvic control. It is also imperative to intensify the strategies of adjuvant therapy for some subgroups of patients.

Key words: Cervical cancer; Negative lymph node; Adjuvant radiotherapy; Radiation morbidity.

Introduction

The conventional treatment of Stage IB and IIA cervical cancer consists of either radical hysterectomy or primary radiotherapy. These treatment modalities are recognized as equally efficient with respect to local control and survival [1, 2]. For patients treated with radical surgery, several histological features have been reported as poor prognostic factors for pelvic control and survival. Patients are subjected to postoperative adjuvant radiotherapy if the histopathological examination reveals some risk factors. Involvement of pelvic lymph nodes is the strongest predictor of pelvic failure [3-7]. Additional pathological factors that influence outcome include surgical margin, lymphovascular invasion, deep stromal invasion, and microscopic invasion of the parametrium, myometrium, or endometrium [5, 8, 9]. Patients with negative pelvic lymph node metastasis have a lower risk of disease recurrence, but still account for half of the total cervical cancer recurrences [10]. Histological type [8, 10], tumor size [8], lymphovascular invasion [10, 11], and depth of cervical invasion [8] have been identified as poor prognostic factors in patients with negative lymph nodes. One or more of these surgical-pathological variables may persuade a clinician to recommend adjuvant radiotherapy.

There are two issues for the optimization of adjuvant treatment with respect to lymph node negative patients. The first is to identify the group who are at high risk of local recurrence or distant metastasis in spite of postoperative radiotherapy. From the analysis of pattern of failure, further refinement of treatment strategies can be achieved.

The second issue was optimization of the radiation field. Radiation morbidity is correlated highly with the irradiation volume [12-14]. For patients with lymph node positive cervical cancer, the standard irradiation field usually includes the whole pelvis for full coverage of lymphatic drainage. However, a clinical review of the records of our patients showed that most of local recurrences occurred in the vagina or parametrium. Therefore, there seemed to be little benefit in extending the upper border of the treatment field to the L4-L5 interface as in

Revised manuscript accepted for publication July 7, 2003

the standard field. However, suggestions regarding the efficacy of adjuvant lower pelvic radiation need to be confirmed.

This retrospective study of lymph node negative Stage IB and IIA cervical cancer was undertaken to evaluate the efficacy and sequelae of adjuvant radiotherapy. Since most enrolled patients received lower pelvic field radiation, the effectiveness of this irradiated field will be assessed.

Materials and Methods

Patient selection

From September 1992 to December 1998, 127 patients with uterine cervical cancer completed postoperative adjuvant radiotherapy at Shin Kong Memorial Hospital and Chinese Medical University Hospital. Sixty-seven patients (International Federation of Gynecology and Obstetrics [FIGO] stage distribution: 50 IB, 17 IIA) with negative pelvic lymph node metastasis and who had undergone at least three years of follow-up, were enrolled in the study to compare treatment outcomes and prognostic factors. The number of lymph nodes removed at the time of radical hysterectomy ranged from 10 to 34, with an average count of 21.4 lymph nodes. For the 60 patients who had received postoperative CT scans, none of these patients had obvious residual disease in the pelvic cavity or para-aortic lymph nodes. None of the enrolled patients received adjuvant chemotherapy or concurrent chemotherapy. Patient characteristics are summarized in Table 1.

Table 1. — *Patient characteristics (totally 67 patients).*

Age at treatment	Median 47 (32-69)
FIGO stage	
Ib	50
IIa	17
Histology type	
Squamous cell carcinoma	60
Adenocarcinoma	7
Tumor size	
Non-bulky	60
Bulky	7
Pathology	
Lymphovascular permeation	21
Endometrial invasion	9
Vaginal invasion	20
Parametrial invasion	20
Full thickness	21
Whole circumference	9
Positive resection margin	6
Median follow-up	60 months (37-119)

Note: Bulky tumor is defined when the lateral dimension of the tumor was more than 4 cm.

Radiotherapy

The median time from surgery to commencement of postoperative radiotherapy was five weeks (range, 4-7 weeks). Radiation therapy consisted of external beam radiotherapy (EBRT) followed by a high-dose-rate intravaginal brachytherapy (Table 2). For 46 patients without lymphovascular invasion, the radiation field was confined to the lower pelvis with a prescribed dose of 50-58 Gy over five to six weeks. For the other 21 patients with lymphovascular invasion, the irradiation strategy

Table 2. — *Radiotherapy technique.*

External RT
Equipment: Siemens linear accelerator, KDS-2
Portal: AP/PA, Box (AP diameter > 20 cm)
Energy: 10MV X-ray
Daily dose: 2.0 Gy
Strategy
1) Whole pelvis dose 44 Gy + lower pelvis boost 10 Gy: 21 patients with lymphovascular invasion
2) Lower pelvis 50~58 Gy (median 54 Gy): 46 patients without lymphovascular invasion
Brachytherapy
Equipment: Nucletron Ir-192 HDR remote afterloading system
No. of insertions:
2 fractions: 62
1 fraction: 5
Prescribed dose: 750cGy to vaginal surface
Fractions: once/week
Overall duration of the treatment: 32-68 days (median 54 days)

Table 3. — *Anteroposterior and lateral portals of external beam radiation: Whole pelvic field vs lower pelvic field.*

Portals	Whole pelvic field	Lower pelvic field
Anteroposterior		
Superior	L4-L5 junction	2 cm above upper margin of pelvic rim
Inferior	Inferior ischial tuberosity	Inferior ischial tuberosity
Lateral	1.5 cm lateral to pelvic rim	1.5 cm lateral to pelvic rim
Lateral		
Anterior	1 cm anterior to outer edge of pubic symphysis	Outer edge of pubic symphysis
Posterior	Anterior sacral plane	Anterior sacral plane

followed those who had positive pelvic lymph nodes. After 44 Gy/22 fractions to the whole pelvis, the radiation field was reduced to the lower pelvis for a further 10 Gy/5 fractions. Table 3 compares the anteroposterior and lateral portals of the lower pelvic field with those of the standard whole pelvic field. For patients treated with two-field techniques, the EBRT dose was calculated at midplane, while the dosimetry of the box field was calculated using computer-based software.

After the completion fo EBRT, high-dose-rate intravaginal brachytherapy was performed using an Ir-192 remote afterloading technique at one-week intervals. Sixty-two patients (92.5%) received two insertions, while five patients had only one insertion. The standard prescribed dose for each HBRIVB was 7.5 Gy to the vaginal surface and the whole vagina was included within the treatment lenght. Overall duration of the treatment ranged from 32-69 days (median, 54 days).

Follow-up

After completion of radiotherapy, patients received regular follow-up every two months in the first year, then every three months subsequently. A pelvic examination was performed during each follow-up, while tumor markers (squamous cell and carinoembryonic antigens) were checked every three to six months, and a radiographic examination (chest X-ray, abdominopelvic CT scan) was conducted yearly. Patients who had bloody stools underwent sigmoidoscopy to identify the site of the bleeding, and a blood count every two to four weeks for surveillance of the severity of rectal complications.

Complication analysis

Rectal and bladder complications and non-rectal gastrointestinal sequelae (small bowel complications) were scored according to the RTOG grading scale [15]. Grade 3~4 complications were categorized as major complications.

Statistical analysis

Patient survival was measured from date of radiotherapy initiation to that of last follow-up examination. The survival rate was determined using the Kaplan-Meier method. Long rank tests were used for univariate analysis, with Cox's multiple regression model utilized for multivariate analysis. Logistic regression analysis was performed for assessment of patient and treatment factors associated with late complications.

Results

Survival

After 37 tp 119 months of follow-up (median, 60 months), 53 patients were alive without evidence of disease; 13 patients died of the disease (4 with pelvic recurrence, 8 with distand metastasis, 1 with both); one patient died of treatment related complications. The patterns of failure are listed in Table 4. None of the enrolled patients died of other concurrent diseases.

Table 4. — *Pattern of failure.*

Pelvic recurrence		
Patient	Risk factors	Site of recurrence
1.	MA, VA	periurethral area
2.	AD, MA, EM	pelvic wall (RT field)
3.	PA, FT, VA	parametrium (RT field)
4.	BU, AD, EM	prevesicle region (RT field)
5.*	BU, MA, LP, FT, PA	parametrium and rectum (RT field)
Distant metastasis		
Patient	Risk factors	Site of distant metastasis
1.	LP, AD	lung
2.*	BU, MA, LP, FT, PA	para-aortic LN (combined pelvic recurrence)
3.	PA, LP	lung, neck LN
4.	PA, VA	lung
5.	BU, LP	lung, para-aortic LN
6.	LP	bone
7.	PA	lung, bone
8.	BU	lung
9.	BU, LP	bone, para-aortic LN

The 5-year actuarial survival (AS), pelvic relapse-free survival (PRFS), and distant metastasis-free survival (DMFS) for all patients were 79%, 93% and 87%, respectively. The survival curves of AS, PREFS, and DMFS are depicted in Figures 1, 2, 3.

The results of the univariate and multivariate analyses for AS and DMFS are listed in Table 5 and Table 6. Multivariate analysis identified two prognostic factors for AS: bulky tumor (p = 0.003), and positive resection margin (p = 0.03). The independent prognostic factors for DMFS was bulky tumor (p = 0.003), while lymphovascular invasion showed a marginal impact to DMFS (p = 0.08).

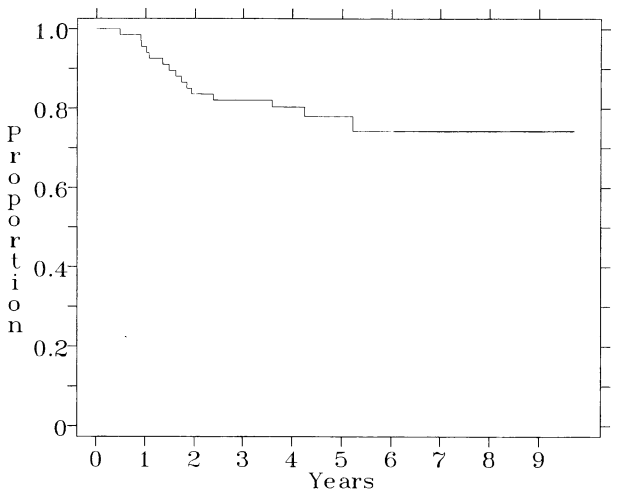

Figure 1. — Actuarial survival curve for all patients.

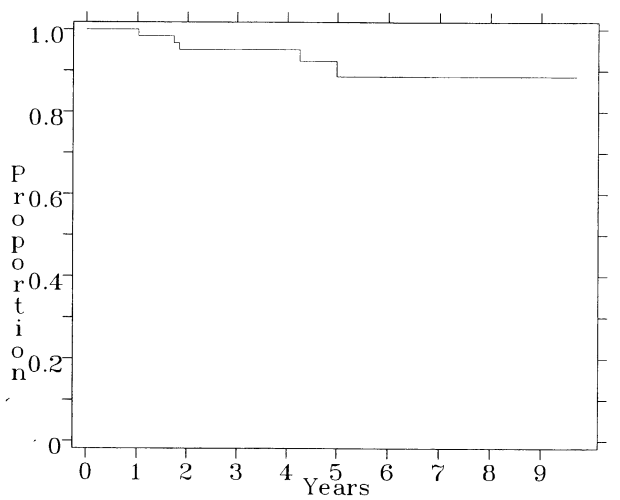

Figure 2. — Pelvic relapse-free survival curve for all patients.

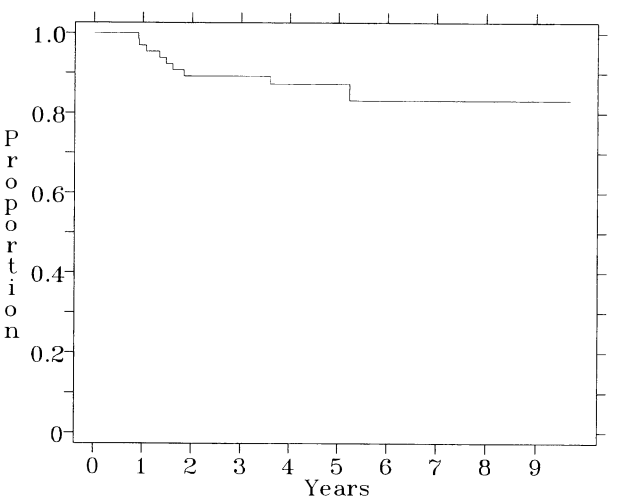

Figure 3. — Distant metastasis-free survival curve for all patients.

Table 5. — *Prognostic value of clinical and pathological parameters in univariate analysis.*

	No. of patients	Relative risk of cancer-related death		Relative risk of distant metastasis	
Age					
≥ 40	57	1		1	
< 40	10	1.60	p = 0.43	3.64	p = 0.08
Bulky					
Non-bulky	60	1		1	
bulky	7	12.5	p = **0.001**	14.6	p = **0.0001**
Histology					
squamous cell carc.	60	1		1	
adenocarcinoma	7	3.0	p = 0.23	1.028	p = 0.94
Margin					
negative	62	1		1	
positive	5	6.25	p = **0.01**	1.68	p = 0.49
Lymphatic permeation					
negative	46	1		1	
positive	21	1.64	p = 0.3	5.25	p = 0.03
Parametrial invasion					
negative	47	1		1	
positive	20	1.23	p = 0.64	1.21	p = 0.77
Vaginal invasion					
negative	47	1		1	
positive	20	0.82	p = 0.67	0.65	p = 0.49
Endometrial invasion					
negative	58	1		1	
positive	9	0.98	p = 0.95	0.78	p = 0.86
Full thickness					
negative	46	1		1	
positive	21	0.47	p = 0.19	1.33	p = 0.77
Whole circumference					
negative	58	1		1	
positive	9	0.39	p = 0.15	0.78	p = 0.86

Complications

Table 7 summarized the radiation-related chronic complications in this study. Fourteen patients (20.9%) developed RTOG grade 1~4 rectal complications, while one of the patients was categorized as a grade 3 complication. This patient received a colostomy 28 months after radiotherapy for the relief of intractable rectal bleeding. The median time for the development of rectal complications was 12 months (range, 8-22 months) after radiotherapy. Thirteen patients (19.4%) developed RTOG grade 1~4 small bowel complications. Three of the 13 patients were categorized as grade 3-4, and one of the patients died of small bowel necrosis soon after salvage surgery. From the logistic-regression analysis, the only independent factor for total grastrointestinal injury was age over 60 years (p = 0.047, relative risk 4.1, 95% CI 1.2~11.7). The incidence of small bowel injury for the patients receiving whole pelvic irradiation and lower pelvic irradiation was 28.5% and 15.2%, respectively (p = 0.25). Although, there was no statistical significance for small bowel injury between two different external beam irradiation strategies, two of the three patients with major small bowel injuries received whole pelvic irradiation. The other patient receiving lower pelvic irradiation was over 60 years old.

One patient developed RTOG grade 3~4 bladder complications. Four patients developed lower leg edema.

Table 6. — *Multivariate analysis of prognostic factors.*

Prognostic factors	5-year actuarial survival Risk ratio	95% CI	p-value	5-year distant metastasis-free survival Risk ratio	95% CI	p value
Tumor size						
bulky vs non-bulky	12.5	1.56~27.8	0.003	14.6	1.43~30.2	0.003
Surgical margin						
positive vs negative	6.25	1.12~14.9	0.03			
Lymphovascular invasion						
positive vs negative				5.25	0.98~16.3	0.08

Multivariate analysis was performed using the significant variable at a level of 10%.

Table 7. — *Radiotherapy related complications.*

Complication	Number	Median time to complication (months)
Rectal		12
Grade 1-2	13 (19.4%)	
Grade 3-4	1 (1.5%)	
Non-rectal gastrointestinal		14
Grade 1-2	10 (14.9%)	
Grade 3-4	3 (4.4%)	
Bladder (Grade 3-4)	1 (1.5%)	26
Lower leg edema	4 (5.9%)	17
Obstructive uropathy	2 (2.9%)	23

Discussion

There is increasing evidence that some subgroups of the patients with Stage IB-IIA lymph node negative cervical carcinoma are at high risk of recurrence [4, 11, 16-18] and that the recurrences occur predominantly in the pelvis [19, 20]. Although the survival benefit of adjuvant radiotherapy for lymph node negative cervical carcinoma is still controversial, optimization of the strategies for 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; we were able to assess the patterns of failure after definitive adjuvant radiotherapy according to the extent of surgical pathological findings.

Our experience with adjuvant radiotherapy for patients with lymph node negative cervical cancer achieved a compatible pelvic control with other series [16, 17, 21]. However, since nearly 20% of the patients died of the disease, it is justified to intensify the strategies of adjuvant treatment for some subgroups of the patients. In our study, tumor size and lymphovascular invasion were two surgical pathological factors for the development of distant metastasis, while tumor size and positive surgical margins were two factors for cancer death. Because 69% (9/14) of failures occurred at distant sites, the most feasible approach for the improvement of treatment outcome is a combination of systemic chemotherapy. As has been suggested in recent studies [22, 23], 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 these subgroups of patients.

On the other hand, in view of 19.4% and 20.9% of the patients developing RTOG Grade 1~4 small bowel and

rectal complications, it should be more conservative and cautious either to routinely extend the field for para-aortic lymph node irradiation, or to indiscriminately escalate irradiation doses to the pelvis. Since there was no obviously detectable residual tumor in the postoperative CT scan for the patients who ultimately developed local recurrence or para-aortic lymph nodes metastasis, the introduction of postoperative MRI or positron emission scans may be considered for more precise delineation of residual tumor if radiation dose escalation or extended field should be done for patients with unfavorable prognostic factors.

In this study, the major difference between the two methods of external beam radiation was the inclusion of the common iliac lymph nodes. Since none of the patients with lower pelvic field irradiation were recorded to have recurrent disease at the common iliac lymph nodes, there was no evidence that the use of lower pelvic irradiation might jeopardize pelvic control. On the other hand, two of three patients with major small bowel morbidity received whole pelvic irradiation. Therefore, it is advisable to use a smaller lower pelvic field for postoperative radiotherapy for lymph node negative cervical cancer.

Takamura *et al.* [18] 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 of 50 Gy. Local control was achieved in 66 of 70 patients (94%). However, 28 (40%) complications requiring medical treatment occurred, and six of the 66 patients (9%) developed major complications requiring further surgery. On the other hand, Kridelka *et al.* [21] reported 25 patients with negative lymph nodes receiving 50.4 HGy (1.8 Gy per fraction) of adjuvant small field irradiation to the pelvis. There was one recurrence (4%) recorded at 16 months. No major radiation morbidity was reported.

A multicenter GOG study of patients with negative lymph node Stage IB cervical carcinoma found the disease-free interval to be significantly lower for patients with lymphovascular invasion [11]. Vavra *et al.* reviewed 54 lymph node negative Stage IB patients with lymphovascular invasion; the recurrence-free interval was prolonged for those who received adjuvant radiotherapy, but there was no difference in 5-year survival [24]. Schorge *et al.* reported lymphovascular invasion as an important prognostic variable in lymph node negative Stage IB and IIA cervical cancer. Although adjuvant radiotherapy may decrease the risk of recurrence, adjuvant radiotherapy doubled the risk of major complications requiring surgical intervention [16]. In this study, six of the 21 patients with lymphovascular invasion were recorded as developing systemic metastasis (3 in para-aortic lymph nodes). The development of distant metastases 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 [12-14], for patients with lymph node negative and lymphovascular invasion positive early cervical cancer we suggest using a lower pelvic field to minimize gastrointestinal complications. Moreover, we advocate the introduction of randomized studies to elucidate the role of chemotherapy for this subgroup of patients.

Conclusion

For patients with lymph node negative cervical cancer following radical hysterectomy, adjuvant lower pelvic radiation appears to be effective for pelvic control, and is recommended to minimize gastrointestinal complications. It is also imperative to intensify the strategies of adjuvant therapy for some subgroups of patients with unfavorable surgical pathological factors.

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