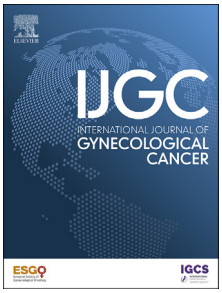
ORIGINAL RESEARCH

Minimally invasive compared to open surgery in patients with low-risk cervical cancer following simple hysterectomy: An exploratory analysis from the Gynegologic Cancer Intergroup/Canadian Cancer Trials Group CX.5/SHAPE trial



Marie Plante[a,*], Sven Mahner[b], Alexandra Sebastianelli[c], Paul Bessette[d], Eric Lambaudie[e], Frederic Guyon[f], Jurgen Piek[g], Ramon Smolders[h], John Tidy[i], Karin Williamson[j], Lars Hanker[k], Frederic Goffin[l], Irina Tsibulak[m], Brynhildur Eyjolfsdottir[n], Noreen Gleeson[o], Jung-Yun Lee[p], Yuwei Ke[q], Janice S. Kwon[r], Sarah E. Ferguson[s], Lois Shepherd[q], Dongsheng Tu[q]

[a]*Centre Hospitalier Universitaire de Québec, Québec City, Canada*
[b]*Ludwig Maximilians University Munich, Munich, Germany*
[c]*Centre Hospitalier Universitaire de Québec de Québec, Québec City, Canada*
[d]*Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Canada*
[e]*Institut Paoli-Calmettes, Marseilles, France*
[f]*Institut Bergonié, Bordeaux, France*
[g]*Catharina Hospital and Catharina Cancer Institute, Eindhoven, The Netherlands*
[h]*Erasmus MC Cancer Institute, Rotterdam, The Netherlands*
[i]*Sheffield Teaching Hospitals National Health Services Foundation Trust, Sheffield, United Kingdom*
[j]*Nottingham University Hospitals, National Health Services, Nottingham, United Kingdom*
[k]*University Hospital Munster, Munster, Germany*
[l]*Centre Hospitalier Universitaire de Liege, Liege, Belgium*
[m]*Medical University of Innsbruck, Innsbruck, Austria*
[n]*Oslo University Hospital, Radium Hospital, Oslo*
[o]*St James's Hospital University Hospital, Dublin, Ireland*
[p]*Yonsei University College of Medicine, Seoul, Korea*
[q]*Queens' University, Kingston, Canada*
[r]*University of British Columbia, Vancouver, Canada*
[s]*Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada*

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ABSTRACT

Objective: The Laparoscopic Approach to Cervical Cancer trial demonstrated that minimally invasive radical hysterectomy was associated with worse disease-free survival and overall survival among women with early-stage cervical cancer. It is unknown whether this applies to patients with low-risk disease following simple hysterectomy.

Methods: Among patients who underwent simple hysterectomy in the Simple Hysterectomy And PElvic node assessment trial, univariate and multivariate Cox models were used to assess the association of minimally invasive versus open surgery with clinical outcomes, including pelvic and extra-pelvic recurrence-free survival, overall recurrence-free survival, and overall survival. Other variables included age, race, performance status,

WHAT IS ALREADY KNOWN

The Simple Hysterectomy And PElvic node assessment trial demonstrated that simple hysterectomy is not inferior to radical hysterectomy in patients with low-risk cervical cancer meeting the strict SHAPE criteria.

WHAT THIS STUDY ADDS

This exploratory analysis from the SHAPE trial indicates that there is no difference in outcome between patients undergoing minimally invasive versus open surgery.

* ***Correspondence to***; *marie.plante@crhdq.ulaval.ca (M. Plante)*

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body mass index, stage, histologic type and grade, diagnostic procedure, lymphovascular space invasion before surgery and on final pathology, lymph node status, residual disease, and lesions >2 cm on final pathology.

Results: A total of 338 patients underwent simple hysterectomy. Of those, 281 (83%) were performed by minimally invasive surgery and 57 (17%) by open surgery. With a median follow-up of 4.5 years, a total of 12 (4.3%) recurrences were observed in 281 patients having simple hysterectomy by minimally invasive surgery versus 3 in 57 (5.3%) having open surgery ($p = .73$ from Fisher exact test). Although not randomized, the 2 groups were comparable except for histology and residual disease in the hysterectomy specimen. Patients with minimally invasive surgery had more adenocarcinoma and less adenosquamous compared to open surgery (35.9% versus 22.9% and 3.6% versus 14%, respectively; $p = .005$). Significantly fewer patients treated by minimally invasive surgery had residual disease in the hysterectomy specimen compared to open surgery (43.1 versus 57.9%; $p = .04$). No statistically significant difference between minimally invasive and open surgery in pelvic and extra-pelvic recurrence-free survival, overall recurrence-free survival, or overall survival was found.

Conclusion: Our data indicate no statistical evidence that minimally invasive surgery is associated with poorer clinical outcomes for patients meeting the SHAPE criteria who underwent simple hysterectomy. Because the surgical approach was not a randomization factor, a large prospective trial is needed to confirm our results before a routine simple hysterectomy by minimally invasive surgery can be recommended.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

The results of our study suggest that simple hysterectomy by minimally invasive surgery may be a safe option for the management of patients with low-risk disease. Results need to be confirmed in a larger clinical trial.

Keywords:
early-stage cervical cancer;
simple hysterectomy;
minimally invasive surgery

INTRODUCTION

The Simple Hysterectomy And PElvic node assessment (SHAPE) trial was a prospective randomized study designed to evaluate the safety of simple hysterectomy compared to radical hysterectomy in patients with low-risk early-stage cervical cancer.[1] In the SHAPE trial, the low-risk disease was defined as lesions measuring ≤2 cm with limited depth of stromal invasion (either <10 mm on diagnostic loop electrical excision procedure or cone), or <50% depth of invasion on pre-operative pelvic magnetic resonance imaging and limited to human papillomavirus-related histologies (squamous, adenocarcinoma, and adenosquamous). The study concluded that in low-risk early-stage patients, simple hysterectomy was not inferior to radical hysterectomy with respect to a 3-year pelvic recurrence rate (2.52% vs 2.17%, respectively). The 3-year extra-pelvic recurrence-free survival (98.1% vs 99.7%) and overall survival (99.1% vs 99.4%) were also comparable between simple and radical hysterectomy. The SHAPE trial provides level-1 evidence and suggests that simple hysterectomy can now be considered "the new standard of care" for patients meeting the SHAPE criteria.

However, in the SHAPE trial, the surgical approach (minimally invasive surgery versus open surgery) was not a randomization factor, and thus a comparison of surgical approach was not part of the primary and secondary objectives of the study. As such, the trial was not specifically designed to assess the outcomes of patients in relation to the surgical approach versus the type of hysterectomy (simple versus radical).

The publication of the Laparoscopic Approach to Cervical Cancer (LACC) trial in 2018 drastically changed the surgical treatment paradigm for cervical cancer as the results indicated significantly worse disease-free and overall survival in patients with early-stage cervical cancer (with lesions up to 4 cm) undergoing laparoscopic compared to open radical hysterectomy in terms of recurrence and survival.[2] However, the LACC trial was not powered to specifically evaluate outcomes in the subgroup of patients with lesions measuring ≤2 cm. An update of the LACC trial was recently published confirming worse outcomes following laparoscopy compared to open surgery even for patients with lesions ≤2 cm (disease-free survival at 4.5 years was 99.5% following open surgery versus 90.4% following laparoscopy).[3]

Since the initial LACC publication, numerous retrospective studies and reviews have reported conflicting results with some reporting either worse or no difference in outcomes following laparoscopic radical hysterectomy compared to open surgery in lesions <2 cm,[4-6] while others found outcomes of both approaches to be comparable when laparoscopic surgery is performed following very careful technical considerations such as pre-operative conization with negative margins, no use of uterine manipulator, protective maneuvers, closure of the vaginal cuff, etc.[7-14] Therefore, it is unclear at this point if laparoscopic radical hysterectomy is safe for patients with lesions <2 cm.

There are very few studies specifically evaluating the safety of minimally invasive surgery in patients with lesions ≤2 cm undergoing simple hysterectomy. The available studies are retrospective and suffer significant biases.[15-17] Therefore, the objective of this exploratory analysis of the SHAPE trial was to evaluate if a simple hysterectomy performed by laparoscopy is safe compared to open surgery in patients with low-risk early-stage cervical cancer meeting the SHAPE criteria.

METHODS

SHAPE is a phase III, prospective, multicenter, international trial comparing simple hysterectomy to radical hysterectomy with lymph node evaluation in patients with low-risk disease. Details of the SHAPE trial have been published recently.[1] Briefly, inclusion criteria included patients with HPV-related histology (squamous, adenocarcinoma, and adenosquamous), any histologic grade, FIGO 2009 stage IA2/IB1 with lesions ≤2 cm and limited depth of stromal invasion (either <10 mm on diagnostic loop electrical excision

procedure or cone or <50% depth of invasion on pre-operative pelvic magnetic resonance imaging), and no evidence of lymph node metastasis on pre-operative imaging. The presence of lymphovascular space invasion was allowed.

The surgical approach was not a randomization factor and was left at the discretion of the surgeon. Magnetic resonance imaging was mandatory except for FIGO 2009 stage IA2 patients who underwent pre-operative loop electrical excision procedure or conization. Exclusion criteria included other histologic subtypes, lesions measuring >2 cm, or evidence of metastatic disease on pre-operative imaging. After providing written informed consent, eligible patients were randomized 1:1 to receive simple or radical hysterectomy by a minimization method after stratification by cooperative group, intended sentinel node mapping, stage, histological type, and grade. The protocol was developed by the Canadian Cancer Trials Group. The required ethical review board approval was obtained from the principal investigator's institution (Comité d'éthique de la recherche du Centre Hospitalier Universitaire de Québec-Université Laval) to enroll patients in this study. Ethics approval was also obtained from each local participating institution in the trial.

Statistical Analysis

Fisher exact test or Wilcoxon tests together with standardized mean difference were used to compare the baseline characteristics and surgical outcomes between minimally invasive and open surgery groups for respectively categorical and continuous variables. Cox model with a single covariate was used to compare minimally invasive and open surgery and each level of other baseline factors and surgical outcomes in univariate analyses for time-to-event outcomes which include pelvic recurrence-free survival, extra-pelvic recurrence-free survival, recurrence-free survival, and overall survival. Multivariate analysis was performed using the Cox models with surgical approach and the following covariates which were included in the multivariate Cox models of both the LACC trial[2] and the population-based study by Melamed and colleagues[18] and available in the data collected in our study: race (White vs Other), age (≤65 vs >65 years), performance status (0 vs 1), body mass index (<20, 20-25, vs >25), histologic grade (1, 2, 3 vs not assessable), lymph vascular space invasion before surgery (yes vs no), a positive node on final pathology (yes vs no), tumor size (>2 cm vs ≤2 cm on final pathology), adjuvant treatment (yes vs no). Diagnostic procedure (loop electrical excision procedure/cone ± cervical biopsy vs cervical biopsy only) was considered an important factor by our investigators and, therefore, was also included as a covariate in the model. Minimally invasive and open surgery were also compared by an inverse probability of treatment weighting approach with stabilized weights constructed from a logistic regression model with the same covariates listed above. As an exploratory analysis, *p*-values were not adjusted for multiple comparisons and any difference with *p*-value less than .05 was considered statistically significant.

RESULTS

Among the 700 patients initially randomized in the trial, 350 patients were allocated to the simple hysterectomy arm and 336 underwent the allocated procedure. Two patients allocated to radical hysterectomy were treated by simple hysterectomy. Therefore, a total of 338 patients underwent simple hysterectomy. Of those, 281 (83%) were performed by minimally invasive surgery and 57 (17%) by open surgery. Table 1 summarizes patients' characteristics. A significant difference between patients who received laparoscopic and open surgery was found only in histological type ($p = .005$) with more patients with adenocarcinoma and fewer patients with adenosquamous carcinoma undergoing laparoscopic surgery (35.9% versus 22.8% and 3.6% versus 14%, respectively). The standardized mean difference was, however, higher than 0.1, which denotes a meaningful imbalance, for almost all baseline characteristics except age and body mass index.

The outcomes of the surgery are summarized in Table 2. Significantly fewer patients treated by laparoscopy had residual disease in the hysterectomy specimen than those treated by open surgery (43.1 versus 57.9%, $p = .04$). No statistically significant difference between the 2 surgical approaches was found in rates of lymphovascular invasion, positive surgical margins on the hysterectomy specimen, positive nodes, lesions >2 cm and adjuvant treatments but lesion >2 cm was the only variable with a standardized mean difference less than 0.1. Of note, although numerically more patients in the laparoscopy group received adjuvant treatment compared to the open surgery group (10% versus 5.3%) this difference was not statistically significant ($p = .32$) and may be a reflection of the fact that more patients in the laparoscopy group had positive nodes on final pathology (4% versus 0%, $p = .22$).

With a median follow-up of 4.5 years, a total of 12 (4.3%) recurrences (pelvic or extra-pelvic) were observed in 281 patients who had laparoscopic surgery versus 3 (5.3%) in 57 patients having open surgery. A total of 4 deaths related to cervical cancer were observed, all in the laparoscopy group. Table 3 summarizes the location of the recurrences and cause of deaths as well as unadjusted and adjusted HRs from both the multivariate Cox model and inverse probability of treatment weighting approach and associated p-values for the comparison between minimally invasive and open groups in the pelvic, extra-pelvic and recurrence-free survival and overall survival. No statistically significant difference between minimally invasive and open surgery in any of the clinical outcomes was found, as evidenced by the Kaplan-Meier curves presented in Figure A through D.

The number of events and oncologic outcomes at 3 years for other baseline variables and surgical outcomes is presented in Tables S1 through S4 for respectively the pelvic, extra-pelvic, and recurrence-free survival and overall survival. Significant differences were found in univariate analyses for the following variables and oncologic outcomes: residual disease in the hysterectomy specimen for pelvic recurrence-free survival (Table S1); lymph vascular space invasion before surgery and on final pathology, lesions >2 cm on final pathology and adjuvant therapy for extra-pelvic recurrence-free survival (Table S2); lymphovascular space invasion before surgery, residual disease in the hysterectomy specimen, lesions >2 cm on final pathology, and adjuvant therapy for recurrence-free survival (Table S3); lymph vascular space invasion before surgery, lesions >2 cm on final pathology, and adjuvant therapy for overall survival (Table S4). For the variables and oncologic outcomes included in the multivariate Cox model, diagnostic procedure was found as a significant and independent predictor for pelvic recurrence-free survival, lymphovascular space invasion before

Table 1 Characteristics of the Patients at Baseline (Before Randomization)

Characteristics	Number of subjects (%)		*p*-Value	Standardized mean difference
	MIS *n* = 281	Open *n* = 57		
Race[a]			.11	0.46
White	206 (73.3)	50 (87.7)		
Asian	17 (6.1)	3 (5.3)		
Black or African American	3 (1.1)	1 (1.8)		
American Indian or Alaska Native	1 (0.4)	0 (0.0)		
Not reported (or refused)	43 (15.3)	2 (3.5)		
Unknown	11 (3.9)	1 (1.8)		
Age (y)			.16	0.03
Median (range)	42 (26-74)	43 (28-72)		
≤50	216 (76.9)	49 (86.0)		
>50	65 (23.1)	8 (14.0)		
ECOG performance status			.27	0.16
0	271 (96.4)	53 (93.0)		
1	10 (3.6)	4 (7.0)		
Body mass index			.44	0.02
Median [range]	24.7 [16.4-53.3]	28.5 [18.3-39.0]		
Histological type			.005	0.44
Squamous	170 (60.5)	36 (63.2)		
Adenocarcinoma	101 (35.9)	13 (22.8)		
Adenosquamous	10 (3.6)	8 (14.0)		
FIGO stage			.44	0.15
IA2	26 (9.3)	3 (5.3)		
IB1	255 (90.8)	54 (94.7)		
Histologic grade			.33	0.27
1	61 (21.7)	12 (21.1)		
2	108 (38.4)	16 (28.1)		
3	39 (13.9)	8 (14.0)		
Not assessable	73 (26.0)	21 (36.8)		
Diagnostic procedure			.21	0.24
LEEP/cone	234 (83.3)	51 (89.5)		
Cervical biopsy only	45 (16.0)	5 (8.8)		
Not reported	2 (0.7)	1 (1.8)		
Lymph vascular space invasion before surgery			.78	0.11
Yes	62 (22.1)	15 (26.3)		
No	175 (62.3)	34 (59.7)		
Not reported	44 (15.7)	8 (14.0)		

Abbreviations: ECOG, Eastern Cooperative Oncology Group; LEEP, loop electrosurgical excision procedure; MIS, minimally invasive hysterectomy.
[a] Self-reported by participants.

surgery for extra-pelvic and recurrence-free survival, and adjuvant therapy for extra-pelvic recurrence-free and overall survival (Tables S1-S4).

DISCUSSION

Summary of Main Results

This exploratory analysis from the SHAPE trial aimed to examine specifically the group of patients who underwent a simple hysterectomy and compare outcomes between patients who underwent minimally invasive surgery and open surgery. We found no statistically significant difference between minimally invasive and open surgery in any of the clinical outcomes (pelvic recurrence, extra-pelvic recurrence, and death). On both univariate and multivariate analyses, 2 factors appear to be consistently associated with worse outcomes: the presence of lymph vascular space invasion and adjuvant treatment.

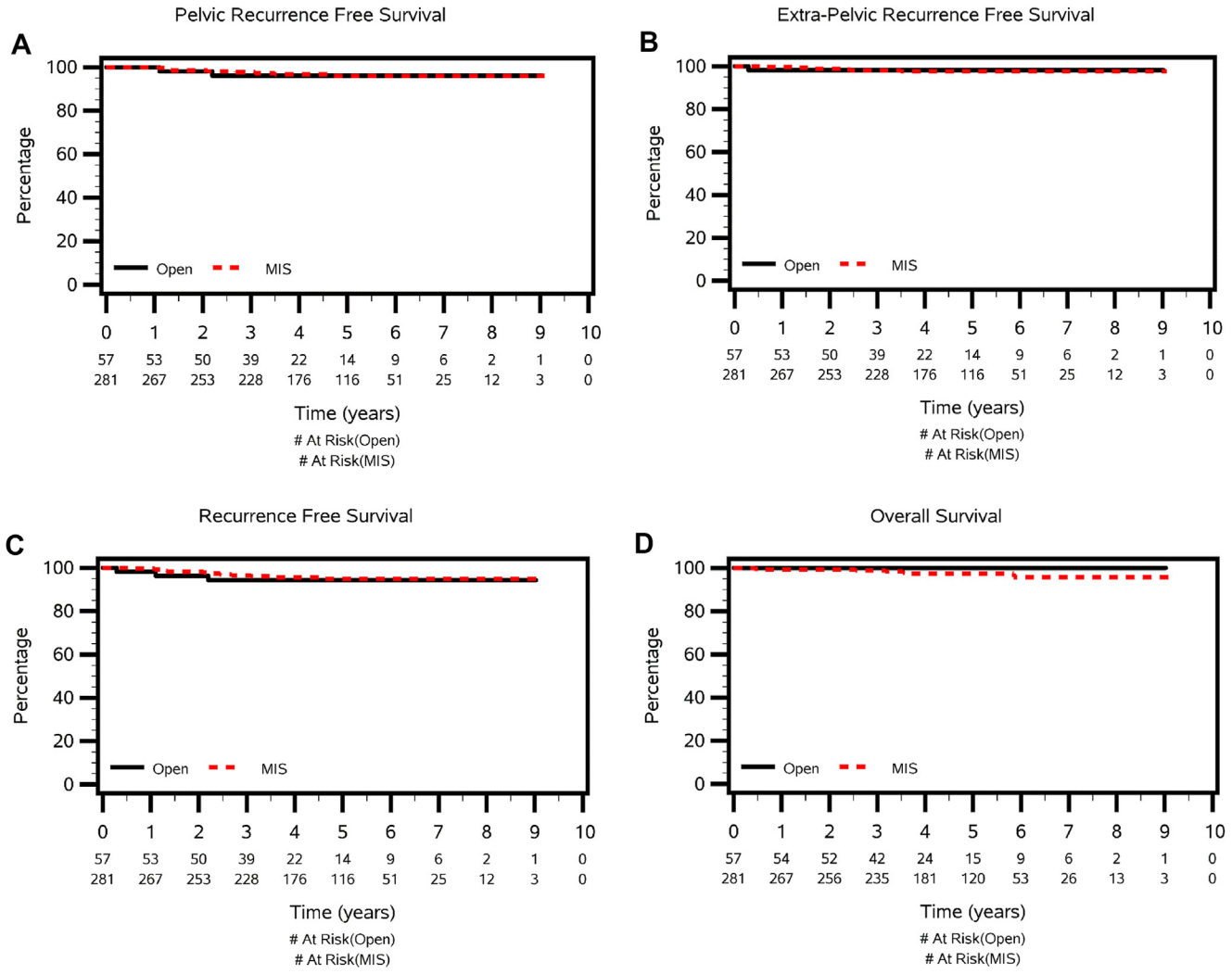

Figure Kaplan-Meier curves for the MIS group (red dotted line) versus open surgery group (black line). The 3-year pelvic recurrence-free survival was respectively 97.7% (95% CI 94.9-99.0) in the minimally invasive group versus 96.1% (95% CI 85.3-99.0) in open surgery group (**A**), extra-pelvic recurrence-free survival was 98.1% (95% CI 95.4-99.2) versus 98.1% (95% CI 87.6-99.8) (**B**), recurrence-free survival was 96.5% (95% CI 93.4-98.2) versus 94.3% (95% CI 83.4-98.1) (**C**), and overall survival was 98.9% (95% CI 96.5-99.6) versus 100% (95% CI 100-100) (**D**). MIS, minimally invasive surgery. A, Kaplan-Meier curves for pelvic recurrence-free survival by surgical approach. B, Kaplan-Meier curves for extra-pelvic recurrence-free survival by surgical approach. C, Kaplan-Meier curves for recurrence-free survival by surgical approach. D, Kaplan-Meier curves for overall survival by surgical approach.

Results in the Context of Published Literature

The 3-year recurrence-free survival in the minimally invasive surgery group with simple hysterectomy was 96.5% (95% CI 85.3-99.0) in our study. This rate is actually better than the 3-year disease-free survival reported in the updated LACC trial following laparoscopic radical hysterectomy for the subgroup of patients with lesions <2 cm with a rate of 92% (95% CI 86.0-98.0), confirming that for patients with low-risk small volume lesions meeting the SHAPE criteria, radical hysterectomy does not offer benefits over simple hysterectomy.[3] In addition, the 3-year overall survival in the minimally invasive group in our study was 98.9% (95% CI 96.5-99.6) versus 100% in the open surgery group which is reassuring and suggests that laparoscopy did not appear to be detrimental in terms of survival. However, this should be interpreted with caution given the surgical approach was not randomized in our study and because of the small number of recurrences observed.

Although not statistically significant, one concerning observation is that 6 of the 7 extra-pelvic recurrences and all 4 cervical cancer-related deaths occurred in the minimally invasive surgery group (Table 3). There were 2 abdominal recurrences (carcinomatosis) in that group (16%) versus none in the open surgery group. Similar rates of carcinomatosis were observed in other series including in the recent LACC trial update (23% versus 9% following laparoscopic compared to open radical hysterectomy), and in the systematic review by Hoegl and colleagues[19] (22.2% versus 8.8%, respectively).[3,19]

A diagnostic procedure was found to be a significant and independent predictor for pelvic recurrence-free survival. This would be in keeping with the observation that the presence of residual cancer on the cervix at the time of hysterectomy has been associated with a higher risk of cancer recurrence following laparoscopic surgery, possibly because of the risk of peritoneal

Table 2 Surgical Outcomes on Final Pathology and Adjuvant Treatments by Surgical Approach Among Patients Who Had Simple Hysterectomy

Surgical Outcome and Adjuvant Treatment	Number of subjects (%)		*p*-Value	Standardized mean difference
	MIS $n = 281$	Open $n = 57$		
Presence of lymphovascular space invasion	37 (13.2)	8 (14.0)	.83	0.32
Positive surgical margins on hysterectomy specimen	6 (2.1)	2 (3.5)	.63	0.31
Positive nodes on final pathology	11 (3.9)	0 (0.0)	.22	0.29
Residual disease in the hysterectomy specimen	121 (43.1)	33 (57.9)	.04	0.30
Lesions >2 cm on final pathology	11 (3.9)	3 (5.3)	.71	0.06
Any adjuvant treatment	28 (10.0)	3 (5.3)	.32	0.18
Chemotherapy only	1	0		
Radiotherapy only	13	2		
Both chemotherapy and radiotherapy	14	1		

Abbreviation: MIS, minimally invasive hysterectomy.

and vaginal contamination. Indeed, the hypothesis for the worse outcome associated with laparoscopy in the LACC trial included the use of a uterine manipulator, the presence of macroscopic disease on the cervix, and performing intra-abdominal colpotomy exposing the abdominal cavity to cancer cells.[20] Recent studies have shown that the use of "protective maneuvers" (such as vaginal cuff formation and closure of the cervix) may represent a strategy to reduce the risk of recurrence with laparoscopy.[7,13] Pre-hysterectomy conization with negative margins might be another strategy to lower the risk of recurrence.[7-12] Following the results of the updated LACC trial publication, Bercow and colleagues[21] reviewed the surgical management in early-stage

Table 3 Number of Recurrences and Deaths with HRs for Event-Free Survival of Specific Events

Recurrence or Death	Number of events (%)		Unadjusted[a]		Adjusted[b]		IPTW[c]	
	MIS $n = 281$	Open $n = 57$	HR (95% CI)	*p*-Value	HR (95% CI)	p-Value	HR (95% CI)	*p*-Value
Recurrence[d]	12 (4.3)	3 (5.3)	0.74 (0.21-2.61)	0.63	0.81 (0.20, 3.33)	0.77	0.77 (0.18, 3.21)	0.72
Pelvic recurrence	9 (3.2)	2 (3.5)	0.81 (0.18-3.77)	0.79	0.89 (0.16, 4.75)	0.87	0.61 (0.13, 2.93)	0.54
Vaginal vault	7	2						
Parametrium	1	0						
Pelvic node	1	0						
Extra-pelvic recurrence	6 (2.1)	1 (1.8)	1.11 (0.13-9.24)	0.95	1.17 (0.10, 13.4)	0.90	4.22 (0.49, 35.7)	0.19
Abdomen	2	0						
Para-aortic lymph nodes	2	0						
Supraclavicular nodes	1	0						
Extra-pelvic nodes	1	0						
Vaginal introitus	0	1						
Death	7 (2.5)	0 (0.0)	NE (NE-NE)	0.99	NE (NE-NE)	0.99	NE (NE-NE)	NA
Cervical Cancer	4	0						
Other primary malignancy	1	0						
Other medical condition	2	0						

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IPTW, inverse probability of treatment weighting; LEEP, loop electrosurgical excision procedure; MIS, minimally invasive hysterectomy; NE, not estimable; NA, not available.

[a] From Cox proportional hazards model with a surgical approach as a single covariate.

[b] From multivariate Cox models with surgical approach, race (white versus others), age (≤65 versus >65 years), ECOG performance status (0 versus 1), body mass index (<20. 20-25, versus >25), histologic grade (1, 2, 3 versus not assessable), lymph vascular space invasion before surgery (yes vs, no), positive node on final pathology (yes versus no), tumor size (>2 cm versus ≤2 cm on final pathology), adjuvant treatment (yes versus no), and diagnostic procedure (LEEP/Cone ± cervical biopsy versus cervical biopsy) as covariates.

[c] From IPTW approach with stabilized weights constructed from a logistic regression model with the same covariates listed above.

[d] A total of 3 patients in the MIS group but no patient in the open group had both pelvic and extra-pelvic recurrences as their first event.

cervical cancer and urged surgeons to be cautious and make all efforts to avoid peritoneal contamination using the strategies outlined above.

Strengths and Weaknesses

The major strength of this study is that the data used for this exploratory analysis is derived from a large international trial database with robust data collection. Limitations include the fact that the choice of surgical approach was not randomized and was not a stratification factor and thus potentially subject to surgeons' biases. However, although the study was not powered to test surgical approach, a lack of statistical evidence of difference is not necessarily evidence of a lack of a clinically important difference as suggested by the wide CI around the HR estimate, which is consistent with large differences in oncologic outcomes between groups. In addition, the small number of events (12 recurrences) and the low number of open (57) compared to minimally invasive surgery (281) makes it difficult to adjust the potential biases by multivariable models. Adjuvant treatment was administered at the discretion of treating physicians in accordance with local practice. Lastly, the results can only be applied to patients meeting the SHAPE low-risk criteria ($\leq$2 cm with limited depth of stromal invasion).

Implications for Practice and Further Research

At this point, the results of our exploratory analysis of the SHAPE trial cannot support the use of minimally invasive surgery since the trial was not designed to study this question. Of concern, all deaths and peritoneal carcinomatosis recurrences occurred in patients treated with minimally invasive surgery although only a small number of patients were treated with open surgery. Additional studies are needed to determine the safety of minimally invasive surgery particularly in patients with previous conization and negative margins.[22,23] The LASH trial (minimally invasive simple hysterectomy in low-risk cervical cancer; NCT06416748), a prospective single-arm study, will be initiated soon to specifically assess the role and safety of minimally invasive simple hysterectomy in patients meeting the "SHAPE criteria" and following conization.[24]

CONCLUSION

In conclusion, this exploratory analysis of the SHAPE trial observed a low rate of recurrence. For patients meeting the SHAPE criteria, there was no difference in terms of clinical outcomes (pelvic recurrence, extra-pelvic recurrence, and death) between simple hysterectomy performed by minimally invasive surgery or open surgery, although the study was not powered to test surgical approach. A larger prospective trial designed specifically to assess the safety of simple hysterectomy by minimally invasive hysterectomy in carefully selected low-risk patients is warranted to confirm our results.

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Author contributions Marie Plante: Conceptualization, Data curation, Formal analysis, Writing — original draft, Writing — review & editing. Irina Tsibulak: Writing — review & editing. Sven Mahner: Formal analysis, Validation, Conceptualization, Methodology. Brynhildur Eyjolfsdottir: Writing — review & editing. Alexandra Sebastianelli: Formal analysis, Validation, Writing — review & editing. Noreen Gleeson: Writing — review & editing. Paul Bessette: Writing — review & editing. Eric Lambaudie: Writing — review & editing. Jung-Yun Lee: Writing — review & editing. Frederic Guyon: Writing — review & editing. Yuwei Ke: Formal analysis, Writing — review & editing. Janice S. Kwon: Conceptualization, Validation, Writing — review & editing. Jurgen Piek: Writing — review & editing. Ramon Smolders: Writing — review & editing. Sarah E. Ferguson: Conceptualization, Visualization, Writing — review & editing. John Tidy: Writing — review & editing. Lois Shepherd: Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Validation, Writing — review & editing. Karin Williamson: Writing — review & editing. Dongsheng Tu: Conceptualization, Data curation, Formal analysis, Methodology, Validation, Visualization, Writing — review & editing. Lars Hanker: Writing — review & editing. Frederic Goffin: Writing — review & editing.

Declaration of Competing Interests None declared.

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