

## MINI-REVIEW

# Phase III clinical trials of radical hysterectomy with minimal parametrectomy for patients with early-stage cervical cancer: a review

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**Abstract**

The standard surgery for patients with International Federation Gynecology and Obstetrics (FIGO) stage IB–II cervical cancer is a Piver-Rutledge-Smith class III radical hysterectomy with pelvic lymphadenectomy involving a wide resection of parametrial and paravaginal tissue to control parametrial involvement. However, adverse events can occur such as severe long-term neurogenic bladder due to parametrectomy. This review evaluates ongoing and completed phase III clinical trials of less radical hysterectomy with regard to parametrectomy. The PubMed database, Clinical Trials.gov, and Cochrane Central Register of Controlled Trials were used to extract information on two completed and four ongoing clinical trials. Less radical surgery led to similar oncologic outcomes to standard surgery in two phase III randomized controlled trials (Piver class II vs. class III, and class I vs. class III radical hysterectomy with pelvic lymphadenectomy). Less radical surgery also led to fewer complications, including urologic morbidity; however, more than 50% of patients received radiotherapy following such surgery, and showed higher morbidity rates because their enrolment was due to the presence of a large tumor (>4 cm). Three phase III randomized controlled trials and a phase III nonrandomized confirmatory trial are presently ongoing. Major inclusion criteria include FIGO stage IA, IB, or IIA1, a mainly ≤2-cm tumor, limited depth of stromal invasion, and/or no lymph node metastasis. Surgery for the standard arm is a class II or class III radical hysterectomy, and the experimental surgery is a simple extrafascial hysterectomy or class II radical hysterectomy. Primary endpoints are overall, disease-free, or recurrence-free survival. Although primary endpoints, eligibilities or types of radical hysterectomy differ between trials, if noninferiority in overall, disease-free or recurrence-free survival is observed in any trial, new standard, less radical, curative hysterectomy may be established for early-stage, small-sized, invasive, cervical cancer.

**Keywords**

Early-stage cervical cancer; Less radical hysterectomy; Parametrectomy; Tumor size; Phase III clinical trial

## 1. Introduction

The standard surgical procedure for patients with International Federation Gynecology and Obstetrics (FIGO) stage IB–II invasive cervical cancer has been widely viewed as a radical hysterectomy with pelvic lymphadenectomy, corresponding to class III of the Piver-Rutledge-Smith (Piver) classification system [1]. A radical hysterectomy involves a parametrectomy to completely remove cancerous tissues around the cervix. The aim of this pivotal procedure is to reduce parametrial involvement and pelvic lymph node metastasis, which are the most important independent adverse prognostic factors, thereby enhancing patient survival [2, 3]. In class III radical hysterectomy with pelvic lymphadenectomy, a wide radical excision of parametrial and paravaginal tissue is made. The

ureter is dissected from the pubovesical ligament to the entry of the bladder. Excision of the uterosacral ligaments occurs at their attachments and resection of the cardinal ligaments occurs at the pelvic side wall. Half of the vagina is removed and systematic lymphadenectomy is routinely performed [1]. However, a wide resection of parametrial and paravaginal tissues may inadvertently damage the pelvic autonomic nerve. A severe long-term neurogenic bladder may result whereby patients experience loss of a sense of urgency to void after radical hysterectomy and are unable to empty their bladder [4–7]. Therefore, in patients with a low risk of parametrial involvement, a smaller portion of the parametrium is resected near the cervix without compromising the radicality of the procedure to reduce or prevent postoperative bladder dysfunction altogether. This procedure basically corresponds to a

Piver class I or class II hysterectomy [1]. As an extrafascial simple hysterectomy, uterosacral and cardinal ligaments are not removed in the class I procedure. In what is a moderately extended radical hysterectomy, a class II hysterectomy aims to remove further paracervical tissue but preserve blood supply to distal ureters and the bladder. The ureters are moved from a paracervical position but remain attached to the pubovesical ligament. The uterosacral ligaments between ureters and their sacral attachments are resected midway. The upper one-third of the vagina and medial half of the cardinal ligament are removed. In this review, hysterectomy with minimal parametrectomy is defined as a class I or II hysterectomy.

In patients with invasive cervical cancer, microscopic parametrial involvement prior to surgery cannot be evaluated meaning that an established procedure is lacking for curative hysterectomy with minimal parametrectomy that does not result in a neurogenic bladder. The efficacy of curative hysterectomy with minimal parametrectomy is currently being assessed in several clinical trials. This narrative review focuses on ongoing and completed phase III randomized clinical trials of curative hysterectomy with minimal parametrectomy for patients with early-stage invasive cervical cancer.

## 2. Methods

We undertook a review of the English-language medical literature for randomized controlled trials on less radical hysterectomy with minimal parametrectomy for cervical cancer. Literature searches for articles between January 1970 and January 2022 were conducted on PubMed. Search terms included “cervical cancer”, “hysterectomy”, and “clinical trial”. Additional clinical trials were identified from ClinicalTrials.gov and the Cochrane Central Register of Controlled Trials, and other search terms included “cervical cancer” and “hysterectomy”. Inclusion criteria were: a phase III randomized controlled trial or nonrandomized confirmatory trial nearly equal to a phase III randomized controlled trial, and a hysterectomy as primary treatment. Phase I/II trials or retrospective studies were excluded.

## 3. Results

Initial searches retrieved 536 references from the PubMed database, 127 clinical trials from ClinicalTrials.gov, and 193 from the Cochrane Central Register of Controlled Trials. Of these, two completed randomized controlled trials and four ongoing randomized controlled trials met the study criteria.

### 3.1 Completed randomized controlled trials

Completed randomized controlled trials are summarized in Table 1. In studies by Landoni *et al.* [8] (2001), inclusion criteria for patients were FIGO stage (1985) IB or IIA disease with any cervical tumor size. In another study by Landoni *et al.* [9] (2012), such inclusion criteria were FIGO stage IB or IIA disease with a tumor size  $\leq 4$  cm.

Standard and experimental surgeries were classed as III and II radical hysterectomy with pelvic lymphadenectomy according to operative guidelines outlined by Piver *et al.* [1].

A Piver class III radical hysterectomy included removal of the uterus, cervix, and upper third of the vagina, and also parametrial tissue extirpation. A Piver class II radical hysterectomy involved removal of the median half of cardinal and uterosacral ligaments. Patients showing pelvic node metastasis, parametrial involvement, lymph-vascular space invasion, or positive or close resection margins as shown by pathological examinations, were administered postoperative radiotherapy to the whole pelvis.

Five-year overall and disease-free survival rates were 81% and 75%, respectively, in the class II arm and 77% and 77%, respectively, in the class III arm, although differences were not statistically significant ( $p = 0.7$  and  $p = 0.9$ , respectively). After class II and III operations, 34% and 42%, respectively, of recurrence sites were observed inside the pelvis, but a significant difference between the two classes was not found ( $p = 0.7$ ). It was concluded that an extension of parametrectomy did not appear to influence pelvic recurrence. The parametrial involvement rate was 27% and 25% in class III and II arms, respectively ( $p = 0.8$ ). Positive lymph nodes were also observed in 23% and 27% of patients in class III and II arms. Late urologic morbidity, including hydronephrosis, stress incontinence, atonic bladder, high-pressure bladder, and actinic cystitis, were significantly lower in the class II (13%) compared to class III (28%) arm. Mean times to voiding were  $16 \pm 10.8$  days in the class II radical hysterectomy group,  $24 \pm 24$  days in the class II radical hysterectomy followed by radiotherapy group,  $31 \pm 42$  days in the class III radical hysterectomy group, and  $37 \pm 40$  days in the class III followed by radiotherapy group, respectively ( $p = 0.02$ ). The mean operative time was significantly ( $p = 0.01$ ) shorter in the class II arm (135 min vs. 180 min). From the above, it was concluded in this study that for patients with FIGO stage IB–IIA cervical cancer, a class II radical hysterectomy was preferred.

Inclusion criteria for patients outlined by Landoni *et al.* [9] (2012) included FIGO stage IB or IIA disease, and, in addition to this, a tumor diameter  $\leq 4$  cm. The experimental treatment arm was Piver class I radical hysterectomy with pelvic lymphadenectomy. A Piver class I procedure included a simple extrafascial hysterectomy, bilateral salpingo-oophorectomy, removal of the upper third of the vagina, and systematic pelvic lymphadenectomy. For parametrial involvement, lymph node metastasis, or positive or close resection margins as revealed by pathological examinations, radiotherapy to the whole pelvis was administered. Five-year overall survival rates in class I and III arms were 85% and 95%, respectively, but no significant difference was observed between groups ( $p = 0.11$ ). Pelvic recurrence rates were equal between groups: 12.9% (8/62) in the class I arm and 12.6% (8/63) in the class III arm. Morbidity rates were higher after class III radical hysterectomy (84%) than class I radical hysterectomy (45%). In particular, most significant differences were observed in the class III arm for urologic complications, neurogenic bladder (52%), ureterovaginal fistula (7%), and hydronephrosis (12%). Although these results suggested the efficacy of a simple extrafascial hysterectomy for small-size, early-stage cervical cancer, the study was closed prematurely.

**TABLE 1. Completed clinical trials of hysterectomy with minimal parametrectomy for cervical cancer.**

Study	Landoni <i>et al.</i> [8] 2001		Landoni <i>et al.</i> [9] 2012	
Start	1987		1981	
Allocation	RCT		RCT	
Inclusion criteria	FIGO stage (1985) IB, IIA		FIGO IB, IIA Tumor diameter $\leq 4$ cm	
Treatment arm	Class III RH (n = 119)	Class II RH (n = 119)	Class III RH (n = 62)	Class I RH (n = 63)
Survival outcomes				
5-year OS	77%	81% ( $p = 0.7$ )	95%	85% ( $p = 0.1$ )
5-year DFS	73%	75% ( $p = 0.9$ )		
Tumor diameter				
$\leq 4$ cm	75% (n = 89)	76% (n = 90)		
$> 4$ cm	25% (n = 30)	24% (n = 29)		
Radiotherapy following surgery	55% (n = 55)	54% (n = 64)	55% (n = 35)	69% (n = 49)
Long-term urologic complications	13% (n = 16)	33% (n = 40)		
Mean time to voiding (days)	31 (RH) 37 (RH + RT)	16 (RH) 24 (RH + RT)		

RCT, Randomized controlled trial; FIGO, International Federation Gynecology and Obstetrics; RH, Radical hysterectomy with pelvic lymphadenectomy; OS, Overall survival; DFS, Disease-free survival; RT, Radiotherapy.

### 3.2 Ongoing randomized controlled trials

Ongoing randomized controlled trials are summarized in Table 2. Four noninferiority trials were identified: Simple Hysterectomy and Pelvic node dissection in Early-stage, low-risk cervical cancer (SHAPE) (NCT02368574) [10], Chinese Gynecological Oncology Group (CGOG)-001 (NCT02368574) [10], Queleu-Morrow-B and Queleu-Morrow-C Hysterectomy for Early Cervical Cancer (QMBCHECC) (NCT04691453) [10], and Japan Clinical Oncology Group (JCOG)1101 (jRCTs 031180167) [11].

#### 3.2.1 Study design

The three ongoing clinical trials are phase III randomized controlled trials, but JCOG1101 is a single arm non-randomized confirmatory trial. The study design for JCOG1101 [12] is described as follows: In a previous observational JCOG study (JCOG0806-A) [13], the 5-year overall survival rate for 323 FIGO IB1 patients with a  $\leq 2$ -cm tumor size, as measured by magnetic resonance imaging (MRI; n = 238), cone biopsy (n = 51), and both MRI and cone biopsy (n = 34), who underwent a Piver class III radical hysterectomy with pelvic lymphadenectomy was quite high (95.8%), but the pathological parametrial involvement rate was extremely low (1.9%). Such a high rate of overall survival in FIGO IB1 patients with a  $\leq 2$ -cm tumor size who underwent a class III radical hysterectomy would not be expected to differ even if a randomized controlled trial is conducted. If the 5-year overall survival rate for class II radical hysterectomy is similarly high, this may be regarded as a new standard procedure. Therefore, JCOG1101 is set as a non-randomized confirmatory trial, which corresponds to a Phase III randomized controlled trial. The expected 5-year overall survival rate in the experimental arm is also set at 95.8%, and the non-inferiority margin is set at 5%. The threshold 5-year

survival rate of this study is set at 90.8%.

JCOG1101 and QMBCHECC have primary endpoints of overall survival and other studies have primary endpoints of pelvic recurrence-free or disease-free survival.

#### 3.2.2 Eligibility criteria

The inclusion criteria for FIGO stage or tumor size differ. The FIGO stage is from IA1 to IIA1, and tumor size covers microinvasion to  $\leq 4$  cm. With regard to tumor size, the QMBCHECC study widens the tumor size to  $\leq 4$  cm, and other studies narrow tumor size to  $\leq 2$  cm. In SHAPE, inclusion criteria narrow down FIGO stage (2008) to IA2 or IB1. For patients who underwent a cone biopsy, a pathological limit is set for cervical stromal invasion, and/or lateral extension of the tumor. Additionally, in CGOG-001, the depth of stromal invasion is also limited. As for histological subtypes, all studies include squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma.

With regard to exclusion criteria, all studies except for JCOG 1101, exclude lymph node metastasis on preoperative imaging.

#### 3.2.3 Surgical techniques

Radical hysterectomy procedures for the standard arm are defined as follows: In SHAPE, the uterus, cervix, medial one-third of the parametria, 2 cm of the uterosacral ligaments and upper 1–2 cm of the vagina are removed en bloc with pelvic lymph adenectomy. In CGOG-001, radical hysterectomy is performed according to a Piver class III radical hysterectomy. The uterosacral ligament is removed near the sacrum, the cardinal ligament is removed near the pelvic wall, and the vagina with perivaginal connective tissues is removed about 3–4 cm from the cervical lesion [14]. In QMBCHECC, a standard radical hysterectomy with pelvic lymphadenectomy is based on a Querleu and Morrow type C procedure, which is mostly

**TABLE 2. Ongoing clinical trials of hysterectomy with minimal parametrectomy for early-stage cervical cancer.**

Study title	Radical versus simple hysterectomy and pelvic node dissection in patients with low-risk early-stage cervical cancer (SHAPE)	Nonrandomized confirmatory trial of modified radical hysterectomy for patients with FIGO stage Ib1 ( $\leq 2$ cm) uterine cervical cancer (JCOG1101)	Comparison of class II and class III hysterectomy in early-stage cervical cancer (CGOG-001)	Randomized clinical trial comparing the oncology outcome and safety of QM-B and QM-C hysterectomy for early cervical cancer (QMBCHECC)
Start (year)	2012	2013	2015	2021
Study type	Interventional	Interventional	Interventional	Interventional
Primary purpose	Treatment	Treatment	Treatment	Treatment
Allocation	Randomized	Non-randomized, confirmatory	Randomized	Randomized
Primary outcome measures	Pelvic RFS	5-year OS	3-year DFS	5-year OS 5-year DFS
Major inclusion criteria	FIGO stage * IA2 FIGO stage * IB1 For patients underwent LEEP or cone 5.1–10 mm stromal invasion and/or 7.1–20 mm lateral extension. For patients who underwent biopsy only <50% stromal invasion on MRI and $\leq 20$ mm on clinical exam or imaging	FIGO stage * IB1 Tumor $\leq 2$ cm on MRI	FIGO stage * IA2 FIGO stage * IB1 Tumor <2 cm on MRI <50% stromal invasion on MRI or <10 mm stromal invasion on the pathology of the LEEP or cone	FIGO stage** 1A1 FIGO stage ** 1A2 FIGO stage ** IB1 FIGO stage ** 1B2 FIGO stage ** IIA1
Major exclusion criteria	Lymph node metastasis		Lymph node metastasis	Lymph node metastasis
Treatment arm Standard	RH (Class II, III RH)		Class III RH	QM-C Hysterectomy (Class III RH)
Experimental	SH (Class I RH)	Modified RH (Class II RH) Postoperative adjuvant radiotherapy (CCRT) for high-risk cases	Class II RH	QM-B Hysterectomy (Class II RH)
Estimated enrollment (participants)	700	240	500	538

RFS, relapse-free survival; OS, overall survival; DFS, disease-free survival; FIGO, international federation gynecology and obstetrics; MRI, magnetic resonance imaging; LEEP, loop electrosurgical excision procedure; RH, radical hysterectomy; QM, Querleu-Morrow; SH, simple hysterectomy; CCRT, concurrent chemoradiotherapy; \*, FIGO stage 2008; \*\*, FIGO stage 2018.

the same as a Piver class III procedure [15]. In JCOG 1101, the control group of the observational study includes patients who also underwent a Piver class III radical hysterectomy with pelvic lymphadenectomy.

As for the experimental arm, all studies except for SHAPE define a Piver class II radical hysterectomy as a new, less radical, standard hysterectomy with minimal parametrectomy for early-stage cervical cancer; however, slight differences exist. In JCOG 1101, the anterior layer of the vesicouterine ligament is cut and a part of the parametrial tissue is removed for more than 1.5 cm to the pelvic side wall and vaginal canal, with perivaginal tissue from 1.5 cm to 2 cm as part of the study procedure. The posterior layer of the vesicouterine ligament was not resected [12]. In CGOG-001, after separating the ureter, half of the uterosacral ligament and from 1 to 2 cm of the vagina were resected [14]. The entire vesicouterine ligament is preserved. In QMBCHECC, in accordance with a Querleu and Morrow type B hysterectomy, the ureter is mobilized laterally, allowing transection of the paracervix at the level of the ureteral tunnel [15]. This resection involves a standard partial resection of the uterosacral peritoneal fold of the rectouterine (dorsal parametrium) and vesicouterine (ventral parametrium) ligaments. Ten millimeters of the vagina, from the caudal edge of the cervix or tumor, is resected; however, the paravaginal tissues are not radically resected. A Piver class II radical hysterectomy, modified radical hysterectomy, and Querleu and Morrow type B hysterectomy are predominantly the same although slight differences exist. In contrast, in SHAPE, an extrafascial simple hysterectomy with a pelvic lymphadenectomy is considered experimental and involves the removal of the uterus with cervix but not adjacent parametria. A maximum of 0.5 cm of vaginal cuff is removed to allow for the complete removal of the cervix.

In CGOG-001, a hysterectomy is performed laparoscopically. In SHAPE, a variety of experimental procedures are performed, including abdominally, laparoscopically or robotically. In contrast, in JCOG1101 only abdominal procedures are carried out.

### 3.2.4 Adjuvant therapy followed by hysterectomy

In JCOG1101, patients showing pelvic lymph node metastasis or parametrial involvement as determined by pathological examination undergo whole-pelvis irradiation with weekly cisplatin. The performance of postoperative adjuvant therapy in the other three studies is unknown.

## 4. Discussion

In the last century, standard curative surgery for patients with invasive cervical cancer involved radical hysterectomy following adjuvant radiotherapy, including the wide resection of parametrium and vagina with paravaginal tissue, and a systematic pelvic lymphadenectomy. However, complications followed many cases of radical hysterectomy, particularly severe neurogenic bladder that persisted on a long-term basis. Other common complications are: urinary tract fistula, ureteral stenosis, bowel dysfunction including constipation, sexual dysfunction, and lymphocystitis and lymphedema caused

by lymphadenectomy [6, 16–18]. In order to minimize a curative hysterectomy, two research strategies were employed: In so-called “minimally invasive surgery”, that is laparoscopic or robotic radical hysterectomy with pelvic lymphadenectomy, the existing surgical approach is changed, but the extent of removing parametrium basically remains unchanged. In 2018, a multicenter phase III noninferiority randomized controlled trial was completed to assess whether minimally invasive surgery was not inferior to open abdominal radical hysterectomy with pelvic lymphadenectomy with respect to disease-free and overall survival (LACC Clinical Trial) [19]. In this study, the main inclusion criteria for patients were FIGO stage IA or IB1 disease, and a tumor size  $\leq 4$  cm. Standard surgery was a Piver class II or III radical hysterectomy with pelvic lymphadenectomy by open laparotomy, and experimental surgery was a radical hysterectomy with pelvic lymphadenectomy by laparoscopic or robotic procedure. The primary outcome was the disease-free survival rate at 4.5 years. It was found that 91.9% of enrolled patients had stage IB1 disease. Disease-free survival at 4.5 years was 86.0% with minimally invasive surgery and 96.5% with open surgery, but noninferiority was not statistically analyzed. A lower disease-free survival rate was noted for minimally invasive compared with open surgery (91.2% and 97.1%, respectively, after 3 years and the hazard ratio (HR) for disease recurrence or death was 3.74 (95% confidence interval (CI); 1.63–8.58). Lower overall survival was also observed with minimally invasive surgery (93.8% and 99.0%, respectively, after 3 years) and the HR for death from any cause was 6.00 (95% CI; 1.77–20.30). This study concluded that minimally invasive radical hysterectomy with pelvic lymphadenectomy in patients with cervical cancer was associated with a higher rate of recurrence and a lower rate of disease-free survival than the open approach; overall survival was also lower. Thus, minimally invasive surgery might not be effective for patients with FIGO stage IB1 disease, which might adversely affect the oncologic outcomes of SHAPE or OGOG-001. The second research strategy is resecting a smaller portion of the parametrium near the cervix without compromising radicality, regardless of abdominal, laparoscopic or robotic radical hysterectomy. Additionally, when demonstrating the efficacy of a new, less radical surgical procedure, a Phase III randomized controlled trial is considered the gold standard. The present review is derived from this viewpoint.

The impossibility of evaluating pathological parametrial involvement before an operation means a biological indicator that correlates with this is therefore required. Tumor size is one of the independent prognostic factors used to assess patient survival, cancer recurrence, and the incidence of pathological parametrial involvement. Kasamatsu *et al.* [20] reviewed 461 patients with FIGO stage IB cervical cancer who underwent a Piver class III radical hysterectomy with pelvic lymphadenectomy according to pathological tumor size ( $\leq 2$  cm,  $>2$  to  $\leq 4$  cm, and  $>4$  cm). It was found that the incidence of pathological parametrial involvement in the  $\leq 2$  cm group was significantly lower (2%) than in  $>2$  to  $\leq 4$  cm (13%) or  $>4$  cm (29%) groups (both  $p < 0.001$ ). The 5-year overall survival rate was significantly higher in the  $\leq 2$  cm group (97%) compared with  $>2$  to  $\leq 4$  cm (90%) and  $>4$  cm (70%) groups (both  $p$

< 0.001). Covens *et al.* [21] evaluated 842 patients with FIGO stage IA1/2 and IB1 disease who underwent radical hysterectomy with pelvic lymphadenectomy. The incidence of pathological parametrial involvement in patients with a tumor size  $\leq 2$  cm, negative pelvic lymph nodes, and depth of stromal invasion  $\leq 10$  mm was 0.6%. Derks *et al.* [22] reviewed 2124 patients with FIGO stage I/II disease who underwent radical hysterectomy with pelvic lymphadenectomy. A multivariate analysis for disease-free survival revealed an independent association with radical hysterectomy with pelvic lymphadenectomy type (less radical or radical) in favor of more radical parametrectomy (HR; 2.0, 95% CI; 1.6–2.5). On further examination, a comparison of the tumor size  $\leq 2$  cm group (HR; 1.9, 95% CI; 1.0–3.7) with the  $> 2$  cm group did not reveal a difference, meaning that the extent of parametrectomy was not associated with survival among patients with a tumor size  $\leq 2$  cm. Such retrospective studies concluded that radical hysterectomy with pelvic lymphadenectomy and minimal parametrectomy was suitable for FIGO stage IB patients with a tumor size  $\leq 2$  cm.

In the observational JCOG study (JCOG0806-A) [13], 323 patients with FIGO stage IB1 with a tumor size  $\leq 2$  cm, as measured by MRI ( $n = 238$ ), cone biopsy ( $n = 51$ ), and both MRI and cone biopsy ( $n = 34$ ), who underwent a class III radical hysterectomy with pelvic lymphadenectomy showed a low incidence of pathological parametrial involvement (1.9%). Therefore, measuring the cervical tumor size by MRI preoperatively, in addition to cone biopsy, is warranted for FIGO stage IB patients with a tumor  $\leq 2$  cm, particularly as MRI is simple and non-invasive compared to cone biopsy. Additionally, cone biopsy is limited by having to obtain intact diagnostic specimens from patients with endocervical disease.

The study of Landoni *et al.* [8] (2001) did not find a significant difference in overall and disease-free survival between Piver class II and III radical hysterectomy with pelvic lymphadenectomy groups, and concluded class II radical hysterectomy with pelvic lymphadenectomy was suitable for patients with FIGO stage IB–IIA cervical cancer. However, more than half of patients with a tumor size  $> 4$  cm in both class II and III radical hysterectomy with pelvic lymphadenectomy groups underwent radiotherapy after surgery. Tumor size was found to predict a requirement for adjuvant radiotherapy ( $p = 0.000003$ ). Adjuvant radiotherapy was given to 80% of patients in the tumor  $> 4$  cm group and 46% of patients in the tumor  $\leq 4$  cm group. Patients who received radiotherapy showed increased urologic morbidity. Urologic complications for class III versus class II arms showed a relative incidence risk of 1.9; for class II + radiotherapy versus class III it was 1.7 and for class III + radiotherapy versus class III it was 2.3. Moreover, compared to patients who exclusively underwent radical hysterectomy with pelvic lymphadenectomy (0/109), those treated with adjuvant radiotherapy showed a higher incidence (9/129, 6.9%) of leg edema. In this study, the eligibility criteria neglected to define tumor size, and patients with a small tumor size were thought to be suitable for hysterectomy with minimal parametrectomy in any subsequent randomized controlled trial study.

In another study by Landoni (2012), overall survival between class I and III groups did not show a significant dif-

ference, with morbidity rates higher for class III than class I [9]. The incidence of radiotherapy was high despite the eligibility criteria setting a limit on a tumor diameter  $\leq 4$  cm. Radiotherapy was given to 69% of patients in the class I group and 55% of patients in the class III group. For patients who underwent radical hysterectomy, both groups showed higher morbidity rates in patients who received radiotherapy: 46% in the class I group and 83% in the class III group. Although overall survival between conventional Piver class III and class I/II radical hysterectomy groups did not significantly differ according to both Landoni *et al.* [8, 9] studies (2001) (2012), the frequency of postoperative radiotherapy should be reduced in subsequent new randomized controlled trials.

Tumor size is restricted to under 2 cm in the three ongoing randomized controlled trials, except for QMBCHECC. As mentioned in the preceding section, the inclusion criteria of QMBCHECC, including FIGO stages (2018) IA1, IA2, IB1, IB2 or IIA1 with a tumor size  $\leq 4$  cm, appear to relate to tumors that are slightly larger. With regard to a smaller tumor size, only QMBCHECC inclusion criteria include FIGO stage IA1. A stage IA1 tumor equates to a microinvasive tumor, and for a tumor with no lymph vascular space invasion (LVSI), simple hysterectomy has been sufficient [23]. Cervical conization has also been used for fertility preservation. A simple hysterectomy or type II radical hysterectomy with pelvic lymphadenectomy have become almost acceptable for a stage IA1 tumor with LVSI [23]. A FIGO stage IA1 tumor might be too small for randomized controlled trials of radical hysterectomy with pelvic lymphadenectomy and minimal parametrectomy considering morbidity due to radical hysterectomy with pelvic lymphadenectomy. Presently, Piver class II radical hysterectomy with pelvic lymphadenectomy is a standard procedure for FIGO stage IA2 disease [23]. In SHAPE, for patients with IA2 disease, a simple hysterectomy with lymphadenectomy is considered experimental. Therefore, for patients with IA2 disease a simple hysterectomy may be a new, less extensive surgery depending on this study's outcomes.

Regarding types of radical hysterectomies, a simple hysterectomy is experimental only in SHAPE; Piver type II radical hysterectomy, including a modified radical hysterectomy or Querleu and Morrow type B hysterectomy, is offered in the remaining three randomized controlled trials as an experimental procedure. Therefore, the inclusion criteria for SHAPE include a tumor size  $\leq 2$  cm as well as cervical stromal invasion limited to less than 10 mm or 50%; pelvic lymph node metastasis is a major exclusion criterion.

Two randomized controlled trials set overall survival as a primary endpoint, which is considered suitable as a study objective. In phase III randomized controlled trials of less radical hysterectomy for early-stage cervical cancer, the overall survival rate directly benefitted patients, highlighting its importance as a primary endpoint.

In conclusion, currently, phase III randomized controlled trials of optimal curative hysterectomy with minimal parametrectomy are ongoing. Although several differences exist in terms of primary outcome measures, eligibilities or types of surgical procedures, a standard, less radical curative hysterectomy with minimal parametrectomy for patients with early-stage cervical cancer may be established instead of traditional Piver class

III radical hysterectomy with pelvic lymphadenectomy after the demonstration of its noninferiority with regard to overall, disease-free or recurrence-free survival.

## AUTHOR CONTRIBUTIONS

TK—Conceptualization; Writing—original draft; Data curation. TA—Writing—review. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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