
GYNAECOLOGY

Laparoscopic Radical Hysterectomy for Early-stage Cervical Cancer: Experiences from Rajavithi Hospital

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ABSTRACT

Objectives: To assess the survival outcomes of women with cervical cancer who had been treated with laparoscopic radical hysterectomy (LRH) at a large referral center in Thailand.

Materials and Methods: Records of women undergoing LRH between January 2010 and December 2018 were reviewed.

Results: Of 67 patients, the median age was 49 years. Fifty-six patients (83.6%) were diagnosed with stage IB cervical cancer. Forty-two (62.7%) patients had squamous cell carcinoma. Twenty-five (37.3%) patients received adjuvant treatment following LRH. With a median follow-up time of 32.6 months, eight (11.9%) patients experienced recurrent disease including pelvic recurrence (six patients) and combined pelvic and distant recurrences (two patients). Their 5-year disease-free (DFS) and overall survivals (OS) were 75.4% and 76.8%, respectively. Patients with squamous cell carcinoma had longer DFS than those with other histological types ($p = 0.028$).

Conclusion: The 5-year DFS and OS of patients undergoing LRH in this study were 75.4% and 76.8%, respectively. Patients with squamous cell carcinoma had longer survival than those with other histological types.

Keywords: cervical cancer, radical hysterectomy, laparoscopy, laparotomy, minimally invasive surgical procedures.

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การตัดมดลูกออกแบบกว้างผ่านกล้องสำหรับมะเร็งปากมดลูกระยะต้น: ประสบการณ์จากโรงพยาบาลราชวิถี

อรรณญา ยันตพันธ์, ชำนาญ เกียรติพิรุณ

บทคัดย่อ

วัตถุประสงค์: เพื่อประเมินผลการรักษาในสตรีที่พบมะเร็งปากมดลูกระยะต้นที่ได้รับการตัดมดลูกออกแบบกว้างผ่านกล้องที่โรงพยาบาลที่เป็นศูนย์รับการส่งตัวขนาดใหญ่ในประเทศไทย

วัสดุและวิธีการ: ทบทวนบันทึกเวชระเบียนของสตรีที่ได้รับการรักษาด้วยการตัดมดลูกออกแบบกว้างผ่านกล้องในช่วงเดือนมกราคม พ.ศ. 2553 ถึง เดือนธันวาคม พ.ศ. 2561

ผลการศึกษา: จากจำนวนผู้ป่วยทั้งสิ้น 67 ราย มีค่ามัธยฐานของอายุเท่ากับ 49 ปี ผู้ป่วย 56 ราย (ร้อยละ 83.6) ได้รับการวินิจฉัยว่าเป็นมะเร็งปากมดลูกระยะ IB ผู้ป่วย 42 ราย (ร้อยละ 62.7) พบมะเร็งชนิดสแควมัสเซลล์ ผู้ป่วย 25 ราย (ร้อยละ 37.3) ได้รับการรักษาเสริมภายหลังการผ่าตัด จากค่ามัธยฐานของระยะเวลาในการติดตามการรักษาที่เวลา 32.6 เดือน ผู้ป่วย 8 รายเกิดการกลับเป็นซ้ำของโรค โดยเป็นการกลับเป็นซ้ำในอุ้งเชิงกรานจำนวน 6 ราย และการกลับเป็นซ้ำที่พบทั้งในอุ้งเชิงกรานและการกลับเป็นซ้ำในตำแหน่งไกลจำนวน 2 ราย การรอดชีวิตปลอดโรคและรอดชีวิตโดยรวมที่ระยะเวลา 5 ปี เท่ากับร้อยละ 75.4 และร้อยละ 76.8 ตามลำดับ ผู้ป่วยที่มีมะเร็งชนิดสแควมัสเซลล์จะมีการรอดชีวิตปลอดโรคนานกว่าผู้ป่วยที่มีมะเร็งชนิดอื่น ($p = 0.028$)

สรุป: การรอดชีวิตปลอดโรคและรอดชีวิตโดยรวมที่ระยะเวลา 5 ปี ของผู้ป่วยมะเร็งปากมดลูกที่ได้รับการตัดมดลูกแบบกว้างผ่านกล้องในการศึกษานี้เท่ากับร้อยละ 75.4 และ ร้อยละ 76.8 ตามลำดับ ผู้ป่วยที่มีมะเร็งชนิดสแควมัสเซลล์จะมีการรอดชีวิตยาวนานกว่าผู้ป่วยที่มีมะเร็งชนิดอื่น

คำสำคัญ: มะเร็งปากมดลูก, การตัดมดลูกออก, การผ่าตัดผ่านกล้อง, การผ่าตัดเปิดหน้าท้อง, การผ่าตัดที่มีการลุกล้ำน้อย

Introduction

Cervical cancer was responsible for an estimated 570,000 cases and 311,000 deaths worldwide in 2018⁽¹⁾. This disease is prevalent in less developed countries with age-standardized incidence rates of 18.2 and 10.4 per 100,000 females in low/medium human development index (HDI) and high/very-high HDI countries, respectively⁽¹⁾. Most cervical cancer deaths occur in low/medium HDI countries^(1,2).

Treatment for cervical cancer depends on the disease stage⁽²⁻⁴⁾. Radical hysterectomy with bilateral pelvic lymphadenectomy is the standard surgical treatment for stage Ia2-IIa cervical cancer when preservation of fertility is not required or feasible⁽²⁻⁴⁾. Concurrent chemoradiation is also accepted as a standard treatment option for women with early-stage cervical cancer⁽⁵⁾. Radical hysterectomy and concurrent chemoradiation are equivalent treatments for early-stage cervical cancer⁽⁵⁾. Decisions regarding treatment therefore depend on individual patient characteristics and preferences and consideration of the perioperative risks with the longer-term risks of radiation⁽²⁾.

Radical hysterectomy can be performed via laparotomy (open surgery) and minimally invasive surgery (MIS). A randomized study by Ramirez, et al⁽⁶⁾ and the Surveillance, Epidemiology, and End Results data analysis by Melamed, et al⁽⁷⁾ consistently observed that the minimally invasive surgical approach for radical hysterectomy for cervical cancer was associated with increased rates of recurrence and death compared with open surgery. These findings were reaffirmed in a population-based cohort study undertaken in the United States that noted that minimally invasive radical hysterectomy was associated with a 2-fold higher rate of death and recurrence compared with open radical hysterectomy in patients with stage IB disease while accounting for mechanistic factors including patient characteristics and surgeon volume⁽⁸⁾. Nevertheless, the difference in survival between MIS and an open surgical approach in the subgroup of women with tumors \leq 2 cm seems to be comparable⁽⁶⁾.

Because the reasons leading to poorer oncological outcomes for women undergoing radical hysterectomy for cervical cancer treated by MIS compared with open radical hysterectomy remain debatable, careful counseling based on the available data to determine the appropriate surgical approach for an individual patient is important. Therefore, information regarding the factors affecting treatment outcome among patients undergoing minimally invasive radical hysterectomy is required to identify a subset of patients who remain suitable for this procedure. This study was conducted to evaluate the outcomes of women with cervical cancer who were treated with laparoscopic radical hysterectomy (LRH) at Rajavithi Hospital, a large referral center in Thailand. Factors associated with the outcomes of this surgical approach were also assessed.

Materials and Methods

After receiving approval from the Research Ethics Committee, the medical records of women with cervical cancer undergoing LRH at Rajavithi Hospital between January 2010 and December 2018 were reviewed. Abstracted data included patients' baseline characteristics, stage of the disease, tumor size, cell types, and survival outcomes.

The cervical cancer was clinically staged according to the International Federation of Gynecology and Obstetrics staging classification⁽⁹⁾. All operations were performed by gynecologic oncologists with in-training fellows as assistants. All patients underwent complete bilateral pelvic lymphadenectomy. The tumor diameter was clinically measured. The deep cervical stromal invasion was defined as invasion of cancer to the outer one-third of the cervical stroma.

Adjuvant treatment was considered if at least one of the following major risk factors for disease recurrence were noted: vaginal margin involvement, parametrial extension, and lymph node metastasis. Adjuvant chemotherapy may be considered in women with neuroendocrine carcinoma of the cervix although there were no major pathological risk factors noted.

Disease-free survival (DFS) was defined as the time between the date of the operation and the date of diagnosis of recurrence. Overall survival (OS) was defined as the time frame between the date of the operation and the date of death from any cause.

Statistical analysis was conducted via STATA (Stata Corporation, College Station, Texas). The demographic characteristics of the patients were summarized as number (percentage) or mean \pm standard deviation (SD) as appropriate. DFS and OS were estimated using the Kaplan-Meier method and differences in survival were compared using the log-rank test.

Results

During the study period, records of 71 women

undergoing LRH as the primary treatment for early-stage cervical cancer were available for review. Four cases were excluded because of conversion to open radical hysterectomy due to bladder injury (1), vascular injury (1), and technical difficulty (2), which left 67 records for analysis.

Baseline characteristics and perioperative outcomes

Table 1 displays patients' baseline characteristics and perioperative outcomes. The median age of the patients was 49 years (interquartile range 41, 56 years). Four patients (6.0%) were nulliparous. Fifty-six patients (83.6%) were diagnosed with stage IB cervical cancer. Forty-two (62.7%) patients had squamous cell carcinoma. Urinary tract injury was noted in two (3.0%) patients.

Table 1. Population characteristics.

Characteristic	N = 67
Parity status	
Nulliparous	4 (6.0%)
Multiparous	63 (94.0%)
Presence of underlying medical comorbidity ⁽¹⁾	33 (49.3%)
History of a previous cesarean section	2 (3.0%)
FIGO stage	
IA	11 (16.4%)
IB	56 (83.6%)
Histology	
Squamous cell carcinoma	42 (62.7%)
Adenocarcinoma	16 (23.9%)
Adenosquamous carcinoma	2 (3.0%)
Others	7 (10.5%)
Operative time (hours), median (IQR)	4.10 (3.40-4.55)
Estimated blood loss (mL), median (IQR)	200 (100-300)
Perioperative complications	
None	61 (91.0%)
Urinary tract infection	3 (4.5%)
Ureteric injury	2 (3.0%)
Urinary retention	1 (1.5%)

IQR: interquartile range; FIGO: International Federation of Gynecology and Obstetrics

¹ including hypertension, diabetes, thyroid function disorder, and dyslipidemia.

Histopathological outcomes

Of 67 LRH specimens, nine (13.4%) and twelve (17.9%) had parametrial invasion and vaginal margin involvement, respectively. Lymphovascular space invasion and deep cervical stromal invasion were noted in 31 (46.3%) and 45 (67.2%) of LRH specimens, respectively. The median number of pelvic lymph nodes yielded per case was 13 (interquartile range 10, 17). Pelvic lymph node metastasis was observed in five (7.5%) patients (Table 2).

Oncological outcomes

Twenty-five (37.3%) patients received adjuvant treatment following LRH. With a median follow-up time of 32.6 months (interquartile range 19.8, 44.8), eight (11.9%) patients experienced recurrent disease including pelvic recurrence (six patients) and combined pelvic and distant recurrences (two patients) (Table 2). The 5-year DFS and OS of the entire cohort were 75.4% and 76.8%, respectively.

Table 2. Histopathological and oncological outcomes.

Oncological outcomes	N = 67
Pelvic lymph node metastasis	5 (7.5%)
Parametrial metastasis	9 (13.4%)
Lymphovascular space invasion	31 (46.3%)
Vaginal margin involvement	12 (17.9%)
Outer one-third of cervical stromal invasion	45 (67.2%)
Type of adjuvant treatment received	
Pelvic radiation	14 (20.9%)
Concurrent chemoradiation	7 (10.5%)
Chemotherapy	4 (6.0%)
None	42 (62.7%)
Recent status	
Alive without disease	59 (88.1%)
Alive with disease recurrence	4 (6.0%)
Death	4 (6.0%)
Recurrence	
None	59 (88.1%)
Pelvic recurrence	6 (9.0%)
Distant recurrence	0 (0.0%)
Combined pelvic/distant recurrences	2 (3.0%)

Fig. 1 and 2 show the DFS stratified by the histological type and size of the tumor. Patients with squamous cell carcinoma had longer DFS than those with other histological types ($p = 0.028$). There was no statistically significant difference in terms of DFS between patients with tumor size ≤ 2 cm and those

who had larger tumors ($p = 0.573$). Patients with squamous cell carcinoma tended to have longer OS than those with other histological types ($p = 0.069$) (Fig. 3). No statistically significant difference in OS was noted when patients were stratified by tumor size ($p = 0.658$) (Fig. 4).

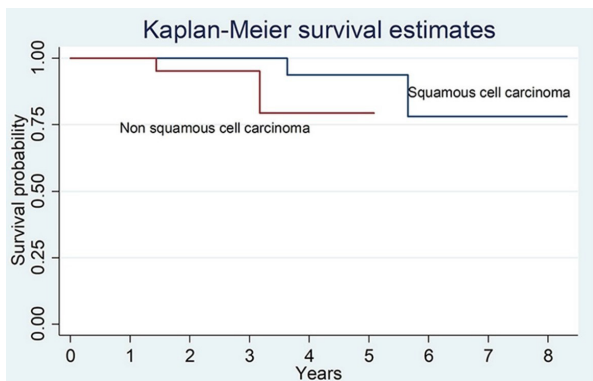


Fig. 1. Disease-free survival stratified by tumor histological type.

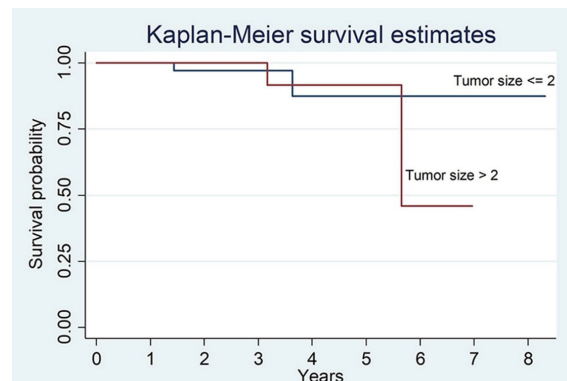


Fig. 2. Disease-free survival stratified by tumor size.

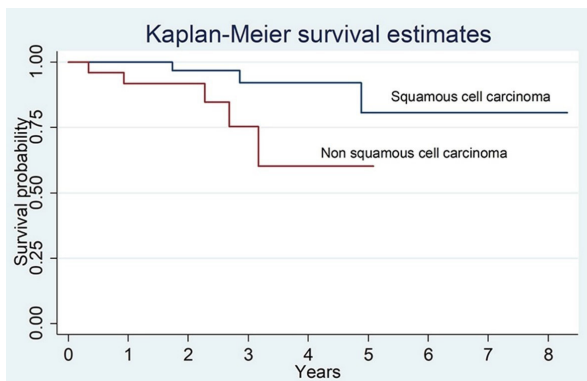


Fig. 3. Overall survival stratified by tumor histological type.

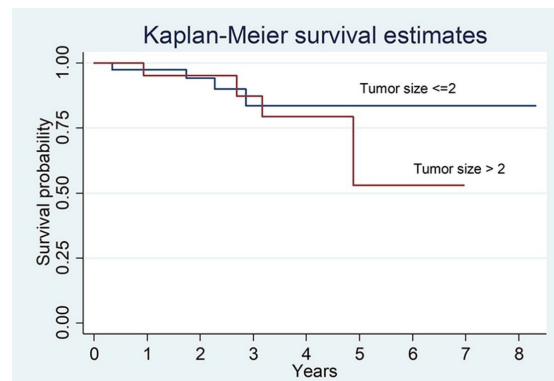


Fig. 4. Overall survival stratified by tumor size.

Discussion

In this study, we reported the survival and prognostic factors of patients with early-stage cervical cancer treated by LRH. Patients' 5-year DFS and OS were 75.4% and 76.8%, respectively. The factor potentially associated with poorer outcome was tumor histological type. To our knowledge, this study is the first to report on LRH in Thailand, regarding survival outcomes.

In this study, the survival of patients with cervical cancer stage IA-IB who were treated with LRH was considerably lower than that of patients who underwent open radical hysterectomy in previously reported findings⁽¹⁰⁻¹²⁾. The 5-year survival rates of women undergoing open radical hysterectomy for

stage Ia2 to IIa cervical cancer are over 80%⁽¹⁰⁻¹²⁾. Mahawerawat et al⁽¹¹⁾ found that the 5-year DFS and OS among women with cervical cancer stage IA2 who were treated with open radical hysterectomy were 97.4% and 97.4%, respectively. Srisomboon, et al⁽¹²⁾ noted that the 5-year DFS of 680 patients with cervical cancer stage IB treated with open radical hysterectomy ranged from 83% to 98% depending on the tumor size. The significant inferiority of the minimally invasive approach for radical hysterectomy has been demonstrated in a recent prospective randomized trial and some large cohort studies⁽⁶⁻⁸⁾.

Determination of the factors affecting treatment outcome among patients undergoing minimally invasive radical hysterectomy may be helpful for

identifying a subset of patients for whom minimally invasive radical hysterectomy remains safe. Ramirez, et al⁽⁶⁾ showed a significantly better survival using open surgery for cervical cancer for large tumors (> 2 cm) compared with minimally invasive radical hysterectomy. In a subgroup analysis of data from the Surveillance, Epidemiology, and End Results study, the impact of surgical approach routes for radical hysterectomy on survival of patients with small tumors was not apparent. For patients with tumors smaller than 2 cm in the greatest dimension, the likelihood of death following minimally invasive radical hysterectomy was comparable with open radical hysterectomy (hazard ratio 1.46, 95% confidence interval 0.70-3.02)⁽⁷⁾. In our study, patients with tumors larger than 2 cm who underwent LRH tended to have shorter survival than those with smaller tumors, although the difference was not statistically significant (Fig. 2 and 4). Additionally, patients with squamous cell carcinoma had longer survival than those with other histological types. The oncological safety following minimally invasive radical hysterectomy in women with small cervical tumors and those who had squamous cell carcinoma histology should be confirmed in a large-scale study.

The dissemination of cancer cells into the peritoneal cavity has been proposed to be a potential reason for the inferior oncologic outcomes after minimally invasive radical hysterectomy⁽⁶⁾. Intervention to limit tumor cell spillage and contamination of the peritoneal cavity during minimally invasive radical hysterectomy may therefore improve treatment outcomes. Recently, Kohler, et al⁽¹³⁾ reported their experience in performing vaginally assisted laparoscopic radical hysterectomy with transvaginal closure of the vaginal cuff to avoid using a manipulator and potentially prevent tumor spillage. The 389 patients who underwent this operation were characterized using the same initial International Federation of Gynecology and Obstetrics stages as Ramirez, et al⁽⁶⁾. Kohler, et al⁽¹³⁾ found that the 3-year OS and DFS of this cohort were equivalent to those of patients who underwent open radical hysterectomy in Ramirez, et al⁽⁶⁾. Vaginally assisted laparoscopic

radical hysterectomy with transvaginal closure of the vaginal cuff seems to be oncologically safe in patients with early cervical cancer and its promising results should be validated in further randomized trials⁽¹³⁾.

Unexpectedly, the rate parametrial involvement (13.4%) in this study was considerably high. Previous conducted in Thailand noted that parametrial involvement in women with early-stage cervical cancer was generally less than 5%⁽¹⁴⁾. This might raise the concern regarding the accuracy of clinical staging in our setting. Additionally, the rate of vaginal margin involvement in this study was 17.9% which was notably high. The high rate of vaginal margin involvement may indicate an inadequate radicality of vaginal excision during our LRH. The high rate of parametrial and vaginal margin involvement therefore may contribute to the high rate of adjuvant treatment given in our study population.

Our study has several drawbacks. First, it contained a relatively small sample size, which could be a factor precluding prognostic significance of the tumor size, as has been noted in previous reports^(11, 12). The relatively small sample size also precluded the ability of this study to determine the associations between the survival outcomes and various clinical factors i.e., patients' age, parity status, and minor pathological factors. The follow-up time in our series was also relatively short, which might influence the assessment of survival outcomes. Finally, the retrospective nature of this study impeded our ability to assess the homogeneous performance of the procedure conducted in our center.

Conclusion

In conclusion, the 5-year DFS and OS of patients undergoing LRH in this study were 75.4% and 76.8%, respectively, which were considerably lower than those previously reported for open radical hysterectomy. Patients with squamous cell carcinoma had longer survival than those with other histological types.

Potential conflicts of interest

The authors declare no conflicts of interest.

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