Identifying selection criteria for non-radical hysterectomy in FIGO stage IB cervical cancer

Takahiro Kasamatsu¹, Mitsuya Ishikawa², Naoya Murakami³, Satoshi Okada⁴, Shun-Ichi Ikeda², Tomoyasu Kato² and Jun Itami³

¹Department of Obstetrics and Gynecology, Tokyo Metropolitan Bokutoh Hospital, Departments of ²Gynecology, ³Radiation Oncology, National Cancer Center Hospital and ⁴Department of Women’s Oncology Center/Gynecology, Sanno Hospital, Tokyo, Japan

Abstract

Aim: This retrospective study sought to identify the selection criteria required for a non-radical hysterectomy with minimal parametrectomy in patients with International Federation of Gynecology and Obstetrics (FIGO) stage IB invasive cervical cancer.

Methods: Overall, 461 patients with FIGO stage IB cervical cancer who underwent a radical hysterectomy were reviewed clinicopathologically according to pathological tumor size (≤2 cm, >2 – ≤4 cm, and > 4 cm).

Results: The pathological parametrial involvement rate in the less than equal to 2 cm group (2%) was significantly lower than in greater than 2 – less than equal to 4 cm (13%) or greater than 4 cm (29%) groups (both P < 0.001). The 5-year overall survival rate was significantly higher in the less than equal to 2 cm group (97%, 95% confidence interval [CI] 94–99%) compared with greater than 2 – less than equal to 4 cm (90%, 95% CI 94–86%) and greater than 4 cm (70%, 95% CI 79–60%) groups (both P < 0.001). Cox model analysis identified tumor size to be an independent prognostic factor for survival (95% CI 1.33–5.78) and recurrence (95% CI 1.31–5.66) compared to other pathological factors. However, a significant difference between the three groups was not found in rates of Grade 3 or 4 adverse events following radical hysterectomy (P = 0.19).

Conclusions: Tumor size is an independent prognostic factor for survival in patients with FIGO stage IB invasive cervical cancer. This retrospective study suggests that FIGO stage IB patients with a less than equal to 2 cm tumor size are optimal candidates for non-radical hysterectomy with minimal parametrectomy, and without resulting bladder dysfunction.

Key words: FIGO stage IB, neurogenic bladder, non-radical hysterectomy, uterine cervical cancer.

Introduction

Radical hysterectomy, corresponding to class III of the Piver–Rutledge classification system,¹ is widely accepted as a standard surgical procedure for patients with International Federation of Gynecology and Obstetrics (FIGO) stage IB–II invasive cervical cancer.² During radical hysterectomy, undergoing a parametrectomy is a crucial fundamental procedure.³ However, surgical damage to the pelvic autonomic nerve can occur after a wide resection of parametrial and paravaginal tissue, causing a severe long-term neurogenic bladder.⁴-⁷ Therefore, the development of a non-radical surgical approach, by resecting a smaller part of the parametrium near the cervix without compromising radicality, among patients with a low risk of parametrial involvement may reduce or avoid postoperative bladder dysfunction altogether.

The difficulty of evaluating microscopic parametrial involvement before surgery means a standard non-
radical hysterectomy that avoids bladder dysfunction in FIGO stage IB disease has not yet been established. However, if patients who have a low risk of pathological involvement could be identified before surgery, they would be able to undergo a non-radical hysterectomy with minimal parametrectomy. Tumor size in cervical cancer patients is a prognostic factor, with a small tumor size having a good prognosis; it follows that such patients likely have a low risk of parametrial involvement and therefore may be optimal candidates for non-radical surgery. We undertook a retrospective study to identify potential selection criteria for non-radical surgery with minimal parametrectomy to avoid neurogenic bladder in patients with FIGO stage IB disease by analyzing clinico-pathological features, including parametrial involvement rates and adverse events, in those patients who underwent a radical hysterectomy according to pathological tumor size.

Methods

Patients and tumors
Medical records were reviewed of 1400 patients with FIGO stage IB – IVA invasive cervical cancer treated at the Department of Gynecology, National Cancer Center Hospital in Tokyo, Japan between 1984 and 2006. Study patients met the following criteria: FIGO stage IB disease; underwent primary surgery consisting of a radical hysterectomy with pelvic systemic lymphadenectomy; and had a squamous cell carcinoma, adenosquamous cell carcinoma, or common histological subtypes of endometrioid adenocarcinoma and mucinous endocervical type adenocarcinoma. Patients with uncommon histological subtypes of other epithelial carcinomas and mesenchymal tumors, or those who received adjuvant therapy before primary surgery, were excluded. All patients were staged according to the FIGO (1994) staging system. Patients treated before 1994 were restaged retrospectively.

Treatment

Our standard surgical procedure for patients with FIGO stage IB disease is radical hysterectomy with a systemic pelvic lymphadenectomy, based on Kobayashi’s technique and the Tokyo method, and corresponding to class III or IV of the Piper–Rutledge classification system. When using this technique, the anterior, medial and posterior retinacula were divided and cut along the pelvic side wall while preserving the pelvic autonomic nerve bundle under the cardinal ligament. The vaginal canal, including the paracolpium, was cut for at least 3 cm. During the study period, laparoscopic or robotic surgery, or radical trachelectomy were not employed.

A bladder catheter was inserted in patients before the operation and maintained for 7–14 days following surgery. Patients were encouraged to void themselves every 4 h after catheter removal. The residual urine volume was measured every urination by a temporary catheter. Measurements ceased when the residual urine volume decreased to less than 50 mL.

In patients with pelvic lymph node metastasis (pT1bN1, pT2aN1 or pT2bN1) or parametrial involvement (pT2b) proven by pathological examination, adjuvant postoperative irradiation of the whole pelvis was performed. The total irradiation dose for the whole pelvis was 50 Gy in 25 fractions administered by external beam radiation therapy. If the surgically cut vaginal margin was positive, then high-dose rate intracavitary brachytherapy was performed using a remote after-loading system of 192Ir at a one fraction dose of 6 Gy to 5 mm under the vaginal surface, for a total of two fractions. Concurrent chemoradiotherapy was not administered.

Pathology

The maximum horizontal extension of the tumor was examined microscopically. Tumor size was defined by maximum diameter. Regarding the cut margin of the vaginal canal, a tumor-free space greater than 10 mm in length was defined as a tumor-free surgical margin. A tumor-free space less than 10 mm in length was defined as a close surgical margin. The resected parametrium was sectioned into proximal, center and distal portions. Parametrial lymph node metastasis was classified as a positive pelvic lymph node, and any lymph–vascular space invasion (LVSI) observed in the parametrium was classified as parametrial involvement. Histological typing was evaluated according to the World Health Organization International Histological Classification of Tumors.

Statistical analysis

The impact of pathological variables, such as tumor size, parametrial involvement, number of positive nodes, depth within the cervical wall, LVSI, infiltration into the vagina, adnexal metastasis and histological subtype on survival and recurrence were analyzed. Overall survival (OS) and recurrence-free
survival (RFS) curves were obtained by the Kaplan–Meier method and compared by nonparametric survival analysis (log-rank test). Patients were followed up through May 2013 for survival and RFS analyses. Pathological variables were also analyzed based on a Cox proportional hazard model with a stepwise method (forward selection). A P-value of 0.05 was adopted as an inclusion criterion, and a P-value of 0.10 was adopted as an exclusion criterion for the forward selection. Fisher’s exact or \( \chi^2 \) tests were used to examine the differences in distribution for categorical variables. A two-sample t-test or one way-analysis of variance was used for the statistical analysis of continuous variables. \( P < 0.05 \) was considered statistically significant. Adverse events were assessed using the Common Terminology Criteria for Adverse Events version 4.0. All statistical analyses were performed with \( \text{R} \) statistics (version 19) software.

Ethics
All authors observed the ethical guidelines for medical and health research involving human subjects of the Ministry of Health, Labor and Welfare, Japan. The study was approved by the institutional review board of the National Cancer Center, Japan and conforms to the provisions of the Declaration of Helsinki as revised in Tokyo 2004.

Results
Patients and tumor characteristics
Overall, 461 patients with FIGO stage IB cervical cancer met the study criteria. Table 1 summarizes the characteristics of patients according to tumor size (\( \leq 2 \text{ cm}, > 2 \leq 4 \text{ cm} \) and \( > 4 \text{ cm} \)). The mean tumor size was 14.6 \( \pm \) 3.9 mm, 30.2 \( \pm \) 5.4 mm and 54.3 \( \pm \) 12.3 mm for patients in less than or equal to 2 cm, greater than 2 – less than or equal to 4 cm and greater than 4 cm groups, respectively. The pathological parametrial involvement rate for patients in the less than or equal to 2 cm group (2%) was significantly lower than that of patients in the greater than 2 – less than or equal to 4 cm group (13%; \( P < 0.001 \)). Five other pathological variables, including number of positive pelvic lymph nodes, proportion of advanced pathological stages, proportion of deep cervical wall invasion, degree of LVSI and vaginal infiltration rate, were also significantly lower for patients in the \( \leq 2 \text{ cm} \) group compared with those in the greater than 2 – less than or equal to 4 cm group (\( P < 0.05 \)). Thus, pathological variables, including the parametrial involvement rate, were significantly lower in patients with a small tumor size.

For patients with positive pelvic nodes, positive common iliac nodes were observed in 7.6% (1/13) of patients in the less than or equal to 2 cm group, 20.7% (11/53) of those in the greater than 2 – less than or equal to 4 cm group, and 26.8% (11/41) of those in the greater than 4 cm group. Two patients in the greater than 2 – less than or equal to 4 cm group and one patient in the greater than 4 cm group had positive paraaortic nodes.

Among patients with pathological parametrial involvement, 66.6% (38/57) showed involvement in the proximal portion of the parametrium, 21.1% (12/57) in the central portion, and 12.3% (7/57) in the distal portion. All patients with positive parametrial involvement in central or distal portions also had parametrial involvement in the proximal portion; 34.0% (16/47) showed involvement on both sides of the parametrium.

Survival
All 461 patients were followed for between 1 and 305 months (median, 92), including those who eventually died. OS and RFS were assessed using a log-rank test for patients stratified by eight pathological subgroups (tumor size, parametrial involvement, number of positive nodes, depth in cervical wall, LVSI, infiltration into vagina, adnexal metastasis and histological subtype [Table 2]). The 5-year OS rate for patients with a tumor size less than or equal to 2 cm was 97% (95% CI, 94–99%), which was significantly greater than those of patients with a tumor size greater than 2 – less than or equal to 4 cm, or greater than 4 cm (\( P = 0.001 \) for both). Multivariate analysis of the eight subgroups using a Cox model demonstrated that tumor size, number of positive nodes, and adnexal metastasis were independent adverse risk factors for survival (Table 3). Using the same subgroups as for OS, the RFS rate at 5 years was 95% (95% CI, 92–99%) for patients with a tumor size less than or equal to 2 cm, which was significantly better than that for patients with a tumor size greater than 2 – less than or equal to 4 cm, and greater than 4 cm (\( P = 0.001 \) for both; Table 2). A Cox model analysis showed that the tumor size and number of positive nodes were significant adverse risk factors for cancer recurrence (Table 3; \( P < 0.001 \) for both). Thus, a small tumor size is linked to increased survival and is an adverse risk factor for cancer recurrence.
Failure sites and spread pattern

Seventy-four patients suffered tumor recurrence at a median interval of 14 months (range, 1–132 months). An analysis of the distribution of initial failure sites showed that in 148 patients with a tumor size less than or equal to 2 cm, 8 (5%) suffered a tumor recurrence, with initial failure sites inside and outside the pelvis in four (50%) patients, respectively. Of 226 patients with a tumor size greater than 2–less than or equal to 4 cm, 34 (15%) patients suffered a tumor recurrence. Of these, initial failure sites were found inside the pelvis for 15 (44%) patients, outside the pelvis for 18 (53%) patients, and inside and outside for one (3%) patient. Of the 32 (37%) patients with a tumor size >4 cm who suffered a tumor recurrence, initial failure sites were found inside the pelvis for 11 (34%) patients, outside the pelvis for 19 (60%) patients, and both inside and outside for two (6%) patients.
Table 2 OS and RFS in 461 patients with stage IB disease

|                                | No. (%) | 5-year OS (%) | Log-rank P-value | 5-year RFS (%) | Log-rank P-value |
|--------------------------------|---------|---------------|------------------|----------------|-----------------|
| **Tumor size (cm)**            |         |               |                  |                |                 |
| ≤2                             | 148 (32)| 97            | <0.001           | 95             |                |
| >2–≤4                          | 226 (49)| 90            |                  | 88             |                |
| >4                             | 87 (19) | 70            |                  | 66             |                |
| **Parametrial involvement**    |         |               |                  |                |                 |
| Negative                       | 404 (88)| 91            | <0.001           | 90             |                |
| Positive                       | 57 (12) | 68            |                  | 61             |                |
| **Number of positive nodes**   |         |               |                  |                |                 |
| 0                              | 354 (77)| 93            |                  | 92             |                |
| 1–4                            | 83 (18) | 79            |                  | 74             |                |
| >5                             | 24 (5)  | 45            |                  | 37             |                |
| **Depth in cervical wall**     |         |               |                  |                |                 |
| <1/3                           | 118 (26)| 96            | <0.001           | 95             |                |
| 1/3–2/3                        | 128 (28)| 92            |                  | 91             |                |
| 2/3 <                          | 215 (46)| 81            |                  | 78             |                |
| **LVSI**                       |         |               |                  |                |                 |
| None                           | 152 (33)| 96            |                  | 94             |                |
| Few                            | 156 (34)| 89            |                  | 87             |                |
| Several                        | 102 (22)| 84            |                  | 84             |                |
| Many                           | 51 (11) | 74            |                  | 66             |                |
| **Infiltration into vagina**   |         |               |                  |                |                 |
| Negative                       | 382 (83)| 90            |                  | 88             |                |
| Positive                       | 79 (17) | 79            |                  | 77             |                |
| **Adnexal metastasis**         |         |               |                  |                |                 |
| Negative                       | 367 (80)| 88            |                  | 86             |                |
| Positive                       | 5 (1)   | 20            |                  | 25             |                |
| Not resected                   | 89 (19) | 94            |                  | 89             |                |
| **Histological subtype**       |         |               |                  |                |                 |
| Squamous cell                  | 302 (66)| 89            | 0.905            |                | 0.114           |
| Adenosquamous cell             | 48 (10) | 89            |                  | 81             |                |
| Adenocarcinoma                 | 111 (24)| 87            |                  | 86             |                |

OS, overall survival; RFS, recurrence-free survival; LVSI, lymph-vascular space invasion.

Table 3 Multivariate analysis of prognostic factors for OS and RFS in 461 patients with stage IB disease (with a stepwise method, forward selection)

|                                | OS       | RFS      |
|--------------------------------|----------|----------|
|                                | HR       | 95% CI   | P-value | HR       | 95% CI   | P-value |
| **Tumor size (cm)**            |          |          |         |          |          |         |
| ≤2                             | 1        | 1        |         | 1        | 1        |         |
| >2–≤4                          | 2.78     | 1.33–5.78| 0.006   | 2.72     | 1.31–5.66| 0.007   |
| >4                             | 4.69     | 2.14–10.26| <0.001 | 4.84     | 2.22–10.55| <0.001 |
| **Number of positive nodes**   |          |          |         |          |          |         |
| 0                              | 1        | 1        |         | 1        | 1        |         |
| 1–4                            | 1.915    | 1.14–3.19| 0.013   | 1.97     | 1.18–3.28| 0.009   |
| >5                             | 4.05     | 2.14–7.68| <0.001 | 4.4      | 2.31–8.35| <0.001 |
| **Adnexal metastasis**         |          |          |         |          |          |         |
| Negative                       | 1        |          |         |          |          |         |
| Positive                       | 3.29     | 1.22–8.85| 0.018   | 2.58     | 0.96–6.93| 0.060   |
| Not resected                   | 0.52     | 0.25–1.11| 0.092   | 0.52     | 0.25–1.10| 0.091   |

OS, overall survival; RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval. †The analysis was adjusted for tumor size, parametrial involvement, cervical wall depth, number of positive nodes, lymph-vascular space invasion, infiltration into vagina, adnexal metastasis and histological subtype.
patients. A significant difference in the location of initial failure sites according to tumor size between groups was not found ($P = 0.838$).

The pelvic control rate was 97% for patients in the less than or equal to 2 cm group, 93% for those in the greater than 2–less than or equal to 4 cm group, and 85% for patients in the greater than 4 cm group; the pelvic control rate for patients in the less than or equal to 2 cm was significantly higher compared to that of patients in the greater than 4 cm group ($P = 0.002$). Of 33 patients with pelvic recurrence, 14 (42%) showed central recurrence, and 19 (58%) had a lateral recurrence. Thus, a small tumor size is associated with a higher pelvic control rate.

**Complications**

The mean period of continuous bladder drainage by retention urine catheter inserted before surgery was 14 ± 13 days (median 14 days, range, 4–233 days). After removal of the catheter, 69% (318/461) of patients could initiate micturition immediately, a total of 94% (433/461) could initiate micturition within 7 days, and 96% (444/461) initiated micturition by 14 days after removal of the catheter. Thirteen patients (3%) who could not self-micturate left the hospital after self-catheterization from 10 to 65 days after surgery. Excluding the 13 patients who could not self-micturate, the mean period between removal of the retention catheter and initiating self-micturition was 1.0 ± 2.8 days (median 0 day, range 0–37 days) in 448 patients. Forty-two patients with residual urine and one patient with a vesicovaginal fistula left the hospital after self-catheterization. Of the remaining 405 patients, the mean period between removal of the retention catheter and the disappearance of residual urine was 8.4 ± 7.5 days (median 6 days, range 0–51 days). Of all 461 patients, the population of patients with residual urine, according to a Kaplan–Mayer estimate, was 88% 3 days after the removal of the retention catheter, 54% at 7 days, 26% at 14 days, 16% at 21 days, 8% at 28 days, and 4% at 56 days. Finally, none of the 461 patients needed permanent self-catheterization.

Other morbidities are summarized in Table 4. A significant difference in the rate of grade 3 or 4 adverse events according to tumor size between the three patient groups was not evident: 6.8%, 8.8% and 13.8% for patients in less than 2 cm, greater than 2–less than or equal to 4 cm, and greater than 4 cm groups, respectively ($P = 0.191$). Significant differences in the mean volume of blood loss for patients in all groups (1134 mL ≤2 cm; 1314 mL, >2 – ≤4 cm; 1345 mL, >4 cm groups) or in the mean operating time ($P = 0.693$; 355 min, ≤2 cm; 359 min, >2 – ≤4 cm; 358 min, >4 cm groups) were not noted ($P = 0.088$). In summary, the rate of grade 3 or 4 adverse events was not associated with tumor size.

**Discussion**

The present study suggests that patients with a pathological tumor of less than or equal to 2 cm are suitable candidates for non-radical hysterectomy with minimal parametrectomy. Tumor size was found to be an independent prognostic factor for survival and recurrence, with the prognosis for patients with a small tumor size (≤2 cm) significantly better than for those with a larger tumor size. Furthermore, those with a small tumor size (≤2 cm) were found to have a low risk for pathological parametrial involvement (2%). However, a statistical difference was not found in the incidence of complications or tumor spread between the three groups of patients with different tumor sizes and FIGO stage IB disease who underwent radical hysterectomy, especially those with bladder dysfunction.

Recent studies have focused on the use of non-radical hysterectomy or the minimization of hysterectomy for early stage cervical cancer. Several studies described retrospective case series of microinvasive (stage IA) and early invasive disease (stage IB), with the risk of parametrial invasion less than 4% in patients with a less than or equal to 2 cm tumor size. Furthermore, for patients with lesions with a limited depth of stromal invasion, and without LVSI or node metastasis, the risk was less than 1%. In accord with these findings, the present study suggests that FIGO stage IB patients with a less than or equal to 2 cm tumor size may be appropriate candidates for non-radical hysterectomy. Currently, the standard surgical option for patients with microinvasive disease is a simple extrafascial hysterectomy for stage IA1 disease, and modified radical hysterectomy for stage IA2 disease; these rationales are universally accepted. However, a standard surgical option does not exist for patients with a frank small-sized invasive carcinoma who usually undergo radical hysterectomy. A study of 83 FIGO stage IB patients, with a squamous cell lesion of greater than 3 mm stromal invasion depth, a less than or equal to 2 cm size tumor, no LVIS and who underwent radical hysterectomy, showed a lack of parametrial nodal involvement.
| Table 4 Morbidities |
|----------------------------------|
| Tumor size | Grade 3 | Grade 4 | Grade 5 | Grade 3 or 4 (%) | Grade 3 | Grade 4 | Grade 5 | Grade 3 or 4 (%) | Grade 3 | Grade 4 | Grade 5 | Grade 3 or 4 (%) |
| ≤2 cm | n = 148 | >2–≤4 cm | n = 226 | >4 cm | n = 87 |
| Adverse event | | | | | |
| Morbidity during surgery | | | | | |
| Procedural complications | | | | | |
| Ureteral injury | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0.9 | 0 | 0 | 0 | 0 |
| Early morbidity | | | | | |
| Urinary disorders | | | | | |
| Fistula | 2 | 0 | 0 | 1.3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Vascular disorders | | | | | |
| Lymphocele | 1 | 0 | 0 | 0.6 | 1 | 0 | 0 | 0.4 | 0 | 0 | 0 | 0 |
| Thromboembolic event | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1.1 |
| Gastrointestinal disorders | | | | | |
| Ileus | 1 | 0 | 0 | 0.6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Perforation | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0.4 | 0 | 0 | 0 | 0 |
| Wound complications | | | | | |
| Abdominal hernia | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0.4 | 0 | 0 | 0 | 0 |
| Wound separation | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0.4 | 0 | 0 | 0 | 0 |
| Infections | | | | | |
| Urinary tract infection | 1 | 0 | 0 | 0.6 | 1 | 0 | 0 | 0.4 | 1 | 0 | 0 | 1.1 |
| Late morbidity | | | | | |
| Urinary disorders | | | | | |
| Fistula | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1.1 |
| Urinary tract obstruction | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0.9 | 1 | 0 | 0 | 1.1 |
| Bladder perforation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 2.3 |
| Vascular disorders | | | | | |
| Lymphocele | 2 | 0 | 0 | 1.4 | 1 | 0 | 0 | 0.4 | 0 | 0 | 0 | 0 |
| Lymphedema | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0.4 | 1 | 0 | 0 | 1.1 |
| Gastrointestinal disorders | | | | | |
| Ileus | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0.9 | 0 | 0 | 0 | 0 |
| Wound complications | | | | | |
| Abdominal hernia | 2 | 0 | 0 | 1.4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Infections | | | | | |
| Urinary tract infection | 1 | 0 | 0 | 0.7 | 4 | 0 | 0 | 1.8 | 2 | 0 | 0 | 2.3 |
| Lymphocele infection | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 1.3 | 1 | 0 | 0 | 1.1 |
| Lymph channel | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1.1 |
| Total | 10 | 0 | 0 | 6.6 | 19 | 1 | 0 | 8.6 | 12 | 0 | 1 | 14.5 |

†One patient died of a pulmonary thromboembolism.
metastasis, and a 5-year disease-free survival rate of 97.6%.\textsuperscript{17} Another study of patients with stage IB squamous cell or adenocarcinoma who underwent radical hysterectomy (Piver class III) followed by concurrent chemoradiotherapy showed the 5-year OS rate was significantly longer in patients with a less than or equal to 2 cm tumor size (94.0%) compared with patients with a tumor size of greater than 2 less than or equal to 4 cm (85.1%) or greater than 4 cm (69.9%).\textsuperscript{20} In the present study, pathological parametrial involvement spread from the proximal to distal portion of the parametrum. All patients with positive parametrical involvement in central or distal portions showed parametrical involvement in the proximal portion. This pathological finding indicates that a minimal resection of the parametrium along the cervix may be safe without compromising radicality. On the basis of these and previously described findings, patients with a less than or equal to 2 cm tumor size may be considered candidates for a non-radical hysterectomy of minimal parametrectomy without bladder dysfunction.

The development of a severely neurogenic bladder—an inability to empty the bladder and loss of the sense of urgency to void—is unavoidable after radical hysterectomy. In the present study, the median period between removing the retention catheter and the disappearance of residual urine was 6 days. Patients underwent bladder rehabilitation to reduce straining while micturating and the loss of a sense of urgency to void. This finding is in agreement with a previous study that reported a median of 7 days for complete bladder emptying,\textsuperscript{21} although bladder dysfunction existed from several months to years after surgery. Indeed, 12 months after a radical hysterectomy, a urinary reflex was still absent in 70% of patients, while 18% had reduced bladder compliance on a cystomanometric curve and 9% showed stress incontinence.\textsuperscript{22} Notably, a bladder residue (>100 mL) remained in 6% of patients 12 months after surgery, further highlighting severe and prolonged bladder dysfunction following radical hysterectomy.

Other common severe complications that follow radical hysterectomy\textsuperscript{4} are bowel dysfunction including constipation (18%),\textsuperscript{23} sexual dysfunction (26%),\textsuperscript{24} urinary tract fistula information (0–12.8%),\textsuperscript{14,25} ureteral stenosis (9%),\textsuperscript{26} lymphocysts (6%) and lymphedema (8–25%) caused by lymphadenectomy.\textsuperscript{23,26} Therefore, it is important to define new selection criteria for non-radical surgery with minimal parametrectomy to prevent the development of unnecessary, severe complications, including bladder dysfunction, associated with radical hysterectomy.

Based on the findings of the present study, non-radical hysterectomy was defined as the following: the cutting of the anterior layer of the vesicouterine ligament, and removal of part of the parametrial tissue. Consequently, almost all of the bladder branch from the inferior hypogastric nerve is preserved. The posterior layer of the vesicouterine ligament is not resected. This procedure is considered to be somewhere between a simple and type II radical hysterectomy.

The present study was based on pathological tumor size, and clearly identified potential selection criteria for non-radical surgery. However, the evaluation of preoperative characteristics, including the measurement of tumor size by diagnostic imaging, was not undertaken. To more decisively demonstrate the efficacy of non-radical hysterectomy for patients with invasive cervical cancer, a prospective study is required. In this regard, four ongoing prospective studies are currently evaluating the use of less invasive and damaging non-radical surgery for patients with small-sized lesions\textsuperscript{27,28}: The Japanese Clinical Oncology Group study 1101 is a multi-institutional non-randomized confirmatory Phase III trial that is evaluating the efficacy of modified radical hysterectomy for patients with a less than or equal to 2 cm tumor diameter in FIGO stage IB1 disease confirmed by magnetic resonance imaging (MRI) before surgery in comparison with radical hysterectomy.\textsuperscript{28} The eligibility criteria for this study are patients with FIGO IB1 disease, and a clinical maximum tumor diameter (confirmed by MRI) of less than or equal to 2 cm with any depth of invasion or any degree of LVSI. In the present study, MRI was employed for the measurement of tumor size before surgery. In the gynecologic oncology group study 278, changes in bladder, bowel and sexual function in patients with IA1, IA2 or IB1 (tumor size ≤2 cm and depth of invasion ≤10 mm on cone) are being investigated, before and after non-radical surgery.\textsuperscript{29} The Conservative Surgery for Women with Low-risk, Early stage Cervical Cancer (ConCerv)\textsuperscript{4} trial is currently evaluating the safety and feasibility of performing conservative surgery in patients with stage IA2 or IB1 disease (tumor size ≤2 cm, depth of invasion <10 mm, and no LVSI on conization).\textsuperscript{30} Finally, the Gynecologic Cancer Intergroup randomized trial (SHAPE Trial) is comparing radical and simple hysterectomies for patients with IA2 or IB1 disease (tumor size <2 cm, depth of
invasion <10 mm on conization, and < 50% stromal invasion).31

In conclusion, this retrospective study suggests that FIGO stage IB patients with a less than or equal to 2 cm tumor size are optimal candidates for non-radical hysterectomy with minimal parametrectomy.

Acknowledgments

This study was supported by the National Cancer Center Research and Development Fund (A-23-17, A-26-4), and Practical Research for Innovative Cancer Control from Japan Agency for Medical Research and Development (JP15ck0106052, 16ck0106052, 17ck0106316, 18ck0106316), AMED. The authors thank Ms. Yukari Matsubayashi and Ms. Renko Yamazki for excellent secretarial assistance.

Disclosure

None declared.

References

1. Piver MS, Rutledge F, Smith JP. Five classes of extended hysterectomy for women with cervical cancer. Obstet Gynecol 1974; 44: 265–272.
2. Koh WJ, Greer BE, Abu-Rustum NR et al. Cervical Cancer, Version 2.2.2015. J Natl Compr Canc Netw 2015; 13 (4): 395–404 quiz.
3. Kasamatsu T, Onda T, Sawada M, Kato T, Ikeda S. Radical hysterectomy for FIGO stage IB cervical cancer: Clinico-pathological characteristics and prognostic evaluation. Gynec Oncol 2009; 114: 69–74.
4. Carenza L, Nobili F, Giacobini S. Voiding disorders after radical hysterectomy. Gynecol Oncol 1982; 13: 213–219.
5. Scotti RJ, Bergman A, Bhatia NN, Ostergard DR. Urodynamics: changes in urethrovaginal function after radical hysterectomy. Obstet Gynecol 1986; 68: 111–120.
6. Bandy LC, Clarke-Pearson DL, Soper JT, Mutch DG, MacMillan J, Creasman WT. Long-term effects on bladder function following radical hysterectomy with and without postoperative radiation. Gynecol Oncol 1987; 26: 160–168.
7. Zullo MA, Manci N, Angioli R, Muzii L, Panici PB. Vesical dysfunctions after radical hysterectomy for cervical cancer: A critical review. Crit Rev Oncol Hematol 2003; 48: 287–293.
8. Park JY, Kim DY, Kim JH, Kim YM, Kim YT, Nam JH. Outcomes after radical hysterectomy according to tumor size divided by 2-cm interval in patients with early cervical cancer. Ann Oncol 2011; 22: 59–67.
9. Benedet JL, Bender H, Jones H 3rd, Ngan HY, Pecorelli S. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. Int J Gynaecol Obstet 2000; 70: 209–262.
10. Sakamoto S. Radical hysterectomy with pelvic lymphadenectomy - The Tokyo method. In: Coppleson M (ed). Gynecol Oncol, 1st edn. New York, NY: Churchill Livingstone, 1981; 877–886.
11. Kasamatsu T, Onda T, Sawada M et al. Radical hysterectomy for FIGO stage I-II B adenocarcinoma of the uterine cervix. Br J Cancer 2009; 100: 1400–1405.
12. Arimoto T, Kawana K, Adachi K et al. Minimization of curative surgery for treatment of early cervical cancer: A review. Jpn J Clin Oncol 2015; 45: 611–616.
13. Ramirez PT, Pareja R, Rendon GJ, Millan C, Frumovitz M, Schmeler KM. Management of low-risk early-stage cervical cancer: Should conization, simple trachelectomy, or simple hysterectomy replace radical surgery as the new standard of care? Gynecol Oncol 2014; 132: 254–259.
14. Reade CJ, Eiriksson LR, Covens A. Surgery for early stage cervical cancer: How radical should it be? Gynecol Oncol 2013; 131: 222–230.
15. Covens A, Rosen B, Murphy J et al. How important is removal of the parametrium at surgery for carcinoma of the cervix? Gynecol Oncol 2002; 84: 145–149.
16. Frumovitz M, Sun CC, Schmeler KM et al. Parametrial involvement in radical hysterectomy specimens for women with early-stage cervical cancer. Obstet Gynecol 2009; 114: 93–99.
17. Kinney WK, Hodge DO, Egorshin EV, Ballard DJ, Podratz KC. Identification of a low-risk subset of patients with stage IB invasive squamous cancer of the cervix possibly suited to less radical surgical treatment. Gynecol Oncol 1995; 57: 3–6.
18. Smith AL, Frumovitz M, Schmeler KM et al. Conservative surgery in early-stage cervical cancer: What percentage of patients may be eligible for conization and lymphadenectomy? Gynecol Oncol 2010; 119: 183–186.
19. Stegeman M, Louwen M, van der Velden J et al. The incidence of parametrial tumor involvement in select patients with early cervix cancer is too low to justify parametrectomy. Gynecol Oncol 2007; 105: 475–480.
20. Horn LC, Bilek K, Fischer U, Einenkel J, Hentschel B. A cutoff value of 2 cm in tumor size is of prognostic value in surgically treated FIGO stage IB cervical cancer. Gynecol Oncol 2014; 134: 42–46.
21. Covens A, Rosen B, Murphy J et al. Changes in the demographics and perioperative care of stage IA(2)/IB(1) cervical cancer over the past 16 years. Gynecol Oncol 2001; 81: 133–137.
22. Zanolla R, Monzeglio C, Campo B, Ordesi G, Balzarini A, Martino G. Bladder and urethral dysfunction after radical abdominal hysterectomy: Rehabilitative treatment. J Surg Oncol 1985; 28: 190–194.
23. Bergmark K, Avall-Lundqvist E, Dickman PW, Henningsohn L, Steineck G. Lymphedema and bladder-emptying difficulties after radical hysterectomy for early cervical cancer and among population controls. Int J Gynecol Cancer 2006; 16: 1130–1139.
24. Bergmark K, Avall-Lundqvist E, Dickman PW, Henningsohn L, Steineck G. Vaginal changes and sexuality in women with a history of cervical cancer. New Eng J Med 1999; 340: 1383–1389.
25. Averette HE, Nguyen HN, Donato DM et al. Radical hysterectomy for invasive cervical cancer. A 25-year prospective experience with the Miami technique. Cancer 1993; 71: 1422–1436.

26. Landoni F, Maneo A, Cormio G et al. Class II versus class III radical hysterectomy in stage IB-IIA cervical cancer: A prospective randomized study. Gynecol Oncol 2001; 80: 3–12.

27. Lennox GK, Covens A. Management of early stage cervical cancer: When is non-randomized data good enough? Gynecol Oncol 2017; 146: 1–2.

28. Kunieda F, Kasamatsu T, Arimoto T et al. Non-randomized confirmatory trial of modified radical hysterectomy for patients with tumor diameter 2 cm or less FIGO stage IB1 uterine cervical cancer: Japan clinical oncology group study (JCOG1101). Jpn J Clin Oncol 2015; 45: 123–126.

29. Covens A. GOG Protocol 278. [Cited 21 August 2018.] Available from URL: (https://clinicaltrials.gov/ct2/show/NCT01649089?term=gog-0278&rank=1).

30. Schmeler K. Conservative Surgery for Women With Cervical Cancer. [Cited 21 August 2018.] Available from URL: https://clinicaltrials.gov/ct2/show/NCT01048853.

31. Plante M. The SHAPE trial. [Cited 21 August 2018.] Available from URL: https://clinicaltrials.gov/ct2/show/record/NCT01658930.