Research Article

Survival after Minimally Invasive Surgery versus Abdominal Radical Hysterectomy for Early-Stage Cervical Cancer in dr. Cipto Mangunkusumo National Hospital, Jakarta

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Abstract

Cervical cancer is one of the most frequent cancer among women in the world. Indonesian's gynecologic oncologists have started using laparoscopic approach for radical hysterectomy for early stage cervical cancer. There are still limited data and studies reporting survival outcomes after laparoscopic or open abdominal radical hysterectomy, thus we would like to compare the survival outcomes between laparoscopic and open technique of radical hysterectomy in early stage cervical cancer. A retrospective study included 415 early stage cervical cancer was conducted in dr. Cipto Mangunkusumo Hospital. Patient were treated with radical hysterectomy, laparotomy, or laparoscopy, and followed for 3 years period. Survival outcome was reported in univariate and multivariate design, to know the effect of age, parity, tumor size, free margin, and lymph nodal status on overall survival. From 415 patients, 268 patients fulfilled the inclusion criteria. A total of 44 patients underwent laparoscopy radical hysterectomy and 224 to open surgery. Positive resection margins rate for laparoscopic patient was lower than open group (25,9% versus 12.5%). The mean survival of laparoscopic patient was 30 months while open surgery patient was 34 months. The overall 3-year survival rate in open surgery group was 90.2% and 81.8% among those who underwent minimally invasive surgery (hazard ratio 1.7; 95% confidence interval 0.9 to 3.1; p=0.11 by the log-rank test). Laparoscopic approach for radical hysterectomy is a feasible method for early stage cervical cancer other than laparotomy.
Keywords: *cervical cancer, survival rate, radical hysterectomy, laparoscopy, histopathology.*

Sintasan Bedah Invasif Minimal Dibandingkan Radikal Abdominal Histerektomi pada Kanker Serviks Stadium Awal di RSUPN dr. Cipto Mangunkusumo Jakarta

Abstrak

Kanker serviks adalah kanker yang paling sering pada perempuan di dunia. Onkologi ginekologis Indonesia telah menggunakan pendekatan laparoskopi untuk melakukan histerektomi radikal pada kanker serviks stadium awal. Data dan penelitian yang melaporkan hasil sintasan laparoskopi atau radikal abdominal histerektomi, masih terbatas sehingga perlu penelitian untuk membandingkan kesintasan laparoskopi dan radikal abdominal histerektomi pada kanker serviks stadium awal. Studi dilakukan secara retrospektif dengan menginklusi 415 data pasien kanker serviks stadium awal di RSUPN dr. Cipto Mangunkusumo. Pasien ditatalaksana dengan histerektomi radikal, laparotomi atau laparoskopi, dan ditindaklanjuti selama 3 tahun. Kesintasan dilaporkan dalam data univariat dan multivariat, untuk mengetahui hubungan usia, paritas, ukuran tumor, batas tumor, dan status kelenjar getah bening pada seluruh sintasan. Dari 415 pasien, sebanyak 268 pasien memenuhi kriteria inklusi. Sebanyak 44 pasien menjalani laparoskopi histerektomi radikal dan 224 menjalani laparotomi. Angka kejadian batas reseksi positif untuk pasien laparoskopi lebih rendah dari laparotomi (25,9% versus 12,5%). Rerata kesintasan pasien laparoskopi adalah 30 bulan dan laparotomi adalah 34 bulan. Seluruh sintasan pasien laparotomi dalam 3 tahun adalah 90,2%, dan 81,8% pada pasien operasi invasif minimal (hazard ratio 1,7; 95% confidence interval 0,9-31; p=0,11 dengan tes log-rank). Disimpulkan metode laparoskopi untuk histerektomi radikal dapat dikerjakan untuk pasien kanker serviks stadium awal.
Kata kunci: *Kanker serviks, sintasan, histerektomi radikal, laparoskopi, histopatologi.*

Introduction

Cervical cancer accounts for 569.847 new cases and 311.365 death worldwide.[1] In Indonesia, cervical cancer is regarded as the second most common malignancy causing cancer-related death among women. Cervical cancer contributes 17.2% of all cancer in female and the mortality rate is 8.8% of all cancer.[2] The principal management of early stage cervical cancer is surgery or radiotherapy. Surgery procedure included radical hysterectomy and lymphadenectomy.[3,4] The surgery procedure is preferably because radiotherapy can lead permanently damage normal cells. Futhermore, young patients ovaries and vagina need to be maintained related to sexual function.

Various centers have been performed radical hysterectomies with laparoscopic, combined laparoscopic, vaginal, and robotic-assisted approach.[5] In Indonesia, especially in our center, laparoscopic radical hysterectomy is emerging recently since 2012. This new developing method need emphasis for surgeon experience time which affect to radicality, number of lymph node extraction, and survival rate.

Compared with the open technique, the most evident advantages of the laparoscopic surgery are lesser blood loss, faster recovery, reduced hospital stay, quicker return to normal activities and better cosmetic, but the surgeon need some special trainings related to surgical procedure. We need a number in the learning curve to become master of surgery in laparoscopic radical hysterectomy. The biggest issue is still about its effectiveness with respect to tumor clearance, recurrence rates, complication, short, and long-term outcomes.[6]

In 2017, Laparoscopic Approach to Cervical Cancer (LACC) study showed laparoscopy radical hysterectomy was inferior to open surgery.[7] Thus, we would like to evaluate the survival outcomes between laparoscopic and open technique of radical hysterectomy in early stage cervical cancer.

Methods

This is a retrospective cohort study and data was gathered from medical record of dr. Cipto Mangunkusumo National Hospital. Patients who received diagnosis of early stage cervical cancer from 1 January 2012 until 31 December 2016 were enrolled. Surgical staging and grading follows The International Federation of Gynecology and Obstetrics (FIGO) standards. Patients were included if they had cervical cancer FIGO stage IA1 to IIA and patient undergone laparoscopic radical hysterectomy or open radical hysterectomy. The exclusion criteria was patient without histopathological result and received radiation or neoadjuvant chemotherapy before radical hysterectomy.

For statistical analysis, variables regarding patient characteristics were recorded in the following manner: 1. age, less than 50 years old or more than equal 50 years old; 2. parity; 3. clinical stage; 4. tumor size; 5. histopathological type; 6. cell differentiation; 7. lymph node metastasis; 8. deep stromal invasion; 9. parametrial involvement; 10. Lymphovascular Space Invasion (LVSI); 11. myometrial invasion; and 12. pelvic number examined.

We only analyze survival rate up to 3 years due loss to follow up patients up to 81% in 5 years, which may lead to invalid findings in analyses. Patient was followed by search medical record 3 years after the procedure data and phone call if patient not have follow up data after 3 years from the surgery. Data were analyzed using SPSS 20. Incomplete data were included and analyzed with multiple imputation technique. Kaplan Meier test was used to plot survival curves and included the log-rank test. The cox proportional hazards regression model was used for univariate and multivariate analysis. Differences were considered significant at $p< 0.05$. This study was approved by ethical committee of dr. Cipto Mangunkusumo National Hospital.

Results

We collected 415 early stage cervical cancer patients on January 2012 to December 2016. A total of 268 patients met the study criteria. Patients were followed up until the event (death) or survive for minimal three years or being lost to follow up. From complete set medical records, 44 patients undergo laparoscopy radical hysterectomy, and 224 to open surgery. Table 1 shows the majority of patients were <50 years old (57.6%), multipara (76.8%), stage IB1 (36.2%), and squamous cell carcinoma histotype (60.8%)

Table 1. Patient Characteristics Underwent Open Surgery and MIS

Characteristics of The Subjects	Open Surgery n=224 (%)	MIS n=44 (%)	p-value
Age			
<50	129 (57.6)	21 (47.7)	0.228
≥50	95 (42.4)	23 (52.3)	
Parity			
Nulliparity	30 (13.4)	9 (20.5)	0.298
Primiparity	22 (9.8)	2 (4.5)	
Multiparity	172 (76.8)	33 (75)	
FIGO Stage			
IA1	1 (0.4)	0 (0)	0.273
IA2	2 (0.9)	0 (0)	
IB1	81 (36.2)	23 (52.3)	
IB2	69 (30.8)	8 (18.2)	
IIA1	71 (31.7)	13 (29.5)	
Tumor size			
≤4 cm	112 (53.1)	29 (67.4)	0.084
>4 cm	99 (46.9)	14 (32.6)	
Histotype			
SCC	121 (60.8)	24 (61.5)	0.759
Adenocarcinoma	57 (28.6)	11 (28.2)	
Adenosquamous	16 (8)	4 (10.3)	
Others	5 (2.6)	0 (0)	
Degree of differentiation			
Grade I	70 (35)	11 (26.2)	0.390
Grade II	96 (48)	25 (59.5)	
Grade III	34 (17)	6 (14.3)	
Resection margin involvement			
Positive	28 (25.9)	3 (12.5)	0.160
Negative	80 (74.1)	21 (87.5)	
LVSI			
Yes	47 (22)	9 (20.4)	0.814
No	166 (78)	35 (79.6)	
Parametrial involvement			
Yes	13 (17.8)	6 (33.3)	0.194
No	60 (82.2)	12(66,7)	
Free margin			
≤5 mm	17 (15.6)	3 (12.5)	0.999
>5 mm	92 (84.4)	21 (87.5)	
Deep stromal invasion			
<2/3 parts	16 (36.4)	7 (46.7)	0.547
≥2/3 parts	28 (63.6)	8 (53.3)	
Myometrial invasion			
Yes	30 (38.4)	3 (9.1)	*0.048
No	48 (61.6)	17 (90.9)	
Pelvic lymph node number examined	112 (50)	25 (59)	0.07
Examined	112 (50)	18 (41)	
Not examined			
Pelvic lymph node number status			
Positive	5 (4.5)	1(3.9)	0.14
Negative	107 (95.5)	25 (96.1)	

MIS: minimally invasive surgery

There are no significant difference in several characteristics between two groups, such as histologic type, tumor grade, tumor size, lymphovascular invasion, parametrial involvement, and ≥2/3 deep stromal invasion, surgical margin, and positive surgical margin. The only significant difference was a higher rate finding of cancer invasion to myometrium in open surgery compared to laparoscopic surgery (38.4% and 9.1%, p<0.05). The proportion of patients underwent pelvic lymph node sampling was significantly higher in the laparoscopic than in the open surgery group (59%

versus 50%, p=0.07). The positive lymph nodes retrieved was similar in the laparoscopic surgery and open surgery group (4.5 versus 3.9, p=0.14).

Median overall survival rate of laparoscopic patient was 30 months compared with open surgery patient was 34 months. The overall 3-year survival rates for laparoscopy radical hysterectomy and open surgery group were 81.8% and 90.2%, respectively (Table 2). Women who underwent laparoscopy radical hysterectomy had shorter overall survival than patient underwent open surgery (hazard ratio, 1.7; 95% CI, 0.87-3.11; p=0.11 by the log-rank test). Log rank analysis with chi square analysis reported factors which significantly associated with patient's survival were myometrial invasion, the number of pelvic nodes examined, and positive lymph node yield rate.

Table 2. Survival Rate of Cervical Cancer Patients Based on Characteristics of the Subjects

Characteristics	Survival Rate After Diagnosis* 3 years	Unadjusted HR (95% CI)	p-value+
Surgery			
Open surgery	90.2	1.7 (0.87-3.11)	0.11
Minimally invasive surgery	81.8		
Age			
<50	90.8	1.1 (0.68-1.66)	0.80
≥50	90.4		
Parity			
Primipara	89.6	1.6 (0.51-4.91)	0.48
Nullipara	85.7		
Multipara	91.3		
Figo Stage (early stage)			
Stage 1	90.4	1.2 (0.78-1.98)	0.30
Stage 2	91.1		
Tumor size			
≤4cm	88.6	0.7 (0.45-1.22)	0.23
>4cm	92.5		
Histotype			
SCC	90.8		0.09
Adenocarcinoma	86.7	1.4 (0.83-2.38)	
Adenosquamous	100.0		
LVSI			
Absent	88.9	1.0 (0.48-1.87)	0.89
Present	92.6		
Degree of differentiation			
Grade 1	91.7	1.7 (0.98-2.97)	0.08
Grade 2	87.0		
Grade 3	93.3		
Free margin			
Free tumor	90.6	0.04 (<0.01-6.70)	0.06
Present tumor	85.3		
Deep stromal			
Absent	88.9	0.9 (0.38-2.17)	0.83
Present invasion	92.6		
Myometrial invasion			
Absent	84.8	0.9 (0.36-2.02)	0.72
Present invasion	84.8		
Pelvic number examined			
≤ 16 nodes	92.6	2.5 (1.20-5.38)	0.01
>16 nodes	80.6		
Pelvic number Positive			
Negative	93.9	0.4 (0.14-1.03)	0.04
Any Positive	83.2		

*Data are %; +log rank test

Cox multivariate model showed the significant factor were the number of pelvic nodes examined (HR 2.4, p-value<0.01) and positive lymph node yield rate (HR 0.5, p-value 0.01) (Table 3).

Table 3. Adjusted Hazard Ratio of Cervical Cancer Patient Based on Characteristics

Characteristics	Adjusted HR	95% CI HR	p-value
Surgery	1.6	1.20 – 2.18	0.44
Age	0.8	0.66 – 1.10	0.30
Parity	1.1	0.90 – 1.41	0.29
FIGO stage	0.9	0.66 – 1.22	0.50
Tumor size	0.9	0.67 – 1.14	0.33
Histology	1.3	0.85 – 2.1	0.19
LVSI	0.8	0,56 – 1.09	0.42
Differentiation	1.03	0.82 – 1.3	0.44
Free margin	0.8	0.05 – 0.33	0.9
Resection margin involvement	0.6	0.31 – 1.27	0.95
Deep stromal	0.6	0.31 – 0.98	0.19
Myometrial invasion	1.6	0.48 – 5.5	0.44
Pelvic number examined	2.4	1.77 – 3.42	<0.01
Pelvic number Positive	0.5	0.38 – 0.88	0.01

`*cox's proportional hazard

Discussion

Cervical cancer is the second most common cancer in women. The surgery approach for treatment of early stage cervical cancer are open radical hysterectomy or minimally invasive radical hysterectomy. In this retrospective study, patients underwent laparoscopic radical hysterectomy had lower rates of overall survival than patients underwent open abdominal radical hysterectomy, however the result is not statistically significant (log rank test, p-value=0.11). The two methods yielded similar overall survival. Although survival curve did not significant, survival discrepancy was very important for clinical corrrelation. This discrepancy caused by the routine use of uterine manipulator in laparoscopic surgery, which makes the estimation of adequate vaginal resection difficult, and might increase the propensity for tumor spillage, that could cause microscopic metastasis to parametrium (parametrial involvement) which cannot be detected clinically, especially when the vagina is opened and the tumor surface is exposed to circulating CO_2. Furthermore, lack of number of laparoscopic surgery should be improve until learning curves are achieved for surgeons who do laparoscopy radical hysterectomy to be more proficient in laparoscopic surgery.

This study is related to LACC study, despite our result is different.[7,8] Our study is simillar with other reports in the literature that found laparoscopic radical hysterectomy is not associated with better prognostic outcome compared with the open approach.[5,6,9]

Important aspects to evaluate in laparoscopic approach, which equivalent with the standard of care, should consider the applicability, feasibility, and cost effectiveness of the technique, perioperative complications, and the survival.[5,6,9-11]

In this study, laparoscopic radical hysterectomy had significant advantages over open surgery, including lower rate of closed surgical margins and positive surgical margins. When the surgical margins is positive, it increase the risk cancer recurrence.

The data showed that patients treated with laparoscopic surgery had higher rate number of lymph nodes dissection than open surgery. The advantage of minimally invasive is visual magnification thus the surgeon could observe the lymph node precisely. When these factors is present, such as positive surgical resection margins, lymph node metastasis, and also parametrial extension, adjuvant therapy has been conclusively proven to provide better overall survival.[13] The laparoscopic surgery had similar outcome with the open surgery. These findings showed us that laparoscopic surgery is a safe alternative for open surgery.

The primary limitation of this study is a retrospective study, single-center and non-randomized study because lack of patient's follow up. The high numbers of patients lost to follow-up may lead to bias in understanding the survival. This condition is one of problems that we encounter in cancer management at our center. Factors, that we face were the patients' address was change because they lived in a rent house, the patient's address is not in Jakarta, and non-active phone number. This poor follow up also affected survival analysis of this study.

Laparoscopic surgeon's skill is also confounding factor that affect the result. Moreover there are factors that affected survival rate especially in high risk group. For instance, parametrium involvement, and lymph nodes metastasis which should be followed by adjuvant radiation therapy. Minimally invasive is still new in Indonesia, so there is only few case occurred. This is the first study in our institution that reported cervical cancer survival after minimally invasive versus open surgery.

Conclusion

Laparoscopic approach for radical hysterectomy is applicable, feasible, and safe method for early stage cervical cancer other than laparotomy. This study was evidently supported that lymph nodes yield, positive resection margins, and 3-year overall survival by the two surgical techniques were similar. Lower survival in laparoscopic related to the lack of the number of laparoscopic surgery, should be improved until achieve learning curves for laproscopy radical hysterectomy to become a master in laparoscopic. Prospective RCTs is needed to evaluate long-term survival outcomes, oncologic outcome, and quality of life.

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