Outcomes of Complete Radical Hysterectomy in Early-Stage Cervical Cancer Patients with Intra-Operative Detection of Nodal Metastases

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Objective: *To determine the overall 5-year survival rate and treatment-related complications in stage IB-IIA cervical cancer patients with intra-operative detection of pelvic node metastases who underwent complete radical hysterectomy and systematic lymphadenectomy.*
Material and Method: *The medical records of FIGO stage IB-IIA cervical cancer patients who underwent radical hysterectomy and pelvic lymphadenectomy in Rajavithi Hospital between January 1985 and December 2006 were retrospectively reviewed. Of the 247 node-positive stage IB-IIA cervical cancer patients, 121 patients displayed evidence of intra-operative detection and underwent complete radical hysterectomy with systematic lymphadenectomy. These 121 patients were reviewed of which 107 were in stage IB and 14 were in stage IIA. Overall 5-year survival rate and treatment-related complications were investigated.*
Results: *The median follow-up period was 117 months (range 60-312 months). Of the 121 stage IB-IIA cervical cancer patients with intra-operative detection of pelvic node metastases who underwent complete radical hysterectomy and pelvic lymphadenectomy, the overall 5-year survival rate was 70.5%. The major treatment-related complications were intra-operative hemorrhage and post-operative bladder atony which accounted for 43.0% and 10.7%, respectively.*
Conclusion: *Early-stage cervical cancer patients with intra-operative detection of pelvic node metastases who underwent complete radical hysterectomy had favorable survival outcomes and manageable complications.*

Keywords: *Cervical cancer, Radical hysterectomy, Pelvic lymph node metastases, Intra-operative detection, Survival, Complication*

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Cervical cancer is the second most common malignancy worldwide, and almost 85 percent of these patients are found in developing countries[1]. In Thailand also, cervical cancer is the second most common malignancy to affect women: the age standardized rate (ASR) incidence was 18.1 per 100,000 women-year while the death incidence was 7.8 per 100,000 women-year[2].

Early-stage cervical cancer (FIGO stage IB-IIA) can be cured by primary radical surgery or radiation therapy. These two modalities have comparably high survival rates, but differ in associated morbidity and types of complications[3-5]. The combination of surgery and radiation therapy has the worst morbidity, especially in the form of urological complications[4].

The advantages of primary radical surgery include removal of primary disease, shorter duration of treatment, potential for preservation of ovarian function, possibility of better vaginal and coital function, and more accurate assessment of the true extent of disease[4].

Pelvic lymph node metastasis constitutes one of the most important prognostic factors of cervical cancer and is also an indicator of the need for post-operative radiation therapy. The incidence of positive lymph node in early-stage cervical cancer ranges from 12%-20% in stage IB and 17%-26% in stage IIA[6].

Management of the presence of intra-operative detection of nodal metastasis is still controversial. Some gynecologic oncologists perform

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radical hysterectomy and proceed to radiation therapy for better pelvic control and survival while others abandon hysterectomy to avoid the morbidity of combined treatment[7-10]. For positive nodes, some perform complete pelvic lymphadenectomy while others perform only biopsy or remove grossly positive nodes[8].

Rajavithi Hospital serves as a referral center for gynecologic cancer treatment among the hospitals in the Ministry of Public Health. In this, radical abdominal hysterectomy (RH) is the preferred treatment for early-stage cervical cancer. In the event of intra-operative detection of nodal metastasis, most patients undergo pelvic lymphadenectomy with complete radical hysterectomy and proceed to post-operative radiation therapy (RT). Accordingly, the aim of this retrospective study was to evaluate the survival outcomes and treatment related to complications in stage IB-IIA cervical cancer patients with intraoperative detection of pelvic node metastases who underwent complete radical hysterectomy with systematic lymphadenectomy in our institute.

Material and Method

The present study was conducted after approval was received from the Research Ethical Committee of Rajavithi Hospital. Medical records were retrospectively reviewed. Between January 1985 and December 2006, 247 FIGO stage IB-IIA cervical cancer patients treated by radical hysterectomy and lymphadenectomy In this institute had pathological reports of nodal metastasis, and all of them proceeded to post-operative radiation therapy. Of the 247 patients, 126 were excluded as follows: patients who had (1) post-operative pathological report of pelvic node metastasis without evidence of intra-operative detection (n = 123); (2) unusual histologic types (e.g. neuroendocrine carcinoma, lymphoma (n = 2)); and (3) history of pre-operative radiation therapy and chemotherapy (n = 1). The remaining 121 patients were analyzed.

All patients underwent clinical staging according to the staging of cervical cancer by the International Federation of Gynecology and Obstetrics (FIGO)[11] with pelvic examination pre-operatively under anesthesia (EUA) by the consensus of gynecologic and radiation oncologists. Patients in stage IB-IIA without contraindication for surgery were scheduled for a Piver-Rutledge-Smith class III radical hysterectomy, following systematic pelvic lympha-denectomy.

Systematic pelvic lymphadenectomy was carried out by removing all fatty tissue along both sides of the common iliac, external iliac, and internal iliac vessels, and also the fatty tissue inside the obturator fossa. Para-aortic lymphadenectomy was performed only when gross metastasis to the common iliac nodes or para-aortic nodes was suspected.

Positive intra-operative detection of pelvic node metastasis was defined as palpable solid pelvic node larger than 1 cm with irregular cut surface and/or necrotic area during operation. A suspicious node was confirmed by frozen section.

In cases of nodal metastasis, the extent of lymph node dissection and surgical radicality was tailored to reduce treatment complications. In young patients (less than 40 years of age), transposition of the ovaries out of the radiation field was carried out.

All patients with evidence of nodal metastasis were considered for post-operative radiation therapy, which may be given as radiation therapy alone or as radiation concurrent with weekly carboplatin at a dosage of 100 mg/m^2 or a target area under the concentration-time curve (AUC) of 2 mg/mL per minute. Radiation therapy alone was used in patients who refused chemotherapy or had poor performance status.

Radiation therapy consisted of external-beam irradiation of 50 Gy delivered to the whole pelvis with a 10-MV x-ray by parallel-opposed anteroposterior fields or four-field box technique. In cases of common iliac node or para-aortic node metastasis, extended-field irradiation was administered via box portals for 45 Gy. The daily fraction was 2.0 Gy, and 5 fractions per week were administered. High-dose rate brachytherapy using vaginal colpostat or cylinder with Iridium-192 source was also given for all patients. The usual dose per fraction prescribed at 0.5 cm depth from vaginal stump was 6 Gy given in 3 fractions.

After completion of treatment, all patients were scheduled for follow-up by physical examination and conventional Papanicolaou smear every 3 months for the first year, every 4 months for the second year, every 6 months until the fifth year and then once a year thereafter. Chest radiography was performed annually. Some patients were had follow-up telephone interviews. Treatment failure was defined either by pathologic proof of recurrence or by image study showing regrowth of the tumor or enlargement of lymph nodes. Treatment-related complications were recorded and graded according to the Franco-Italian glossary system[12].

Overall survival was calculated from the date of surgical treatment until death or the date of last contact. The treatment-related complications were classified into acute and chronic complications.

Statistical analysis of the data was carried out by SPSS for Windows program (version 11.5). The overall survival distributions were calculated by the Kaplan-Meier method. Multivariable analysis was performed using the Cox proportional hazards regression model.

Results

The characteristics of the 121 FIGO stage IB-IIA cervical cancer patients with evidence of intra-operative detection of pelvic node metastases who underwent complete radical hysterectomy are summarized in Table 1. Most patients had stage IB1 disease (76.0%) and squamous cell carcinoma histologic type (77.5%). The median follow-up period of surviving patients was 117 months (range 60-312 months). Twenty-eight patients (23.1%) died within 5 years of diagnosis. The 5-year overall survival rate for all patients was 70.5% (Fig. 1 and 2). The overall survival rates based on FIGO stage were 71.8%, 71.4% and 61.5% for stage IB1, IB2 and IIA, respectively.

Of the 121 patients, 83 (68.6%) had treatment-related complications, 52 (43.0%) had intra-operative blood loss of more than 1,000 mL, 13 (10.7%) had bladder dysfunction, 8 (6.6%) had lymphocyst and 8 (6.6%) developed radiation proctitis. Details of complications are summarized in Table 2. No pulmonary embolism, radiation cystitis, bladder necrosis, bowel ileus or bowel fistula were found during the study.

Discussion

Lymph node involvement represents one of the most important prognostic factors of cervical cancer[6]. The reported 5-year survival rate for women with stage IB cervical cancer treated with either radical hysterectomy (RH) with lymphadenectomy, or radiation therapy (RT) alone is between 83% and 90%[3,4], and the survival rate of these patients decreases dramatically to as low as 50% if positive lymph nodes are encountered[13].

For early-stage cervical cancer patients who are found to have nodal metastasis during operation, the treatment options include either proceeding with the hysterectomy and giving post-operative radiation therapy, or abandoning hysterectomy and converting to chemoradiation as the primary treatment[7-10].

Garg et al[14] surveyed the practice patterns of members of the Society of Gynecologic Oncologists

Table 1. Demographic and clinic-histological characteristics of the population (n = 121)

Characteristics	Value
Age (years) Mean ± SD	42.76 ± 9.40
Mean height (cm) ± SD	153.71 ± 6.02
Mean body weight (kg) ± SD	55.64 ± 8.62
Body mass index (BMI) (kg/m^2)	23.53 ± 3.53
FIGO stage, n (%)	121 (100.0)
IB1	92 (76.0)
IB2	15 (12.4)
IIA	14 (11.6)
Histological type, n (%)	
SCCA	94 (77.5)
Adeno CA	25 (20.8)
Adenosquamous CA	2 (1.7)
Positive margin (%)	0.08
Microscopic parametrium invasion (%)	20.83
Lympho-vascular space invasion (%)	18.30
Para-aortic nodes involvement (%)	0.80
Tumor size (cm) Mean ± SD	3.15 ± 1.19
Depth of invasion (cm) Mean ± SD	2.94 ± 3.87
Size of node (cm) Mean ± SD	3.06 ± 0.69
Number of dissected pelvic lymph node (median (min-max))	10 (3-26)
Number of positive pelvic lymph node (median (min-max))	3 (1-12)

Abbreviations: SCCA = Squamous cell carcinoma , AdenoCA = Adenocarcinoma, Adenosquamous CA = Adenosquamous carcinoma

(SGO) in clinical situations involving the intra-operative detection of nodal metastasis in early-stage cervical cancer. Of these, most (79%) performed complete RH for an isolated microscopically positive pelvic lymph node, while a large number abandoned RH due to gross involvement of pelvic (45%) or para-aortic lymph nodes (69%). Most of them (90%) completed the lymphadenectomy before abandoning RH. When completing RH, the majority tailored its extent to perform a less radical resection. In the present study, most patients had complete pelvic lymphadenectomy followed by para-aortic node dissection up to the level of the inferior mesenteric artery, and modified radical (class II) or classical radical (class III) hysterectomy was tailored depending on individual operators' preferences.

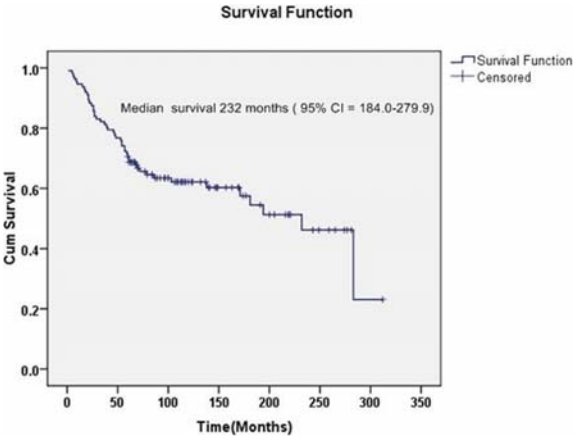

Fig. 1 Survival curve in stage IB-IIA

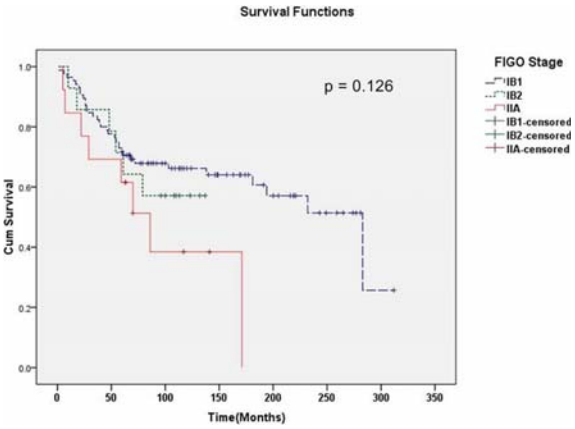

Fig. 2 Survival curve of patients classified by FIGO staging

Table 2. Type of complications

	Type of complications	n	%
Acute	Intraoperative hemorrhage	52	43.0
	Urinary fistula	5	4.1
	Febrile morbidity	5	4.1
	Bowel obstruction	2	1.7
	Surgical site morbidity	1	0.8
	Bladder dysfunction	13	10.7
Chronic	Lymphocyst	8	6.6
	Radiation proctitis	8	6.6
	Anemia	6	5.0
	Lymphedema	5	4.1
	Deep vein thrombosis	2	1.7
	Urological stricture	2	1.7

A report by Richard et al[7] examined the 5-year survival rates for women with intra-operative positive pelvic lymph nodes, and compared the survival rates of patients who had completed hysterectomy versus those who had abandoned hysterectomy. The overall 5-year survival rates were 69% and 71% in the completed RH group and abandoned RH group respectively.

Suprasert et al[8] reported that the overall survival rate of stages IB-IIA cervical cancer patients whose RH was abandoned because of grossly positive pelvic nodes was significantly worse than those of patients whose node metastasis was identified after the operation; this was because the abandoned RH group had worse prognostic factors. However, the complications were not significantly different in the two groups.

Garg et al[10] reviewed the overall 5-year survival rate and found that it ranged from 35% to 88% in the completed RH group and 45% to 61% in the abandoned RH group, and these figures were not significantly different. Recurrence was slightly higher in the abandoned group and no conclusions could be drawn about complications between both groups. In the present study, the overall 5-year survival rate of the 121 patients was 70.5%. Alvarez et al[9] reported that the overall 5-year survival rate of patients who had complete radical hysterectomy after intra-operative detection of nodal metastasis was 75% in stage IB and 62% in stage IIA. Ungar et al[15] also reported 85% overall survival rate in stage IB cervical cancer patients, while Panici et al[16] found that the overall survival rate in stage IA2-IB1 was 74% which is comparable to the outcome in the present study (Table 3). In contrast, Kinney et al[17] reported a 33% overall survival rate in stage IB cervical cancer patients in their study.

In the EORTC-GCG study, removal of more than 11 pelvic nodes was suggested as one of the quality indicators for pelvic lymphadenectomy[18]. Pieterse et

Table 3. Comparative clinical outcome in node-positive patients with early-stage cervical cancer who underwent radical hysterectomy and post-operative chemoradiation

Study	Stage	5-year survival	n	Mean number of node	Note
Present study (2013)	IB-IIA	70.5%	121	1/10*	
Alvarez et al (1989)[9]	IB, IIA	75.0%, 62.0%	185	NA	
Ungar et al (2003)[15]	IB	85.0%	29	NA/41	LEP
Panici et al (2005)[16]	IA2-IB1	74.0%	20	NA	

*Mean number of nodes reported by mean number of positive nodes/dissected node
Abbreviations: LEP = Laterally extended parametrectomy, NA = not available

Table 4. Comparative complications between present study and Ungar et al's study[15]

Complications	Present study, 2013	Ungar, 2003
Bleeding	43.0%	NA
Ureteral fistula	4.0%	5.0%
Lymphocyst	7.0%	15.0%
Febrile morbidity	4.1%	25.0%
Lower limb paresthesias	0%	5.0%
Bladder dysfunctions	10.7%	70.0%

Abbreviation: NA = not available

al[19] found that removing a higher number of nodes had a positive impact on survival in patients with positive lymph nodes, while Suprasert et al[20] found that the number of pelvic nodes removed was not associated with 5-year disease-free survival or the number of positive pelvic nodes. In the present study, the median number of nodes removed was only 10, which may have had an impact on the treatment outcome.

Extensive lymphadenectomy and hysterectomy are independent risk factors for the occurrence of intra- and post-operative complications. The incidence of complications is much increased when adjuvant radiation is added to therapy[5]. Treatment-related complications-mostly intra-operative hemorrhage- in the present study were found in 68.6%, which is rather higher than in other studies. In comparison to a similar study by Ungar et al[15], other complications such as bladder dysfunction, febrile morbidity, lymphocyst, urologic fistula and lower limb paresthesias were higher than in the present study (Table 4). However, additional laterally extended parametrectomy in Ungar's study[15] might have been responsible for the increase in the incidence of complications in these patients. Serious complications such as radiation cystitis, bladder necrosis, bowel ileus and fistula, which may exert a negative influence on the quality of life in these patients[21], were not found in the present study. In order to reduce the morbidity caused by combined treatment, the radicality of lymphadenectomy and hysterectomy should be tailored.

The strength of the present study was that all participants were recruited from a single institution, which meant that uniform treatment guidelines and surgical techniques were used. The limitations of the present study include its retrospective nature and lack of information on cancer-specific survival, its small number of patients and the lack of comparison with patients who had abandoned RH. Some patients with fewer than 10 nodes removed were not consistent with a full nodal dissection.

In conclusion, complete radical hysterectomy in early-stage cervical cancer patients with intra-operative detection of pelvic node metastasis had favorable outcomes and manageable complications. Prospective clinical trials of complete radical hysterectomy versus aborted radical hysterectomy should be conducted in the future. Pretreatment imaging for nodal status may be helpful in treatment selection for individuals.

Potential conflicts of interest

None.

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ผลของการผ่าตัดมดลูกแบบถอนรากถอนโคนในผู้ป่วยมะเร็งปากมดลูกระยะแรกที่พบมีการกระจายไปยังต่อมน้ำเหลืองขณะผ่าตัด

สุเพ็ชร ทุ้ยแป, ชญาดา วงศ์สุวรรณ

วัตถุประสงค์*: เพื่อศึกษาอัตราการรอดชีวิตที่ระยะ 5 ปี และภาวะแทรกซ้อนจากการรักษาของผู้ป่วยมะเร็งปากมดลูกระยะ IB-IIA ที่พบมีการกระจายไปยังต่อมน้ำเหลืองขณะผ่าตัดมดลูกแบบถอนรากถอนโคนในโรงพยาบาลราชวิถี*

วัสดุและวิธีการ*: ทบทวนเวชระเบียนของผู้ป่วยมะเร็งปากมดลูกระยะ IB-IIA ที่ได้รับการผ่าตัดมดลูกแบบถอนรากถอนโคนซึ่งมีการกระจายไปต่อมน้ำเหลืองระหว่างปี พ.ศ. 2528-2549 ในโรงพยาบาลราชวิถี จำนวนทั้งหมด 247 ราย มีผู้ป่วยที่พบมะเร็งการกระจายไปต่อมน้ำเหลืองอุ้งเชิงกรานขณะผ่าตัดจำนวน 121 ราย แบ่งเป็นระยะ IB จำนวน 107 ราย และ ระยะ IIA จำนวน 14 ราย ทำการวิเคราะห์อัตราการรอดชีวิตที่ระยะ 5 ปี และภาวะแทรกซ้อนจากการรักษา*

ผลการศึกษา*: ระยะเวลาในการติดตามผลโดยเฉลี่ย 117 เดือน (ช่วงเวลา 60-312 เดือน) พบอัตราการรอดชีวิตโดยรวมที่ระยะ 5 ปีเท่ากับ ร้อยละ 70.5 โดยมีภาวะแทรกซ้อนที่สำคัญได้แก่ การเสียเลือดระหว่างผ่าตัด และกระเพาะปัสสาวะกลับมาทำงานช้าหลังการผ่าตัด ซึ่งพบได้ ร้อยละ 43.0 และ 10.7 ตามลำดับ*

สรุป*: ผู้ป่วยมะเร็งปากมดลูกระยะแรกที่พบว่ามีการกระจายไปยังต่อมน้ำเหลืองขณะผ่าตัดและได้รับการผ่าตัดมดลูกแบบถอนรากถอนโคนมีผลลัพธ์ที่ดีและมีภาวะแทรกซ้อนที่สามารถแก้ไขได้*