

GYNAECOLOGY

Twelve years experience with radical hysterectomy and pelvic lymphadenectomy in early stage cervical cancer

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Summary

The objective of this study was to evaluate the outcome, prognostic factors and complications of early stage cervical cancer patients treated with radical hysterectomy and pelvic lymphadenectomy (RHPL). The medical records of cervical cancer patients undergoing RHPL at Chiang Mai University Hospital over 12 years, between January 1995 and December 2006 were reviewed. There were 1,253 patients in the study period. The mean age was 44 years of age. Of these, 26.9% had prior diagnostic conisation. The maximum tumour size was 8 cm. The most common histology was squamous cell carcinoma (67%) followed by adenocarcinoma (23%). The distribution of FIGO staging was: stage IA 8.7%; stage IB 15.8%; stage IB1 61%; stage IB2 6.2%; and stage IIA 8.5%. Pelvic nodes, parametrial and vaginal margin involvement were detected in 15.9%, 10.7% and 3.8% of the patients, respectively. A total of 66.5% of patients underwent RHPL without adjuvant treatment; 12.1% received neoadjuvant chemotherapy. The estimated 10-year recurrence-free survival rate was 90%. Stage IB2/IIA, non-squamous cell carcinoma, nodal involvement and positive vaginal margins were independent, significant, poor prognostic factors. The most common long-term complication was lymphoedema. It was concluded that early stage cervical cancer patients treated with RHPL have long-term favourable outcome with minimal morbidity. Stage IB2 and IIA, non-squamous cell carcinoma, nodal and vaginal involvement were independent adverse prognostic factors.

Keywords

Disease-free survival (DFS), early stage, radical hysterectomy

Introduction

Cervical cancer is the most common gynaecological malignancy in developing countries. The standard treatment of early-stage cervical cancer includes either radical hysterectomy with pelvic lymphadenectomy (RHPL), or radiation therapy, which has been accepted as equally effective in terms of local control and survival (Landoni et al. 1997). The 5-year disease-free survival rate for patients with stage IB-IIA cervical cancer treated with radical hysterectomy approaches 80–90% (Holland and Shafi 2005). Adjuvant radiation therapy has been reported to decrease the incidence of locoregional recurrence with little or no effect on overall survival in patients with pathological risk factors such as positive pelvic nodes, positive parametrium and positive surgical margin (Kinney et al. 1989; Larson et al. 1987; Monk et al. 1994; Soisson et al. 1990). Recently, concurrent chemoradiation appears to improve survival rates compared with radiation alone in high-risk patients after radical hysterectomy (Peters et al. 2000). With long experience of performing RHPL in a large number of patients in our institute, we conducted a retrospective study to evaluate the outcomes and complications of this surgical

treatment over a 12-year period. The objectives of this study were to evaluate survival, pathological risk factors for tumour recurrence, and surgical complications.

Materials and methods

Following approval by the Research Ethics Committee, the medical records of cervical cancer patients undergoing RHPL at Chiang Mai University Hospital between January 1995 and December 2006 were reviewed. The operation was carried out with initial pelvic lymphadenectomy followed by radical hysterectomy. Patients with a micro-invasive tumour who revealed positive margin from conisation specimen and who received RHPL operation were included in this study. Neoadjuvant chemotherapy with cisplatin was given if the operative schedule was > 4 weeks after diagnosis or the primary lesion showed the larger size of > 4 cm. Patients with high-risk pathological factors (i.e. lymph node metastasis, parametrial involvement or positive surgical margins) and some of the patients who had intermediate risk factors, including deep stromal invasion and lymphovascular space invasion > 10 spaces were advised to receive adjuvant concurrent cisplatin-based

chemoradiotherapy. Radiation alone was given in patients who refused chemotherapy, had poor performance status, or underwent operation before 1999. The radiation was usually started within 1 month after surgery.

Adjuvant radiation therapy consisted of external beam irradiation 40–50 gray (Gy) delivered to the whole pelvis with a 10-MV X-ray by parallel opposed (anteroposterior) or four-field box beams; the daily fraction size was 1.8–2 Gy, five fractions per week. An additional 45–60 Gy were given in the paraaortic area with the fractionation 1.8–2.0 Gy daily (five fractions per week) when the histology revealed metastasis to the paraaortic node. Patients with positive vaginal margin received intravaginal brachytherapy using a high-dose remote control after-loading technique. Brachytherapy was usually administered in 2–7 fractions with a total dose of 4–6 Gy/0.5–0.75 cm below the vaginal mucosa. Adjuvant chemotherapy with cisplatin was given to patients who had lymphovascular space involvement of >10 spaces. Patients with small cell neuroendocrine carcinoma were also treated with adjuvant cisplatin plus etoposide for six cycles.

Patients were scheduled for follow-up every 3 months in the first year, every 4 months in the second year, every 6 months in the 3rd to 5th years and then annually thereafter. Treatment failure was defined either by pathological proof of recurrence or by image study showing re-growth of tumour or enlargement of lymph nodes. The complications and treatment outcomes were collected by reviewing the medical records.

Statistical analysis of the data was carried out using the SPSS for Window program (Version 10.0). Disease-free survival was estimated by the Kaplan–Meier method and compared with the Log rank test. Multivariate analysis was performed using a Cox proportional hazards regression model.

Results

During the study period, there were 1,368 patients with stage IA–IIA cervical cancers undergoing RHPL but the clinical data were available in 1,253 patients. Their characteristics are displayed in Table I. The mean age was 44 years with a range of 17–79 years. The maximum tumour size was 8 cm. About one-quarter of the patients had prior diagnostic conisation. Approximately 60% of the patients were stage IB1, while 15% were staged as IB because the staging was done before 1997. The 1995 modified FIGO cervical cancer staging was routinely used in our institute after 1998. Squamous cell carcinoma was the most common histology, accounting for 67%, followed by adenocarcinoma. Pelvic nodal involvement was found in 16% of the patients. The mean number of metastatic nodes was two, with a range of 1–10. Parametrial involvement and vaginal margin invasion were noted in 10% and 3% of cases, respectively. Patients with stage IB2 and IIA cervical cancer had higher incidences of pelvic nodes metastases and parametrial invasion, as shown in Table II. Approximately one-third of the patients received adjuvant treatment after operation, as noted in Table III. About one-fifth of the patients received neoadjuvant cisplatin chemotherapy due to either a long waiting period before surgery or large tumour size.

With a median follow-up period of 42 months, 76 patients (6.5%) developed tumour recurrence. Patients with stage IB2 and IIA cervical cancer had 2–3 times higher

Table I. Patient characteristics ($n = 1253$).

	<i>n</i>	(%)
Age (years) (mean, range)	44	17–79
Maximum size (cm)	8	
Prior conisation	338	27.0
Stage		
IA	86	6.9
IA1	7	0.6
IA2	12	1.0
IB	198	15.8
IB1	765	61.1
IB2	78	6.2
IIA	107	8.5
Histology		
Squamous cell carcinoma	840	67.0
Adenocarcinoma	293	23.4
Adenosquamous cell carcinoma	63	5.0
Small cell neuroendocrine	35	2.8
Other	22	1.8
Grade		
Grade 1	294	23.5
Grade 2	529	42.2
Grade 3	182	14.5
Unknown	248	19.8
Positive pelvic lymph nodes	199	15.9
Number of positive nodes (mean, range)	2	1–10
Parametrial invasion	134	10.7
Positive vaginal margin		
For invasive carcinoma	38	3.0
For high-grade squamous intraepithelial lesion	10	0.8

Table II. Pelvic node metastases and parametrial involvement by stage.

Stage	<i>n</i>	Pelvic node metastases (%)		Parametrial involvement (%)	
		<i>n</i>	(%)	<i>n</i>	(%)
IA	86	4	4.6	1	1.1
IA1	7	–	–	–	–
IA2	12	–	–	–	–
IB	198	19	9.6	5	2.5
IB1	765	132	17.3	85	11.1
IB2	78	19	24.4	17	21.8
IIA	107	25	23.4	26	24.3

risk of recurrence compared to those with stage IB1, as shown in Table IV. Local recurrence was found in 37 patients, while 36 developed locoregional recurrence and only three had combined local and distant recurrences. The number of recurrence patients stratified by clinical stage is listed in Table IV.

When using the Cox proportional hazards regression model to identify the significant pathological risk factors, we found stage IB2/IIA, non-squamous cell carcinoma histology, nodal involvement, and positive invasive tumour at vaginal margins were significant prognostic factors for developing recurrence as shown in Table V.

The estimated 10-year disease-free survival (DFS) of all patients was 90%, as shown in Figure 1. Patients with pelvic node metastases, parametrial involvement or

Table III. Treatment methods.

Treatment	n	(%)
RHPL	683	54.4
RHPL + RT	69	5.5
RHPL + CCRT	184	14.7
RHPL + CCRT + extended field of RT + brachytherapy	1	0.1
RHPL + brachytherapy	17	1.4
RHPL + chemotherapy	48	3.8
Neoadjuvant chemotherapy + RHPL	151	12.1
Neoadjuvant chemotherapy + RHPL + brachytherapy	1	0.1
Neoadjuvant chemotherapy + RHPL + RT	4	0.3
Neoadjuvant chemotherapy + RHPL + CCRT	72	5.7
Neoadjuvant chemotherapy + RHPL + chemotherapy	23	1.8

RHPL, radical hysterectomy and pelvic node lymphadenectomy; RT, radiation; CCRT, concurrent chemoradiation.

Table IV. Tumour recurrence by stage.

Stage of disease	Outcome			Total recurrence (%)		
	No evidence	Recurrence		n	(%)	
	Local	Distant	Combined			
IA	103	1	–	1	0.01	
IB	184	9	4	14	7.0	
IB1	722	14	24	40	5.2	
IB2	67	9	2	11	14.1	
IIA	97	4	6	10	9.3	
Total	1,173	37 (3.2%)	36 (3.1%)	3 (0.3%)	76	6.5

Table V. Multivariate analysis of the prognostic factors.

Factors	Relative risk	p value	95% CI
Stage		0.002	1.388–4.066
IA-IB1	1		
IB2-IIA	2.376		
Histology		0.001	2.048–5.748
Squamous cell CA	1		
Non-squamous cell CA	3.431		
Grade		0.317	0.739–2.541
I	1		
II-III	1.370		
Lymph node		0.003	1.340–3.994
Negative	1		
Positive	2.313		
Parametrium		0.130	0.851–3.480
Negative	1		
Positive	1.721		
Vaginal margin		0.016	1.181–5.083
Negative invasive cancer	1		
Positive invasive cancer	2.450		

involved vaginal margins had significantly lower DFS when compared with those without such risk factors as demonstrated in Figure 2.

Among the 1,253 patients, 219 (17.5%) experienced short-term and long-term complications, as shown in Table VI. The most common complication was severe lymphoedema followed by persistent bladder dysfunction and

Cumulative survival rate (%)

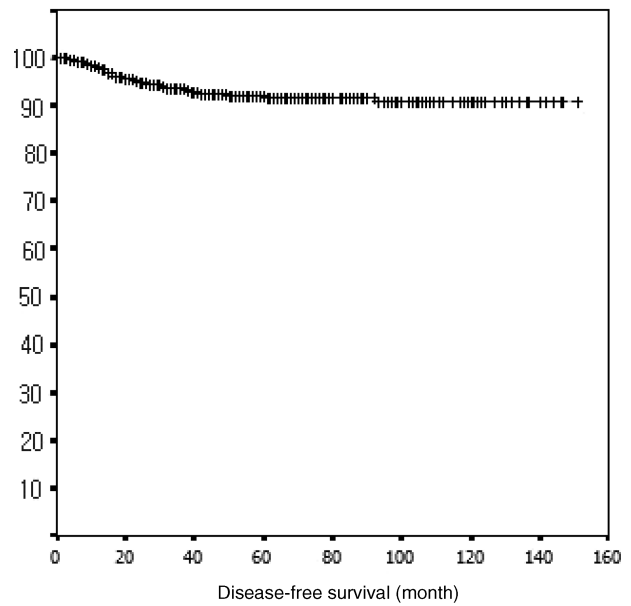


Figure 1. Disease free survival of all studied patients. 10-year estimated disease free survival = 90.8%.

lymphocyst. The incidence of lymphoedema occurred as high as 70% in patients treated with surgery plus radiation, while it occurred only 30% in patients treated with surgery alone.

Discussion

This study, in a single institute with over 1,000 patients, showed that patients with early stage cervical cancer who were treated with radical hysterectomy and pelvic lymphadenectomy had excellent survival outcome with an estimated 10-year DFS of 90%. Patients who had pelvic node metastases, parametrial involvement or positive vaginal margins for invasive cancer had significantly lower survival when compared to those without such risk factors. The survival outcomes in this study were comparable with those in previous reports of 80–90% (Naumann and Shingleton 1996). However, the recurrence rate after surgical treatment for cervical cancer in this study was quite low at 6.1%, compared with 10–20% in previous reports (Naumann and Shingleton 1996). This difference might result from the difference in the patients’ selection for surgical treatment, the follow-up period, and availability of patients for follow-up. Approximately 10% of the patients in the present study were lost to follow-up, which might affect the recurrence rate.

The incidence of pelvic node metastases in patients with stage IB2/IIA cervical cancer (24%) was much higher than those in stage IB1 (17%). These figures are comparable with those of 13–30% reported in the literature (Lee et al. 1989; Panici et al. 2003; Raspagliesi et al. 2003; Rutledge et al. 2004; Yessaian et al. 2004). The incidence of pelvic node metastases depends on the tumour size, the depth of stromal invasion and the presence of lymphovascular space invasion (Raspagliesi et al. 2003). Among the 105 patients with stage IA cervical cancer, four (3.8%) had lymph node metastases, which is within the range of 3–5% in the previous studies (Panici et al. 2003; Raspagliesi et al.

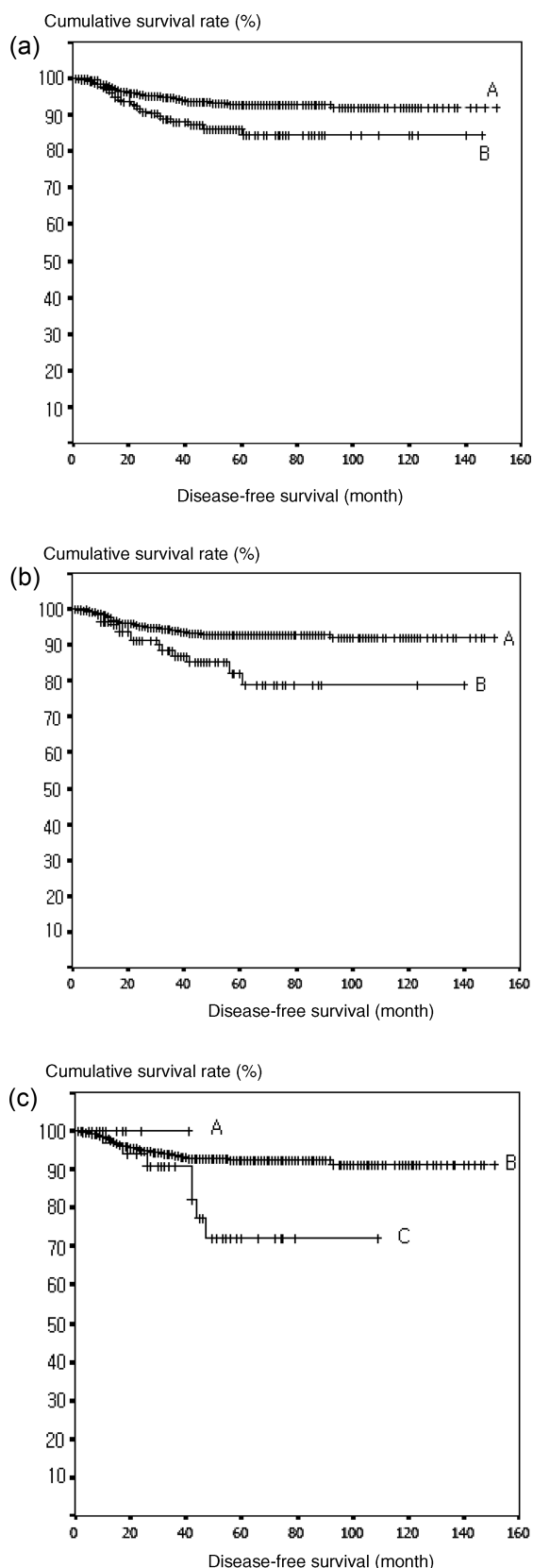


Figure 2. Disease-free survival (DFS) of patients with and without pathological risk factors. (a) 10-year estimated DFS; A, Negative LN = 92.1%; B, Positive LN = 84.4%; $p = 0.002$. (b) 10-year estimated DFS; A, Negative parametrium = 91.9%; B, Positive parametrium = 78.7%; $p = 0.002$. (c) 10-year estimated DFS; A, Negative vaginal margin = 91.4%; B, Positive vaginal margin for HSIL = 100%; C, Positive vaginal margin for invasive = 72.3%; $p = 0.008$.

Table VI. Complications.

	<i>n</i>	(%)
Severe lymphoedema	93	7.4
Persistent bladder dysfunction	64	5.1
Persistent lymphocyst	31	2.5
Urinary tract injury	17	1.3
Bowel obstruction	5	0.3
Bowel injury	2	0.1
Others	7	0.5
Total	219	17.5

2003). Before 1998, the patients with stage IA cervical cancer in the present study were not sub-staged as IA1 or IA2 according to the FIGO staging for cervical cancer, which was proposed in 1995. For microinvasive cervical carcinoma, the incidence of lymph node metastases depends on the depth of stromal invasion and the presence of lymphovascular space invasion (Raspagliesi et al. 2003).

The size of cervical tumour invariably affects the incidence of parametrial involvement. In this study, such incidence was considerably higher in patients with stage IB2/IIA cervical cancer (22–24%) compared to those with stage IB1 (11%). Previous studies noted that the incidence of parametrial invasion in early cervical cancer ranged from 10–30% depending on the tumour size or the stage of cervical cancer (Benedetti-Panici et al. 2000; Burghardt et al. 1987; Delgado et al. 1989; Michel et al. 1998). Parametrial extension was closely related to pelvic node metastases (Yen et al. 2003).

In the present study, the abdominal CT-scan or MRI was not routinely done as pre-treatment evaluation due to the low accuracy of detection of parametrial involvement (Hancke et al. 2008). In addition, imaging only has a sensitivity of 65–73% for lymph node detection, as reported by Bellomi et al. (Bellomi et al. 2005).

In general, pelvic node metastases, parametrial invasion and positive vaginal margins are considered high-risk factors for tumour recurrence after radical hysterectomy for early-stage cervical cancer. Patients with these factors would have significantly lower survival than those without such factors. In this study, when using multivariate analysis, stage IB2/IIA, non-squamous cell carcinoma, pelvic node metastases and vaginal margins invasion were statistically poor prognostic factors, which is similar to previous reports (Takeda et al. 2002; Winter et al. 2002).

Takada et al. (2002) used multivariate analysis to evaluate the histopathological prognostic factors in 187 patients with stage IB to IIB cervical carcinomas treated with radical surgery and noted that nodal metastases, parametrial invasion, lymphovascular space invasion, and adenocarcinoma histology were significant prognostic factors of cervical carcinoma. Meanwhile, Winter et al. (2002) found that parametrial involvement had no influence on disease-free survival in patients undergoing radical hysterectomy for early stage cervical cancer. However, Lee et al. (2006) observed no differences in disease-free survival and overall survival in patients with squamous cell carcinoma compared with adenocarcinoma of the cervix.

In our study, highly aggressive histology such as poorly-differentiated small cell neuroendocrine carcinoma were included in the non-squamous histology for comparison, while such cell types were not included in the study by Lee et al. (2006).

Long-term complications were noted in 18% of the patients undergoing radical hysterectomy in our study. The most common complication was lymphoedema (7%) followed by bladder dysfunction (5%). Such complications were noted in a range of 3–20% for lymphedema and 12–40% for persistent bladder dysfunction (Bergmark et al. 2006). The differences in these findings might result from the difference in definition, the duration of follow-up, the surgical technique, and the data collection method.

In conclusion, patients with early-stage cervical cancer have favorable survival outcome with acceptable long-term morbidity after treatment with radical hysterectomy and pelvic lymphadenectomy. Stage IB2/IIA, non-squamous cell carcinoma, nodal metastases, and positive vaginal margins are poor prognostic factors for tumour recurrence.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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