Abstract

**IMPORTANCE**  The role of surgery in early-stage cervical cancer has been established, but it is controversial in locally advanced cervical cancer.

**OBJECTIVE**  To determine whether a radical hysterectomy method with extended removal of paracervical tissue for locally advanced cervical cancer is associated with satisfactory oncological outcomes.

**DESIGN, SETTING, AND PARTICIPANTS**  This retrospective cohort study was conducted from January 1, 2002, to December 31, 2011, and participants were patients with cervical cancer at a single tertiary center in Northern Japan. The median follow-up period was 106 months, and none of the patients were lost to follow-up at less than 60 months. Data analyses were performed from July 1, 2017, to December 31, 2018.

**EXPOSURES**  Patients underwent radical hysterectomy using the Okabayashi-Kobayashi method. Bilateral nerve preservation was used for stage IB1/IB2 disease and unilateral nerve preservation for stage IIA/IIB if disease extension outside the uterine cervix was 1-sided. Chemotherapy was used as the choice of adjuvant treatment for patients with an intermediate or high risk of recurrence, while some patients chose or were assigned to radiotherapy.

**MAIN OUTCOMES AND MEASURES**  Primary outcomes were the 5-year local control rate and 5-year overall survival rate along with risk factor analysis.

**RESULTS**  Of 121 consecutive patients, 76 (62.8%) had early-stage cervical cancer in 2008 International Federation of Gynecology and Obstetrics stages IB1 and IIA1 and 45 (37.2%) had locally advanced cervical cancer in stages IB2, IIA2, and IIB. The median (range) age was 42 (26-68) years. Adjuvant radiotherapy was used in 2 patients (3%) with early-stage cervical cancer and 3 (7%) of those with locally advanced cervical cancer. The 5-year local control rates for early-stage cervical cancer and locally advanced cervical cancer were 99% and 87%, respectively. The 5-year overall survival rates for early-stage cervical cancer and locally advanced cervical cancer were 95% and 82%, respectively. Cox regression analysis showed that lymph node metastasis and histology of adeno(squamous)carcinoma were independent risk factors for the overall survival of patients with cervical cancer treated with radical hysterectomy.

**CONCLUSIONS AND RELEVANCE**  The nerve-sparing Okabayashi-Kobayashi radical hysterectomy for locally advanced cervical cancer may provide survival not inferior to radical hysterectomy or radiotherapy in published literature. The applicability of radical hysterectomy with adjuvant chemotherapy may be a treatment option for locally advanced cervical cancer besides radiotherapy/chemoradiotherapy.

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chemotherapy for locally advanced cervical cancer needs to be validated by prospective comparative trials.

Introduction

Cervical cancer is the fourth most common type of malignant neoplasm in women. The peak incidence of cervical cancer occurs in the age group of the 30s to 40s in many countries. Surgery has advantages over radiotherapy because the long-term intractable complications of radiation therapy can be avoided, and ovarian and sexual function in younger patients can be maintained. Radical hysterectomy has been evolving over 100 years since the first description of extended abdominal hysterectomy by Wertheim in 1912. The Wertheim operation was modified later worldwide. The Meigs operation is commonly used in Western countries, and the Okabayashi operation is used in Japan and some areas of Asian countries. The Kobayashi method preserves the pelvic splanchnic nerves and the inferior hypogastric plexus (modified Okabayashi radical hysterectomy). The systematic nerve-sparing procedure opens the tissue plane between the parametrium/paracolpium and the pelvic nerve structures.

Nerve-sparing radical hysterectomy is currently a standard treatment for early-stage cervical cancer (ESCC), which provides for nonbulky (≤4 cm in diameter) stage IB1 and IIA1. Locally advanced cervical cancer (LACC) traditionally included stage IIB to stage IVA. Many oncologists now include stages IB2 and IIA2 disease in this category. LACC may be divided into stages IB2 to IIB and stages III to IVA. A clear statement about the stages that LACC indicates is necessary. Stage IB2, IIA2, and IIB disease, which are relatively earlier stages in LACC, may be treated with multidisciplinary therapy, including surgery, chemotherapy, and radiotherapy, and these stages may be defined as early locally advanced disease. The term LACC, which is discussed in this article, denotes stage IB2/IIA2/IIB cervical cancer. Little is known about the oncologic validity of nerve-sparing radical hysterectomy in LACC. There are 3 options for treatment of LACC, including concurrent chemoradiotherapy, neoadjuvant chemotherapy followed by surgery, and upfront surgery with or without adjuvant therapy. Concurrent chemoradiotherapy is the treatment of choice for LACC in the National Comprehensive Cancer Network Clinical Practice Guidelines. In Japan, not only ESCC, but also LACC are treated with radical hysterectomy. Additionally, radical hysterectomy was used in 46.6% of stage II (substage included 15% of IIA1 and 85% of IIA2 and IIB) cervical cancer in 2015. The rate of upfront surgery with or without adjuvant therapy for LACC increased from 22.6% to 31.2% in the United States from 2004 to 2012. The accordance of preoperative diagnosis of parametrial invasion with pathologically confirmed parametrial invasion is as low as 21% to 55%, and some authors have discussed the role of surgery for LACC from the difficulty in the preoperative diagnosis of stage IIB. Nerve-sparing radical hysterectomy can be used for the side that is free of tumor invasion in stage II cervical cancer to the extent that it does not decrease the curability of radical hysterectomy. The current study aimed to determine whether Okabayashi-Kobayashi radical hysterectomy is a useful option for LACC by investigating the patterns of recurrence and long-term survival.

Methods

Patients

We included consecutive patients with 2008 International Federation of Gynecology and Obstetrics (FIGO) stages IB1 to IIB cervical cancer who underwent Okabayashi-Kobayashi radical hysterectomy from January 1, 2002, to December 31, 2011, at Hokkaido University Hospital in...
Sapporo, Japan. This hospital is a tertiary care center in the central Hokkaido area in Northern Japan, and most of the patients were referred to the hospital from primary care obstetricians and gynecologists and the regional cervical cancer screening center (Hokkaido Cancer Society). There was no selection of patients who may have been more likely to respond to surgery and adjuvant chemotherapy. Anonymized clinical information with the type of treatment and the survival outcomes was registered to the gynecologic cancer registry in Japan Society of Obstetrics and Gynecology.

Patients were followed up every 3 months for the first 3 years, every 6 months in years 4 to 5, and at 12-month intervals after this time. We used chest x-rays and either computed tomography, magnetic resonance imaging, or positron emission tomography scan once a year and at any suspicion of recurrence by bimanual examination, symptoms, and an increase in serum tumor marker that was elevated preoperatively.

Data cleaning and analyses were performed from July 1, 2017, to December 31, 2018. This study was approved by the local ethics committee (institutional review board) of Hokkaido University Hospital, and written informed consent was waived because of the retrospective design. We used the opt-out method on the hospital’s website for obtaining consent. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline was followed.

Patient Characteristics

Pathological risk factors were collected and include age, 2008 FIGO stage, histology (squamous cell carcinoma, adenocarcinoma, adenocarcinoma), pT classification (tumor pathologically confined to the cervix: pT1a1 and pT1b2; tumor extended outside the cervix: pT2a1, pT2a2, and pT2b), lymph node metastasis (no, yes), lymphovascular space invasion (no, yes), recurrence risk (low, intermediate, high), postoperative adjuvant therapy (no; yes: chemotherapy, radiotherapy), and recurrence (no; yes: local, regional, and distant). The American Joint Committee on Cancer/International Union Against Cancer TNM staging system was used to describe the extent of cervical cancer. TNM incorporates T (size and extent of the tumor), N (involvement of the regional lymph node), and M (metastasis), which may be determined preoperatively (cTNM or TNM) and postsurgical histologically (pTNM). pT stands for pathologically defined local tumor status. FIGO stages were grouped into the early stage (stage IB1 and IIA1) and locally advanced stage (stage IB2, IIA2, and IIB) for recurrence and survival analyses.

Nerve-Sparing Radical Hysterectomy

We used systematic nerve-sparing Okabayashi-Kobayashi radical hysterectomy as reported elsewhere. We used bilateral nerve preservation for stage IB1/IB2 disease and unilateral nerve preservation for stage IIA/IIB if disease extension outside the uterine cervix was 1-sided. We did not offer radical hysterectomy to patients with stage IIA/IIB disease with bilateral extension of the tumor.

Postoperative Adjuvant Therapy

We used postoperative adjuvant treatment according to the recurrence risk after surgery. Intermediate risk was defined as a large tumor size (>4 cm), deep cervical invasion (>2/3), and lymphovascular space invasion. High risk was defined as lymph node metastasis, pathological parametrial invasion, and a positive/close surgical margin. The choice of adjuvant therapy was chemotherapy consisting of paclitaxel and cisplatinum every 3 weeks for 4 to 6 courses.

Statistical Analysis

The primary outcome measure was the 5-year local control rate and 5-year overall survival. Overall survival included death from any cause. Disease-specific survival included death from cervical cancer. Patients known to be alive or lost to follow-up (the patient was unreachable, and her survival outcome was unknown) at the time of analysis were censored at their last follow-up. The follow-up period was defined as the time from surgery until recurrence or death and the time from surgery until...
Recurrence was defined as relapse of tumor after completion of the primary treatment. The site of the recurrence was categorized into local (relapse in the vaginal stump or paravaginal area), regional (relapse in pelvic lymph nodes), and distant (relapse in the area outside the pelvis including paraaortic lymph nodes, distant organs, and peritoneal cavity). Disease-free survival (DFS) was defined as the time from surgery to recurrence.

Five-year local control rate was defined as the rate of patients without local recurrence at 5 years after surgery. We used Fisher exact test to examine the association between the site-specific recurrence and clinical/pathological variables. Competing risks are events that preclude the occurrence of the event in concern or alter the probability of its occurrence. Regional recurrence, distant recurrence, and death from other causes were considered to be competing risks for local recurrence. We used Gray method to obtain the first event-specific cumulative incidence curves for local recurrences according to FIGO stage (ESCC vs LACC). We used the Fine-Gray proportional subdistribution hazards regression to evaluate the association of clinical/pathological variables with the cumulative incidence of local recurrence.

Survival curves were calculated by the Kaplan-Meier method and compared by the log-rank test. We used Cox regression analysis to evaluate the association of clinical/pathological variables with survival. It is generally assumed that 10 outcome events per independent variable are necessary in Cox regression analysis. We performed a univariable Cox regression analysis for overall survival and then obtained a 2-variable regression model based on the number of events we observed.

These statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R software, version 3.6.1 (R Foundation for Statistical Computing). P values were 2-sided, and the significance level was set at P < .05.

Results

The clinical characteristics of 121 patients are provided in Table 1, and pathological risk factors are provided in Table 2. The median (range) age for patients was 42 (26-68) years; 50 patients (42%) were younger than 40 years, 36 (30%) were aged 40 to 49 years, and 35 (29%) were older than 49 years. Overall, 76 patients (63%) were at early stage, and 45 (37%) were at locally advanced stage. The recurrence risk was low (45 [37%]), intermediate (43 [36%]), and high (33 [27%]). Among 76 patients with intermediate or high risk for recurrence, 68 patients (89.4%) received adjuvant therapy, of whom 63 received chemotherapy, and 5 underwent radiotherapy. The use of adjuvant chemotherapy in ESCC and LACC was 34% (n = 26) and 82% (n = 37), respectively. The use of adjuvant radiotherapy in ESCC and LACC was 3% (n = 2) and 7% (n = 3), respectively. Among 33 patients with a high risk of recurrence, 8 patients were at extremely high risk (≥5 positive nodes with pathological parametrial invasion). Three of these patients received radiotherapy, and the remaining 5 received chemotherapy.

The median (interquartile range) follow-up period was 106 (70.5-125) months (range, 6-203 months). All survival information was available for all 121 patients for more than 60 months after surgery. No patients were lost to follow-up or censored before 60 months. Fifteen patients (12.4%) died of cervical cancer during 60 months of follow-up, 1 patient (0.8%) died of cervical cancer at 104 months after surgery. One patient (0.8%) died of intercurrent disease at 105 months after surgery, and no patient died of any other causes.

We observed 18 cases of recurrence (15%). Fifteen of 18 cases (83%) occurred within 3 years from surgery, and the remaining 3 (17%) occurred more than 3 years after surgery. The median (range) recurrence-free interval of time from surgery until the diagnosis of local, regional, and distant recurrence was 13 (3-32), 12.5 (3-52), and 20 (3-52) months, respectively. The site-specific recurrence risk for local (n = 7), regional (n = 6), and distant (n = 11) is provided in Table 2, which suggested a different pattern of association between clinical/pathological risk factors and the site-specific
recurrence. FIGO stage, pT classification, lymph node metastasis, and lymphovascular space invasion were associated with local recurrence, but histology was not. The association between local recurrence and the factors of pT classification, lymph node metastasis, and lymphovascular space invasion showed complete separation, which may suggest a limitation of the analysis owing to small numbers studied. The association of clinical/pathological risk factors and local recurrence as the first recurrence is provided in Table 3. We observed 1 local recurrence in 72 stage IB1 tumors. None of the stage IB2 and IIA1 tumors were associated with local recurrence, while IIA2 (2 of 5 [40%]) and IIB (4 of 27 [14.8%]) tumors were associated with a high local recurrence rate. Four patients (2 of

| Table 1. Clinical and Demographic Features of Patients With Cervical Cancer Treated With Nerve-Sparing Kobayashi (Modified Okabayashi) Radical Hysterectomy |
|---------------------------------|-----------------|
| **Characteristic**              | **Patients, No. (%)** |
| Total, No.                      | 121             |
| Age, y                          |                 |
| Median (range)                  | 43.0 (28-68)    |
| <40                             | 50 (42)         |
| 40-49                           | 36 (30)         |
| >49                             | 35 (29)         |
| 2008 FIGO stage                 |                 |
| Early stage                     | 76 (63)         |
| IB1                             | 72 (60)         |
| IIA1                            | 4 (3)           |
| Locally advanced stage          | 45 (37)         |
| IB2                             | 13 (11)         |
| IIA2                            | 5 (4)           |
| IIB                             | 27 (22)         |
| pT classification               |                 |
| pT1                             | 91 (75)         |
| pT1b1                           | 74 (61)         |
| pT1b2                           | 17 (14)         |
| pT2                             | 30 (25)         |
| pT2a1                           | 10 (8)          |
| pT2a2                           | 7 (6)           |
| pT2b                            | 13 (11)         |
| Recurrent risk                  |                 |
| Low                             | 45 (37)         |
| Intermediate                    | 43 (36)         |
| High                            | 33 (27)         |
| Postoperative adjuvant therapy  |                 |
| None                            | 53 (44)         |
| Chemotherapy                    | 63 (52)         |
| Radiotherapy                    | 5 (4)           |
| Recurrence                      |                 |
| No                              | 103 (85)        |
| Yes                             | 18 (15)         |
| Site of first recurrence        |                 |
| Local only                      | 6               |
| Regional only                   | 1               |
| Distant only                    | 5               |
| Local and regional              | 0               |
| Local and distant               | 1               |
| Regional and distant            | 5               |

Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.
pT2aIN1M0 and 2 of pT2bN1M0) showed local recurrence in the paracolpium on the same side as the nerve-sparing procedure. The 5-year local control rate for ESCC and LACC was 99% (75 of 76) and 87% (39 of 45), respectively (P = .01). The hazard ratio for cumulative local recurrence rate between early and locally advanced disease was 11.2 (95% CI, 1.3-96.0; P = .03; Figure, A).

The cumulative DFS is provided in the Figure, B. The 5-year DFS for all stages combined was 85% (n = 121). The 5-year DFS rate as obtained by the number of patients without recurrence divided by the number of total patients at 60 months after surgery for ESCC and LACC was 71% (n = 76) and 71% (n = 45), respectively (hazard ratio, 5.0; 95% CI, 1.8-14.1; P < .001).

We observed 16 deaths (13%). The cumulative overall survival is provided in the Figure, C. The 5-year overall survival for all stages combined was 90% (n = 121). The 5-year overall survival rate as obtained by the number of patients alive divided by the total patients at 60 months after surgery for early and locally advanced disease was 99% (P = .01).

### Table 2. Clinical and Pathological Factors and the Site-Specific Recurrence After Nerve-Sparing Radical Hysterectomy (N = 121)*

| Clinical and pathological factor | No. (%) | Site-specific recurrence risk | No. (%) | Site-specific recurrence risk |
|---------------------------------|---------|-------------------------------|---------|-------------------------------|
|                                 |         | Local (n = 7)                 | Regional (n = 6) | Distant (n = 11) |
|                                 |         | P value                       | No. (%) | P value                       | No. (%) | P value |
| 2008 FIGO stage                 |         |                               |         |                               |         |
| Early                           | 76 (63) | 1 (1)                         | 3 (4)   | 4 (5)                         |
| Locally advanced                | 45 (37) | 6 (13)                        | 3 (7)   | 7 (16)                        |
| Histology                       |         |                               |         |                               |         |
| Squamous cell carcinoma         | 79 (65) | 3 (4)                         | 3 (4)   | 5 (6)                         |
| Adeno(squamous)carcinoma        | 42 (35) | 4 (10)                        | 3 (7)   | 6 (14)                        |
| pT classification              |         |                               |         |                               |         |
| pT1b                            | 91 (75) | 0                             | 2 (2)   | 6 (7)                         |
| pT2                             | 30 (25) | 7 (23)                        | 4 (13)  | 5 (17)                        |
| Lymph node metastasis           |         |                               |         |                               |         |
| Negative                        | 88 (73) | 0                             | 3 (3)   | 5 (6)                         |
| Positive                        | 33 (27) | 7 (21)                        | 3 (9)   | 6 (18)                        |
| Lymphovascular space invasion   |         |                               |         |                               |         |
| Negative                        | 67 (55) | 0                             | 4 (6)   | 5 (9)                         |
| Positive                        | 54 (45) | 7 (13)                        | 2 (4)   | 5 (9)                         |

Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.

* Fisher exact test was used to examine the association between the site-specific recurrence and clinical/pathological variables.

### Table 3. Evaluation of the Association of Clinical and Pathological Factors With Cumulative Incidence of Local Recurrence After Nerve-Sparing Radical Hysterectomy*

| Clinical and pathological factor | No. (%) | Local recurrence risk | P value |
|---------------------------------|---------|-----------------------|---------|
| 2008 FIGO stage                 |         | Incidence             | Hazard ratio (95% CI) | |
| Early                           | 76 (63) | 1                      | 11.5 (1.3-96.0)       | <.001 |
| Locally advanced                | 45 (37) | 6                      | 3.8 (1.3-96.0)        | <.001 |
| Histology                       |         |                       |                     |      |
| Squamous cell carcinoma         | 79 (65) | 3                      | 1                    | NA    |
| Adeno(squamous)carcinoma        | 42 (35) | 4                      | 2.7 (0.6-11.8)        | .19   |
| pT classification              |         |                       |                     |      |
| pT1b                            | 91 (75) | 0                      | 1                    | NA    |
| pT2                             | 30 (25) | 7                      | 999 500 (467 500-2 137 000) | <.001 |
| Lymph node metastasis           |         |                       |                     |      |
| Negative                        | 88 (73) | 0                      | 1                    | NA    |
| Positive                        | 33 (27) | 7                      | 539 000 (251 900-1 153 000) | <.001 |
| Lymphovascular space invasion   |         |                       |                     |      |
| Negative                        | 67 (55) | 0                      | 1                    | NA    |
| Positive                        | 54 (45) | 7                      | 100 200 (46 260-217 200) | <.001 |

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; NA, not applicable.

* The Fine-Gray proportional subdistribution hazards regression was used for the analysis.
ESCC and LACC was 72 of 76 (95%) and 37 of 45 (82%), respectively (hazard ratio, 5.4; 95% CI, 1.7-16.8; P = .001). The stage-specific 5-year overall survival for stage IB1, IB2, IIA, and IIB was 96% (95% CI, 88%-99%), 92% (95% CI, 57%-99%), 78% (95% CI, 37%-94%), and 78% (95% CI, 57%-89%), respectively. There was 1 patient with stage IB2 disease who died of intercurrent disease (primary lung cancer) at 105 months after surgery, and the 5-year disease-specific survival was the same as the 5-year overall survival. Univariable Cox regression analysis showed several risk factors associated with the death of patients. We had 16 death events, and we obtained a 2-variable regression model that included lymph node metastasis and histology (Table 4).

Discussion

We observed that Okabayashi-Kobayashi radical hysterectomy with adjuvant chemotherapy resulted in very good survival outcomes for ESCC (stage IB, ≤4 cm; stage IIA, ≤4 cm) and even in LACC (stage IB, >4 cm; stage IIA, >4 cm; stage IIB). Although the number of patients was limited, our study suggested favorable survival outcomes for stage IB2 disease treated with radical hysterectomy compared with published literature. Our finding supports the statement in the National Comprehensive Cancer Network Guidelines, in which type C1 (Querleu-Morrow) nerve-sparing radical hysterectomy is indicated for the new 2018 FIGO stages IB1 (<2 cm) to IB2 (2-4 cm) and...
selected stages IB3 (>4 cm) and IIA1. The 2018 FIGO stage IB3 (>4 cm) corresponds with the 2008 FIGO stage IB2 (>4 cm) without lymph node metastasis.35 Previous reports showed that the 5-year overall survival for stage IB2 disease treated with radical hysterectomy was 72% to 72.8%.36,37 Cost-effectiveness analysis for treatment of stage IB2 cervical cancer showed that upfront radical hysterectomy was the most cost-effective strategy compared with primary chemoradiotherapy or neoadjuvant chemotherapy followed by radical hysterectomy and adjuvant chemoradiotherapy.38 Our study suggested that Okabayashi-Kobayashi radical hysterectomy is applicable for this group of patients. A recent randomized clinical trial (EORTC 55994) for stage IB2-IIIB cervical cancer showed equivalent overall survival for neoadjuvant chemotherapy followed by radical hysterectomy (72%; 95% CI, 66%-77%) and concurrent chemoradiotherapy (76%; 95% CI, 70%-80%) (P = .25). Additionally, a subgroup of patients with stage IB2 treated with neoadjuvant chemotherapy followed by radical hysterectomy showed a trend for better results compared with concurrent chemoradiotherapy.39

Our results showed that pathological vaginal and parametrial invasion and lymph node metastasis were closely associated with local recurrence after nerve-sparing radical hysterectomy. In a 1978 article,40 stage IIA disease had microscopic parametrial involvement at a risk higher than or equivalent to stage IIIB disease. Perineural invasion is associated with deep cervical stromal, vaginal, and parametrial invasion.41,42 Magnetic resonance imaging findings of disruption of the cervical stromal ring are associated with microscopic parametrial invasion,43 and this finding might indicate an increased risk of nervous infiltration. We observed 4 cases of local recurrence in the paracolpium area on the same side as the nerve-sparing procedure, which suggested a possible relationship between the nerve-sparing method and local recurrence in some cases.

The feasibility of upfront surgical therapy for stage IIIB disease using Okabayashi-Kobayashi radical hysterectomy44 or with extended mesometrial resection has been suggested.45 Our results of LACC can be discussed in relation to the 5-year overall survival from the Surveillance, Epidemiology, and End Results database46 and the 2006 FIGO Annual Report.47 The 5-year overall survival from the Surveillance, Epidemiology, and End Results database for stages IIA and IIIB was 62% and 64%, respectively, and that from the 2006 FIGO report was 73% and 66%, respectively. The 5-year overall survival in our study for these stages was 78% and 78%, respectively. Our data appear to be consistent with the results from the Surveillance, Epidemiology, and End Results database and the FIGO Annual Report. Furthermore, the annual report of the committee on Table 4. Univariable and 2-Variable Cox Regression Analyses for the Risk of Decease After Nerve-Sparing Radical Hysterectomy

| Risk factor                  | Total No. | Death (%) | Cox regression analysis for risk factors of decease | Univariable, HR (95% CI) | P value | Two-variable model, HR (95% CI) | P value |
|-----------------------------|-----------|-----------|------------------------------------------------------|--------------------------|---------|--------------------------------|---------|
| 2008 FIGO stage             |           |           |                                                      |                          |         |                                |         |
| Early                       | 76        | 4 (5)     |                                                      | 1 [Reference]            | NA      | NA                             | NA      |
| Locally advanced            | 45        | 12 (27)   |                                                      | 5.4 (1.7-16.8)           | .003    | NA                             | NA      |
| Histology                   |           |           |                                                      |                          |         |                                |         |
| Squamous                    | 79        | 5 (6)     |                                                      | 1 [Reference]            | NA      | 1 [Reference]                  | NA      |
| Adeno(squamous)carcinoma    | 42        | 11 (26)   |                                                      | 4.7 (1.6-13.5)           | .004    | 5.5 (1.9-16.1)                 | .003    |
| pT classification           |           |           |                                                      |                          |         |                                |         |
| pT1b                        | 91        | 5 (5)     |                                                      | 1 [Reference]            | NA      | NA                             | NA      |
| pT2                         | 30        | 11 (37)   |                                                      | 8.3 (2.9-24.0)           | <.001   | NA                             | NA      |
| Lymph node metastasis       |           |           |                                                      |                          |         |                                |         |
| Negative                    | 88        | 4 (5)     |                                                      | 1 [Reference]            | NA      | 1 [Reference]                  | NA      |
| Positive                    | 33        | 12 (36)   |                                                      | 9.3 (3.0-28.8)           | <.001   | 10.5 (3.4-32.8)                | <.001   |
| Lymphovascular space invasion|          |           |                                                      |                          |         |                                |         |
| Negative                    | 67        | 5 (7)     |                                                      | 1 [Reference]            | NA      | NA                             | NA      |
| Positive                    | 54        | 11 (20)   |                                                      | 2.9 (1.0-8.4)            | .05     | NA                             | NA      |

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; NA, not applicable.

* Univariable Cox regression analysis for overall survival was performed for each variable, and then a 2-variable regression model based on the number of events we observed was obtained.
gynecologic oncology of Japan Society of Obstetrics and Gynecology on registered patients who were treated with surgery or radiotherapy in 2010 showed that the 5-year overall survival for stages IIA and IIB was 81% and 72%, respectively. The 5-year overall survival in our cohort corresponds with that in the Japan Society of Obstetrics and Gynecology report. We also compared our data with a nationwide multicenter study conducted by the Japan Gynecologic Oncology Group to evaluate the effect of surgical volume on survival after radical hysterectomy. Five-year DFS for stages IB1 to IIB disease combined in the Japan Gynecologic Oncology Group report was 77%, 80%, and 85% for the low-, mid-, and high-volume groups, respectively. Five-year DFS for stages IB1 to IIB combined in our cohort was 85%, which is consistent with that for the high-volume center in the Japan Gynecologic Oncology Group study.

The Okabayashi-Kobayashi method uses extensive excision of the vagina and paracolpium compared with the Meigs operation, which corresponds to the Piver class III operation. Meigs operation excises only the medial part of the ventral parametrium (anterior layer of the vesicouterine ligament). Complete separation of the bladder and ureter from the vagina and paracolpium seems difficult without excision of the vesicovaginal ligament (posterior layer of the vesicouterine ligament). The Piver class III operation and its equivalent methods would not likely deal with removing a sufficient extent of the vagina and paracolpium. Piver described that his class IV operation excises entire tissue surrounding the terminal ureter for extended excision of the vagina and the paracolpium, which corresponds to the Okabayashi-Kobayashi operation. The length of vaginal cuff removal less than 2 cm was suggested to be associated with increased local recurrence and decreased survival in stage IB-IIA cervical cancer. The surgical radicality for cervical cancer should include not only the extent of parametrial tissue, but also the extent of vaginal/paracolpium resection. We consider that more than 2 cm of vaginal cuff removal is critical for local control of LACC. Okabayashi-Kobayashi radical hysterectomy appears to be the choice of surgery for selected patients with LACC.

Limitations
This retrospective study was done in a single tertiary care center, and it included a relatively small number of patients, which creates a limitation in terms of generalizability of the study. However, surgery was performed with well-standardized, systematic, nerve-sparing Okabayashi-Kobayashi radical hysterectomy. Additionally, an intensive effort was made to ensure that the quality of follow-up was as high as possible, with no cases lost to follow-up at less than 60 months.

Conclusions
The nerve-sparing Okabayashi-Kobayashi radical hysterectomy for LACC may provide survival not inferior to radical hysterectomy or radiotherapy described in the published literature. The applicability of radical hysterectomy with adjuvant chemotherapy for LACC needs to be validated by prospective comparative trials.
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REFERENCES
1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424. doi:10.3322/caac.21492
2. Cancer incidence (1975-2014). Cancer Registry and Statistics. Cancer Information Service, National Cancer Center, Japan. Accessed April 7, 2020. https://ganjoho.jp/reg_stat/statistics/dl/index.html
3. Cervical cancer incidence statistics. Cancer Research UK. Accessed April 7, 2020. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/cervical-cancer/incidence
4. Key statistics for cervical cancer. American Cancer Society. Accessed April 7, 2020. https://www.cancer.org/cancer/cervical-cancer/about/key-statistics.html
5. Cervical cancer in Australia. Australian Government. Accessed April 7, 2020. https://cervical-cancer.canceraustralia.gov.au/statistics
6. Frumovitz M, Sun CC, Schover LR, et al. Quality of life and sexual functioning in cervical cancer survivors. J Clin Oncol. 2005;23(30):7428-7436. doi:10.1200/JCO.2004.00.3996
7. Derks M, van Lonkhuijzen LR, Bakker RM, et al. Long-term morbidity and quality of life in cervical cancer survivors: a multicenter comparison between surgery and radiotherapy as primary treatment. Int J Gynecol Cancer. 2017;27(2):350-356. doi:10.1097/IGC.0000000000000880
8. Wertheim E. The extended abdominal operation for carcinoma uteri (based on 500 cases). Am J Obstet Gynecol. 1912;66:169-232.
9. Latzko W, Schiffmann J. Klinisches und Anatomisches zur Radikaloperation des Gebarmutterkrebses. Zentralbl Gynäkol. 1919;43:715-719.
10. Meigs JV. Radical hysterectomy with bilateral pelvic lymph node dissections; a report of 100 patients operated on five or more years ago. Am J Obstet Gynecol. 1951;62(4):854-870. doi:10.1016/0002-9378(51)90175-5
11. Okabayashi H. Radical abdominal hysterectomy for cancer of the cervix uteri: modification of the Takayama operation. Surg Gynecol Obstet. 1921;33:335-341.
12. Kobayashi T. Abdominal Radical Hysterectomy With Pelvic Lymphadenectomy for Cancer of the Cervix. Nanazando; 1961. In Japanese.
13. Sakamoto S, Takizawa K. An improved radical hysterectomy with fewer urological complications and with no loss of therapeutic results for invasive cervical cancer. Baillieres Clin Obstet Gynaecol. 1988;2(4):953-962. doi:10.1016/0955-3552(88)80022-9
14. Sato K, Sato T. The vascular and neuronal composition of the lateral ligament of the rectum and the rectosacral fascia. Surg Radiol Anat. 1991;13(1):17-22. doi:10.1007/BF01623135
15. Sakuragi N, Todo Y, Kudo M, Yamamoto R, Sato T. A systematic nerve-sparing radical hysterectomy technique in invasive cervical cancer for preserving postsurgical bladder function. Int J Gynecol Cancer. 2005;15(2):389-397. doi:10.1136/ijgc-00009577-200503000-00038
16. Sakuragi N, Murakami G, Konno Y, Kaneuchi M, Watarai H. Nerve-sparing radical hysterectomy in the precision surgery for cervical cancer. J Gynecol Oncol. 2020;31(3):e49. doi:10.3802/jgo.2020.31.e49

17. Fuji S, Takakura K, Matsumura N, et al. Anatomic identification and functional outcomes of the nerve sparing Okabayashi radical hysterectomy. Gynecol Oncol. 2007;107(1):4-13. doi:10.1016/j.ygyno.2007.08.076

18. Koh WJ, Abu-Rustum NR, Bean S, et al. Cervical cancer, version 3.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019;17(1):64-84. doi:10.6004/jnccn.2019.0001

19. Amini A, Robin TP, Stumpf PK, et al. Rising rates of upfront surgery in early locally advanced cervical cancer: what factors predict for this treatment paradigm? Int J Gynecol Cancer. 2018;28(8):1560-1568. doi:10.1097/IGC.0000000000001323

20. Papp Z, Csápo Z, Hupuzsi P, Mayer A. Nerve-sparing radical hysterectomy for stage IA2-IIB cervical cancer: 5-year survival of 501 consecutive cases. Eur J Gynaecol Oncol. 2006;27(6):533-560.

21. Ditto A, Bogani G, Leone Roberti Maggiore U, et al. Oncologic effectiveness of nerve-sparing radical hysterectomy in cervical cancer. J Gynecol Oncol. 2018;29(2):e41. doi:10.3802/jgo.2018.29.e41

22. NCCN Guidelines version 4: cervical cancer. National Comprehensive Cancer Network. Accessed April 7, 2020. https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf

23. Ebina Y, Mikami M, Nagase S, et al. Japan Society of Gynecologic Oncology guidelines 2017 for the treatment of uterine cervical cancer. Int J Clin Oncol. 2019;24(1):1-19. doi:10.1007/s10045-018-1351-y

24. Nagase S, Ohta T, Takahashi F, Enamoto T. 2017 Committee on Gynecologic Oncology of the Japan Society of Obstetrics and Gynecology. Annual report of the committee on gynecologic oncology, the Japan Society of Obstetrics and Gynecology: annual patients report for 2015 and annual treatment report for 2010. J Obstet Gynaecol Res. 2019;45(2):289-298. doi:10.1111/jog.13863

25. Suprasert P, Sirsomboon J, Kasamatsu T. Radical hysterectomy for stage IIB cervical cancer: a review. Int J Gynecol Cancer. 2005;15(6):995-1001. doi:10.1111/j.1525-1438.2005.00259.x

26. Yuan L, Guo J, Zhang X, Chen M, Xu C, Yao L. Feasibility of radical hysterectomy in women with FIGO stage IIB cervical cancer: an observation study of 10-year experience in a tertiary center. Onco Targets Ther. 2018;11:5527-5533. doi:10.2147/OTT.S173208

27. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynecol Cancer. 2009;19(5):103-104. doi:10.1111/j.ijg.2009.02.012

28. What is STROBE? STROBE Statement. Accessed April 7, 2020. https://www.strobe-statement.org/index.php?id=strobe-home

29. Edge SB, Byrd DR, Compton CC, Fritz AG, Green FL, Trotti A III, eds. Cancer Staging Manual. 7th ed. Springer-Verlag. 2010.

30. Miller C, Elkas JC. Cervical and vaginal cancer. In: Berek JS, ed. Berek & Novak’s Gynecology. 15th ed. Lippincott Williams & Wilkins; 2012:1304-1349.

31. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med. 1999;18(6):695-706. doi:10.1002/(SICI)1097-0258(19990330)18:6<695::AID-SIM60>3.0.CO;2-O

32. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat. 1988;16(3):1141-1154. doi:10.1214/aos/1176350951

33. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94:496-509. doi:10.1080/01621459.1999.10474144

34. Kanda Y. Investigation of the freely available easy-to-use software ‘EZR’ for medical statistics. Bone Marrow Transplant. 2013;48(3):452-458. doi:10.1038/bmt.2012.244

35. Bhatla N, Berek JS, Cuello Fredes M, et al. Revised FIGO staging for carcinoma of the cervix uteri. Int J Gynecol Obstet. 2019;145(1):129-133. doi:10.1002/igyo.12749

36. Hlavieskyj LJ, Leath CA, Huh W, et al. Radical hysterectomy and pelvic lymphadenectomy for stage IIB cervical cancer. Gynecol Oncol. 2004;93(2):429-434. doi:10.1016/j.jygyno.2004.01.038

37. Finan MA, DeCesare S, Fiorica JV, et al. Radical hysterectomy for stage IB1 vs IB2 carcinoma of the cervix: does the new staging system predict morbidity and survival? Gynecol Oncol. 1996;62(2):139-147. doi:10.1006/jgyn.1996.0206

38. Rocconi RP, Estes JM, Leath CA III, Kilgore LC, Huh WK, Straughn JM Jr. Management strategies for stage IIB cervical cancer: a cost-effectiveness analysis. Gynecol Oncol. 2005;97(2):387-394. doi:10.1016/j.jygyno.2005.01.028
39. Kenter G, Greggi S, Vergote I, et al. Results from neoadjuvant chemotherapy followed by surgery compared to chemoradiation for stage Ib2-IIb cervical cancer, EORTC 55994. J Clin Oncol. 2019;37(suppl 15):5503. doi:10.1200/JCO.2019.37.15_suppl.5503

40. Burghardt E, Pickel H. Local spread and lymph node involvement in cervical cancer. Obstet Gynecol. 1978;52(2):138-145.

41. Zhu Y, Zhang GN, Shi Y, Cui L, Leng XF, Huang JM. Perineural invasion in cervical cancer: pay attention to the indications of nerve-sparing radical hysterectomy. Ann Transl Med. 2019;7(9):203. doi:10.21037/atm.2019.04.35

42. Vural C, Bayrak BY, Muezzinoglu B, Yucesoy I. Perineural invasion is a valuable prognostic factor in advanced stage and/or node (+) cervical cancer. Indian J Pathol Microbiol. 2017;60(1):27-32.

43. Kong TW, Kim J, Son JH, et al. Preoperative nomogram for prediction of microscopic parametrial infiltration in patients with FIGO stage Ib cervical cancer treated with radical hysterectomy. Gynecol Oncol. 2016;142(1):109-114. doi:10.1016/j.ygyno.2016.05.010

44. Kasamatsu T, Onda T, Sawada M, Kato T, Ikeda S. Radical hysterectomy for FIGO stage IIB cervical cancer: clinicopathological characteristics and prognostic evaluation. Gynecol Oncol. 2009;114(1):69-74. doi:10.1016/j.ygyno.2009.03.026

45. Wolf B, Ganzer R, Stolzenburg JU, Hentschel B, Horn LC, Höckel M. Extended mesometrial resection (EMMR): Surgical approach to the treatment of locally advanced cervical cancer based on the theory of ontogenetic cancer fields. Gynecol Oncol. 2017;146(2):292-298. doi:10.1016/j.ygyno.2017.05.007

46. Huang AJ, Huang KE. Overall survival trends for cervical cancer in the modern era: a U.S.A. population based analysis. J Clin Oncol. 2019;37(suppl 15):e17024. doi:10.1200/JCO.2019.37.15_suppl.e17024

47. Quinn MA, Benedet JL, Odicino F, et al. Carcinoma of the cervix uteri: FIGO 26th annual report on the results of treatment in gynecological cancer. Int J Gynaecol Obstet. 2006;95(suppl 1):S43-S103. doi:10.1016/S0020-7292(06)60030-1

48. Matsuo K, Shimada M, Yamaguchi S, et al. Association of radical hysterectomy surgical volume and survival for early-stage cervical cancer. Obstet Gynecol. 2019;133(6):1086-1098. doi:10.1097/AOG.0000000000003280

49. Nakano R. Abdominal radical hysterectomy and bilateral pelvic lymph node dissections for cancer of the cervix: the Okabayashi operation its modifications. Gynecol Obstet Invest. 1981;12(6):281-293. doi:10.1159/000299658

50. Piver MS, Rutledge F, Smith JP. Five classes of extended hysterectomy for women with cervical cancer. Obstet Gynecol. 1974;44(2):265-272.

51. Zuo N, Hu H, Thapa N, et al. Vaginal cuff length during radical hysterectomy is a prognostic factor for stage IB-IIA cervical cancer: a retrospective study. Cancer Manag Res. 2018;10:5927-5935. doi:10.2147/CMAR.S175726