Original Article

INTERNATIONAL JOURNAL OF SURGERY

OPEN

Surgical approach, preoperative LEEP/conization and patterns of recurrence and death in low-risk cervical cancer – exploratory analysis from the CCTG CX.5/SHAPE trial

Sven Mahner, MD[a,*], Fabian Trillsch, MD[a], Janice S. Kwon, MD[b], Sarah E. Ferguson, MD[c], Paul Bessette, MD[d], Alexandra Sebastianelli, MD[e], François Golfier, MD[f], Tristan Gauthier, MD[g], Cor De Kroon, MD[h], Willemien van Driel, MD[i], John Tidy, MD[j], Karin Williamson, MD[k], Frederic Goffin, MD[l], Stephan Polterauer, MD[m], Brynhildur Eyjólfsdóttir, MD[n], Jung-Yun Lee, MD[o], Patrick Maguire, MD[p], Barbara Schmalfeldt, MD[q], Lois E. Shepherd, MD[r], Dongsheng Tu, PhD[r], Marie Plante, MD[e]

Background: SHAPE demonstrated that simple hysterectomy was not inferior to radical hysterectomy in patients with low-risk cervical cancer. To further understand the role of preoperative LEEP/conization, clear LEEP/conization margins and surgical approach, analyses were performed regarding patterns of recurrence and death.

Patients and methods: Outcomes (pelvic recurrence, extrapelvic recurrence and cervical cancer-related death) by surgical approach (minimally invasive surgery [MIS] vs. open), LEEP/conization (yes vs. no, involved vs. negative margins) and residual disease in the hysterectomy specimen (yes vs. no) are described with 3-year outcome rate estimated by Kaplan–Meier method and compared by Cox models.

Results: With a median follow-up of 4.5 years, 25 (3.7%) recurrences (pelvic or extrapelvic) were observed from 680 patients who underwent simple (338) or radical (342) hysterectomy. At surgeons' discretion, MIS was performed in 524 (77%) and open surgery in 156 (23%). Overall, 19 recurrences occurred following MIS (3.6%) and 6 following open surgery (3.8%). Among 174 patients with clear margins after LEEP/conization, 2 (1.4%) developed pelvic recurrences after MIS and none after open surgery. Among the entire cohort, 9 patients had extrapelvic recurrence, 7/524 (1.3%) following MIS and 2/156 (1.3%) following open surgery. However, no extrapelvic recurrence occurred after either MIS or open surgery among patients who had pre-hysterectomy LEEP/conization with clear margins. With regards to cervical cancer-related deaths, all occurred after MIS (5/524, 0.95%) and none after open surgery or after previous LEEP/conization with clear margins.

Conclusions: Similar rates of recurrence and death were observed between patients who underwent MIS and open surgery within the SHAPE cohort. No extrapelvic recurrences and death occurred in patients with clear margins following prior LEEP/conization, regardless of surgical approach. The concept of pre-hysterectomy LEEP/conization might help to triage the most effective surgical strategy in terms of surgical approach and radicality in low-risk cervical cancer patients to ensure safe outcomes.

Keywords: early stage cervical cancer, simple hysterectomy, surgical approach, pre-hysterectomy LEEP/conization, resection margin, recurrence

Introduction

Results of the SHAPE trial (Simple Hysterectomy and Pelvic Node Assessment) demonstrated that simple hysterectomy (SH) was not inferior to radical hysterectomy (RH) with respect

[a]Department of Obstetrics and Gynecology, University Hospital, LMU Munich, Munich, Germany, [b]Department of Obstetrics and Gynecology, University of British Columbia, Vancouver, Canada, [c]Department of Obstetrics and Gynecology, University of Toronto, Division of Gynecologic Oncology Princess Margaret Cancer Centre, Toronto, Canada, [d]Université de Sherbrooke, Sherbrooke, Canada, [e]Centre Hospitalier Universitaire de Québec, Québec, Canada, [f]Hospices Civils de Lyon - Hôpital Lyon Sud, Lyon, France, [g]CHU de Limoges - Hôpital Dupuytren, Limoges, France, [h]Department of Gynaecology, Leiden University Medical Center, Leiden, The Netherlands, [i]Netherlands Cancer Institute, Amsterdam, The Netherlands, [j]Royal Hallamshire Hospital, Sheffield, UK, [k]Nottingham University Hospitals, Nottingham, UK, [l]Department of Obstetrics and Gynecology, University Hospital of Liège and Hospital of Citadelle, Liège, Belgium, [m]Department of Obstetrics and Gynecology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria, [n]Oslo University Hospital, Oslo, Norway, [o]Yonsei University College of Medicine, Seoul, Republic of Korea, [p]Division of Gynaecological Oncology, St James's Hospital, Dublin, Ireland, [q]University Medical Center Hamburg-Eppendorf, Hamburg, Germany and [r]Canadian Cancer Trials Group/Group canadien des essais sur le cancer/SHAPE Trial/Queen's University, Kingston, Canada

S.M. and F.T. contributed equally to this work.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding author. Address: Department of Obstetrics and Gynecology, LMU University Hospital, LMU Munich, Marchioninistrasse 15, Munich 81377, Germany. Tel.: +49 89 4400 74531; Fax.: +49 89 4400 78892. E-mail: Sven.Mahner@med.uni-muenchen.de (S. Mahner).

International Journal of Surgery (2025) 111:8099–8107

Received 22 May 2025; Accepted 1 July 2025

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.lww.com/international-journal-of-surgery.

Published online 18 July 2025

http://dx.doi.org/10.1097/JS9.0000000000003027

to the 3-year pelvic recurrence for patients with low-risk early-stage cervical cancer[1,2]. However, patient selection with respect to the tumor-specific inclusion criteria of the trial [maximum diameter ≤2 cm, <50% stromal invasion on MRI and/or <10 mm stromal invasion on preoperative loop electrical excision procedure (LEEP)/conization], remains a challenge for reliable transfer of these criteria into routine clinical practice[3].

Several previous retrospective analyses had suggested a very low probability of parametrial infiltration in patients meeting the above mentioned criteria[4–6] so the hypothesis to abandon the parametrial resection for these low-risk cervical cancer patients was proposed. Testing of this hypothesis was the main scope of the SHAPE trial.

In parallel, the LACC trial (Laparoscopic Approach to Cervical Cancer) had evaluated the surgical approach for radical hysterectomy and demonstrated that it had significant impact on the outcome for patients with early-stage cervical cancer with lesions up to 4 cm[7,8]. Minimally invasive surgery (MIS) was associated with unfavorable recurrence-free as well as overall survival, confirmed by several retrospective datasets, leading to a paradigm shift back to open surgery[9–11]. No clear risk factors and differences in patterns for recurrence have been identified to date, although the use of uterine manipulators and potential intra-abdominal spilling of tumor cells at the time of colpotomy during minimally invasive approach for RH have been proposed as factors that may have contributed to the observed impact on survival[12]. Although the updated LACC data also suggest poorer outcomes in lesions <2 cm, the most significant detrimental effects in the LACC trial were seen in tumors measuring 2–4 cm in diameter[13]. Accordingly, it is currently under debate if – based on the results of the SHAPE trial – the reduced surgical radicality of SH could justify a return to minimally invasive approach for low-risk cervical cancer with tumor size ≤2 cm meeting the SHAPE criteria.

As preoperative evaluation of the SHAPE inclusion criteria with tumor size and stromal invasion is challenging[14], objective evaluation of these parameters to tailor radicality of surgery and eventually surgical approach would be helpful to avoid surgical over- as well as under-treatment. Pre-hysterectomy LEEP/conization with clear margins has been suggested and proposed as a potential predictor for recurrence in retrospective analyses[15–17]. In addition to the benefit of an objective estimation of tumor size, preoperative LEEP/conization might also significantly reduce the risk of intra-abdominal tumor spread during colpotomy when a complete resection (R0) of the tumor has already been achieved by the LEEP/conization.

To better understand the potential role of preoperative LEEP/conization, clear LEEP/conization margins and surgical approach with regard to the type of hysterectomy we analyzed these factors in relation to the patterns of recurrence and death within the SHAPE trial.

HIGHLIGHTS

- First large exploratory analysis of patients with low-risk cervical cancer undergoing MIS or open surgery in a prospective trial.
- No extrapelvic recurrences and death following negative margins in pre-hysterectomy LEEP/conization, regardless of surgical approach.
- Within the SHAPE criteria, patients with clear margins in pre-hysterectomy LEEP/conization may be able to safely undergo MIS.
- Pre-hysterectomy LEEP/conization might help to tailor surgical strategy in terms of radicality and surgical approach.

Methods

Trial design and cohorts

SHAPE is a phase III, prospective, multicenter, international trial comparing simple hysterectomy to radical hysterectomy in patients with low-risk disease. Details of the SHAPE trial have been previously reported[1]. Briefly, 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 LEEP or conization or <50% depth of invasion on preoperative pelvic MRI), and no evidence of lymph node metastasis on preoperative imaging were included. The presence of lymphovascular invasion was allowed. Surgical approach was not a randomization factor and was left at the discretion of the surgeon. MRI was mandatory except for stage IA2 patients who underwent preoperative LEEP/conization. Exclusion criteria included other histologic subtypes, lesions measuring >2 cm, or evidence of metastatic disease on preoperative 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 (CCTG) and approved by the institutional review board at each participating institution.

Written informed consent was required for participation in the trial. A more detailed description including the trial protocol and statistical analysis plan can be found in original publication[1]. The analysis has been reported in line with the CONSORT criteria[18]. Within this analysis, no artificial intelligence has been used as reported according to the TITAN guideline 2025[19].

Statistical analysis

Fisher's exact test or Wilcoxon tests were used to compare the baseline characteristics between surgical approaches for respectively categorical and continuous variables. The rates of recurrences (overall, pelvic, or extra pelvic) and cervical cancer-related deaths at 3 years were estimated by Kaplan–Meier method and compared between groups by a Cox model for recurrence free (overall, pelvic, or extra pelvic) or cervical cancer-related survival with a single covariate of group indicator.

Results

Patient baseline characteristics

Of the 700 patients randomized within the SHAPE trial, 350 patients were allocated to each arm, simple or radical hysterectomy, with 336 patients in the simple hysterectomy and 337 patients in the radical hysterectomy arm actually undergoing

the allocated procedure. Two patients allocated to radical hysterectomy were treated by simple hysterectomy, and seven patients intended for simple hysterectomy finally received radical hysterectomy. Therefore, the treated population consists of 338 patients who received simple hysterectomy (49.6%) compared to 344 undergoing radical hysterectomy (50.4%).

Of the 682 patients in the treated population, 524 (76.8%) surgeries were performed by minimally invasive surgery, 156 (22.9%) by open surgery, and 2 (0.3%) with data on surgical approach missing (Supplemental Digital Content Figure S1, available at: http://links.lww.com/JS9/E759). Table 1 summarizes patients' baseline characteristics according to surgical approach. A total of 548 (80.6%) patients had a diagnostic procedure with LEEP/conization and/or cervical biopsy prior to study enrollment, equally distributed between surgical approaches (Table 1).

Surgical characteristics

Of the 524 MIS patients, 281 (53.6%) were allocated to simple hysterectomy and 243 (46.3%) to radical hysterectomy. Among 156 patients undergoing open surgery, 57 (36.5%) compared to 99 (63.5%) received simple versus radical hysterectomy, respectively (Table 2, Fig. 1A).

A total of 174 (25.6%) patients were found to have negative margins (R0) on pathologic evaluation of the pre-hysterectomy LEEP/conization. In the simple hysterectomy arm, 83 of 281 (29.5%) patients with minimally invasive compared to 10 of 57 (17.5%) with open approach had clear margins. In the radical hysterectomy arm, 60 of 243 (24.7%) MIS patients and 21 of 99 (21.2%) of open surgery patients had proven R0 resection following pre-hysterectomy LEEP/conization (Fig. 1A).

Distribution of recurrences and cervical cancer-related deaths by treatment group and surgical approach

The numbers of recurrences (pelvic, extra-pelvic, and total) and cervical cancer-related deaths observed during follow-up at data cutoff on June 2022 are summarized in Tables 2-5 for each group with event rate, 3-year outcomes estimated by Kaplan–Meier method, and comparison between relevant groups by Cox models. In total, 25 of the 680 patients

Table 1

Baseline characteristics for patients by surgical approach

Number of subjects (%)	MIS (N = 524)	Open surgery (N = 156)	*P* value
Race			**0.0002**
White	377 (72.0%)	135 (86.5%)	
Asian	32 (6.1%)	8 (5.1%)	
Black or African American	5 (1.0%)	3 (1.9%)	
American Indian or Alaska Native	2 (0.4%)	0 (0.3%)	
Not reported (or refused)	86 (16.4%)	6 (3.9%)	
Unknown	22 (4.2%)	4 (2.6%)	
Age (years)			0.13
Median (range)	43 (24–80%)	45 (28–77%)	
≤50	389 (74.2%)	115 (73.7%)	
	135 (25.8%)	41 (26.3%)	
ECOG performance status			0.15
0	606 (96.6%)	147 (94.2%)	
1	18 (3.4%)	8 (5.1%)	
3	0 (0.0%)	1 (0.6%)	
Missing	0 (0.0%)	1 (0.6%)	
Body mass index			0.94
Median [range]	25.0 [16.1–57.6]	24.7 [17.7–47.9]	
Histological type			**0.02**
Squamous	319 (60.9%)	96 (61.5%)	
Adeno	193 (36.8%)	49 (31.4%)	
Adenosquamous	12 (2.3%)	11 (7.1%)	
FIGO stage			0.18
IA2	45 (8.6%)	8 (5.1%)	
IB1	479 (91.4%)	148 (94.9%)	
Histologic grade			0.58
1	127 (24.2%)	33 (21.2%)	
2	193 (36.8%)	53 (34.0%)	
3	69 (13.2%)	22 (14.1%)	
Not assessable	135 (25.8%)	48 (30.8%)	
Diagnostic procedure			0.72
LEEP/Conization ± cervical biopsy	422 (80.5%)	126 (80.8%)	
Cervical biopsy only	97 (18.5%)	26 (16.7%)	
Missing	5 (1.0%)	4 (2.6%)	

ECOG = Eastern Cooperative Oncology Group, FIGO = Fédération Internationale de Gynécologie et d'Obstétrique, LEEP = loop electrical excision procedure, MIS = minimally invasive surgery. *Significant P values (<0.05) displayed in bold.*

Table 2

All recurrences by treatment group and surgical approach

	Simple hysterectomy					Radical hysterectomy				
	Events/ subjects	Event rate	3-year outcome	Hazard ratio (95% CI)	*P* value	Events/ subjects	Event rate	3-year outcome	Hazard ratio (95% CI)	*P* value
Surgical approach										
MIS	**12/281**	4.27%	3.47%	0.74 (0.21–2.61)	0.63	**7/243**	2.88%	2.14%	0.83 (0.21–3.22)	0.79
Open	**3/57**	5.26%	5.67%			**3/99**	3.03%	2.21%		
Conization										
Yes	**11/285**	3.86%	3.37%	0.47 (0.15–1.47)	0.19	**7/265**	2.64%	1.60%	0.56 (0.14–2.15)	0.39
No	**4/50**	8.00%	6.95%			**3/73**	4.11%	4.46%		
Resection status following LEEP/conization										
Negative margins (R0)	**1/93**	1.07%	1.18%	0.20 (0.0, 1.61)	0.13	**1/81**	1.23%	0.00%	0.32 (0.04, 2.67)	0.29
Positive margins (R1)	**9/173**	5.20%	4.37%			**6/168**	3.57%	2.51%		
Surgical approach following R0 resection in pre-hysterectomy LEEP/conization										
R0 followed by MIS	**1/83**	1.20%	1.30%	NA	NA	**1/60**	1.67%	0.00%	NA	NA
R0 followed by OPEN surgery	0/10	0.00%	0.00%			0/21	0.00%	0.00%		

CI = confidence interval, MIS = minimally invasive surgery, LEEP = loop electrical excision procedure, NA = not assessable. *Subgroups with events displayed in bold.*

(3.7%) with information on surgical approaches were diagnosed with any kind of recurrence (Table 2). Of these, 15 (4.4%) recurrences were observed in 338 patients following simple hysterectomy (12/281 or 4.3% with MIS vs. 3/57 or 5.3% with open surgery; HR 0.74, 95% CI 0.21–2.61, *P* = 0.63) and 10 (2.9%) in 342 patients following radical hysterectomy (7/243 or 2.9% with MIS vs. 3/99 or 3.0% with open surgery; HR 0.83, 95% CI 0.21–3.22, *P* = 0.79). Following LEEP/conization with negative margins (R0), one recurrence was seen in each of two treatment groups (1/93 or 1.1% on simple hysterectomy and 1/81 or 1.2% on radical hysterectomy). Recurrences were more frequent in patients with positive margins in the LEEP/conization (R1, 9/173 or 5.2% on simple hysterectomy and 6/168 or 3.6% on radical hysterectomy), but no statistically significant difference in recurrence free survival was found between patients with negative and positive margins on pre-hysterectomy LEEP/conization (HR 0.20, 95% CI 0.00–1.61, *P*= 0.13 on simple hysterectomy and HR 0.32, 95% CI 0.04–2.67, *P* = 0.29 on radical hysterectomy). Overall, the only two recurrences following R0 LEEP/conization were both confirmed in patients who received MIS and none in patients with open surgery (Table 2, Fig. 1B).

With focus on specific types of recurrence, a total of 21 (3.1%) pelvic recurrences and nine (1.3%) extrapelvic recurrences were seen in 680 patients who received surgical treatment and had information on surgical approach (Tables 3 and 4). Following LEEP/conization with negative margins, two patients had pelvic recurrences. Both of them underwent MIS, with one (1.2%) recurrence following simple and one (1.7%) recurrence following radical hysterectomy. No pelvic recurrences following pre-hysterectomy R0 resection and open surgery (0/10) were detected during follow-up (Table 3, Fig. 1B).

Extrapelvic recurrences were only seen in patients with positive pre-hysterectomy LEEP/conization margins (R1 resection) or in patients without pre-hysterectomy LEEP/conization (cervical biopsy only). Independent from surgical access and type of hysterectomy, no extrapelvic recurrences were diagnosed in patients with pre-hysterectomy R0 resection at LEEP/conization (Table 4, Fig. 1B).

Cervical cancer-related death was rare with only five cases in total (0.7%). All cases occurred after MIS or following LEEP/conization with positive margins (R1) or without previous LEEP/conization (cervical biopsy only) and none after open surgery or following previous R0 resection (Table 5, Fig. 1B).

Clinical characterization and outcome of patients with recurrent disease

The swimmer plot in Fig. 2 displays detailed characteristics of patients with recurrent disease. Besides age and histological subtypes, information on tumor stage, resection margin status, surgical approach as well as type of hysterectomy and adjuvant treatment are presented for each patient diagnosed with recurrent disease. This enables a correlation of these parameters with clinical outcome in terms of recurrent disease and death. The visualized progression free survival and follow-up time can be compared for the different treatment groups with the corresponding types of recurrence (pelvic vs. extrapelvic). Key characteristics are provided for each patient to put the data in context.

Discussion

Exploratory analysis of surgical parameters from the SHAPE trial suggests similar rates of recurrence and death between patients who underwent minimally invasive versus open surgery. Of note, only two pelvic recurrences (1.4%) and no extrapelvic recurrences or cervical cancer related death occurred in patients with clear margins on pre-hysterectomy LEEP/conization, regardless of surgical radicality or surgical approach. These findings might help to subsequently tailor surgical strategies in patients with low-risk cervical cancer.

Surgical treatment for cervical cancer has undergone significant changes with paradigm shifts in clinical care. The LACC trial in 2018 reversed the previously well-established minimally

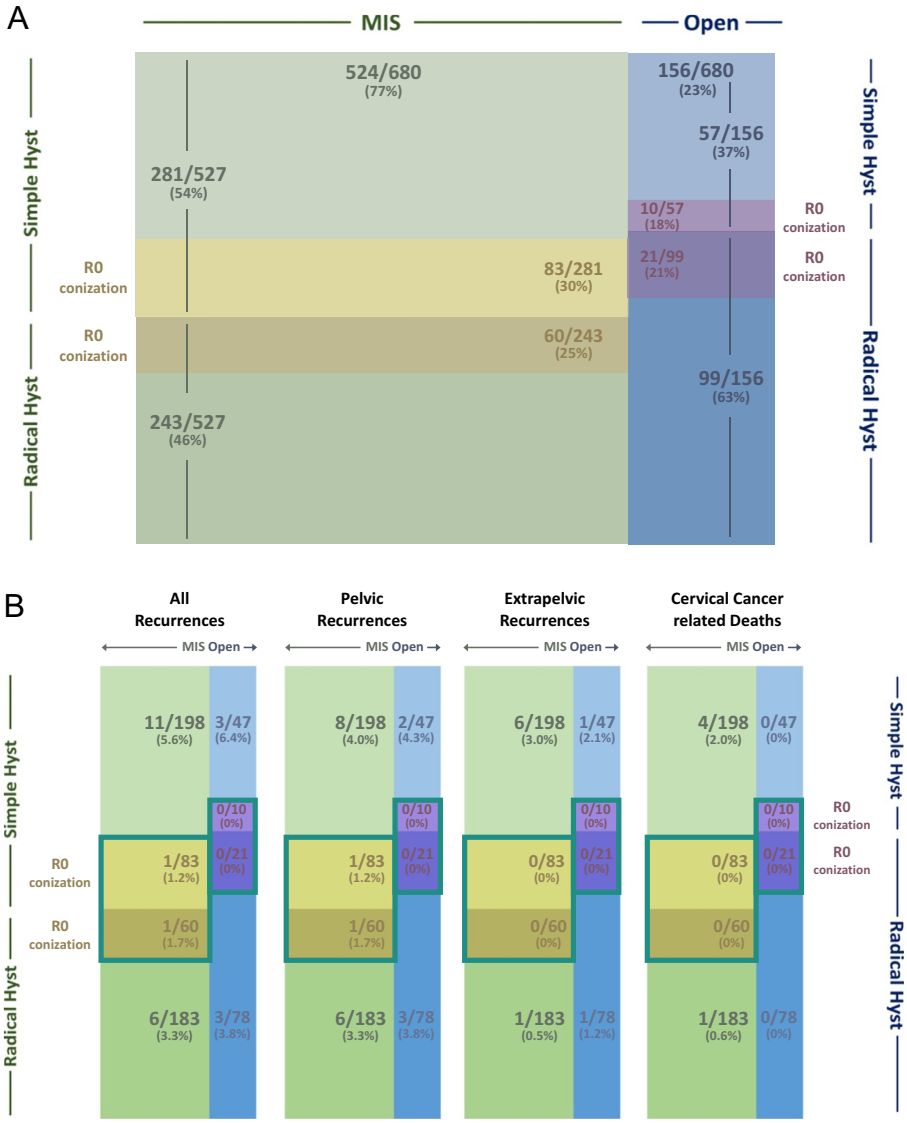

Figure 1. (A) Overview of the included patients accounting for R0 LEEP/conization with respect to type of hysterectomy and surgical access. MIS = minimally invasive surgery, Hyst = hysterectomy. (B) Patterns of (1) all recurrences, (2) pelvic recurrences only, (3) extrapelvic recurrences only, and (4) cervical cancer-related deaths according to the distribution of patients. MIS = minimally invasive surgery, Hyst = hysterectomy.

invasive access for radical hysterectomy showing significantly impaired survival in cervical cancer patients with tumor size up to 4 cm[7]. Supported by several retrospective analyses, this led to the current standard of open surgery for radical hysterectomy in cervical cancer[20]. In addition, SHAPE recently challenged the universally implemented standard of radical hysterectomy, introduced by Ernst Wertheim in 1898, and now enables the option to abandon parametrial resection and perform simple hysterectomy in patients with low-risk, early-stage cervical cancer[1,21]. For this new treatment option, patient selection is crucial. Indeed, while the overwhelming majority of patients with early stage cervical cancer can be cured by surgery alone, recurrences are difficult to treat and can be fatal.

In contrast to the preoperative estimation of the maximum tumor diameter and depth of stromal invasion through clinical examination and/or imaging, pathologic measurement following confirmation of clear margins by pre-hysterectomy LEEP/conization represents the only truly objective evaluation of tumor size and depth of invasion. This strategy could therefore be considered in cases where negative margins appear achievable to enable an objective indication and informed consent based on the evidence obtained in SHAPE. It is important to note that conization in this context still represents a diagnostic procedure that could replace the previous standard of simple biopsy for histologic confirmation.

Within the SHAPE trial, 77% of patients underwent MIS and 23% open surgery reflecting the established preferred surgical approach during large parts of the recruitment period in the pre-LACC era. Between these two cohorts, distribution of pre-hysterectomy LEEP/conization was similar with 80.5% for MIS and 80.8% for open approach. Of note, the rate for R0 resection in the overall cohort was relatively low with 25.6%, the most likely reason for the LEEP/conization was to establish histologic confirmation of cervical cancer but not necessarily to obtain

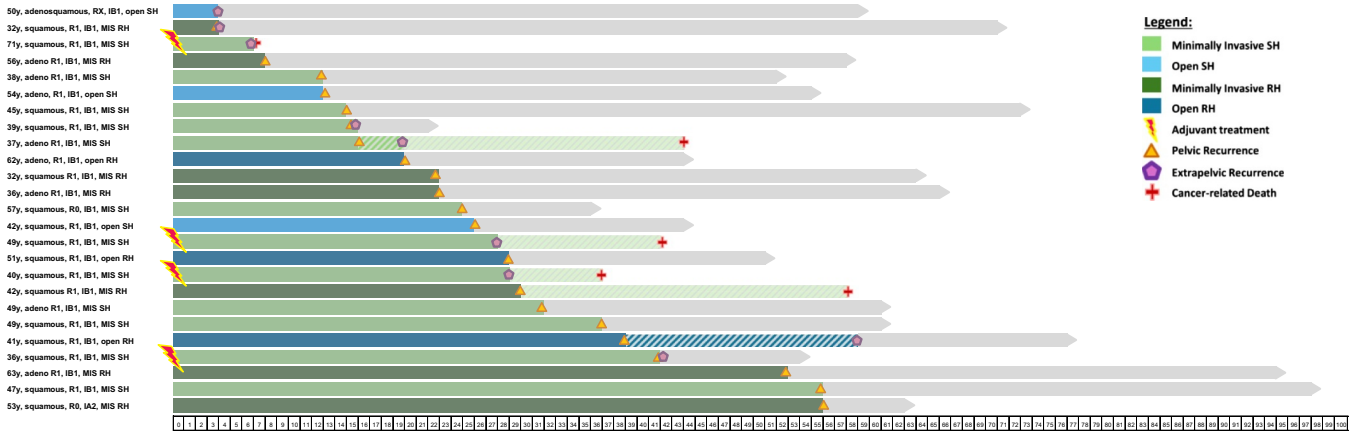

Figure 2. Swimmer plot displaying detailed patient characteristics and the clinical course for all patients with recurrent disease (*N* = 25). y = years, MIS = minimally invasive surgery, RH = radical hysterectomy, SH = simple hysterectomy.

complete tumor removal with clear margins. Indeed, in contrast to the prospective, single-arm multicenter ConCerv trial, negative margins on the pre-hysterectomy LEEP/conization were not required in SHAPE. As a result, the overall rate of residual disease in the hysterectomy specimen was 46.5% in SHAPE compared to 2.5% in ConCerv[9]. Of the nine pelvic recurrences after minimally invasive simple hysterectomy, only one occurred following LEEP/conization with negative margins. Seven pelvic recurrences were observed after minimally invasive radical hysterectomy, and only one in a patient with negative LEEP/conization margins. All other relapses (14 after simple and 9 after radical hysterectomy), independent from surgical approach and type of hysterectomy, occurred in the patients without complete R0 resection at the time of LEEP/conization. Accordingly, no extrapelvic recurrence or cancer related-death was registered for patients following R0 LEEP/conization. Five patients died from cervical cancer after MIS and R1 conization, three of them despite adjuvant radio(chemo)therapy. Although numbers of events are low and patient numbers were not prospectively powered to answer this specific question, this detailed information appears of high relevance for clinical practice as it underlines the potential to reduce the risk of recurrence and death through LEEP/conization with clear margins prior to hysterectomy.

In recent years, the concept of pre-hysterectomy LEEP/Cone with clear margins has increasingly been investigated. In two case series, no impact on recurrence was demonstrated and similar rates for recurrence in MIS versus open surgery were seen following pre-hysterectomy LEEP/conization for patients with no residual tumor in pre-hysterectomy evaluation, and significant risk reduction was noted for patients with R0 resection undergoing MIS[17,22]. Likewise, the ConCerv trial evaluated the feasibility of conservative surgery in women with early-stage, low-risk cervical cancer. Within this cohort of 100 patients, a total 40 patients not desiring fertility underwent simple hysterectomy with negative prior conization margins as part of the trial. In this subgroup, no recurrence was observed during follow-up[9].

Table 3

Pelvic recurrences by treatment group and surgical approach

	Simple hysterectomy					Radical hysterectomy				
	Events/ subjects	Event rate	3-year outcome	Hazard ratio (95% CI)	*P* value	Events/ subjects	Event rate	3-year outcome	Hazard ratio (95% CI)	*P* value
Surgical approach										
MIS	**9/281**	3.20%	2.31%	0.81 (0.18–3.77)	0.79	**7/243**	2.88%	2.14%	0.83 (0.21–3.22)	0.79
Open	**2/57**	3.51%	3.89%			**3/99**	3.03%	2.21%		
Conization										
Yes	**7/285**	2.46%	1.87%	0.30 (0.09–1.02)	0.053	**7/265**	2.64%	1.60%	0.56 (0.14–2.15)	0.39
No	**4/50**	8.00%	6.95%			**3/73**	4.11%	4.46%		
Resection status following LEEP/conization										
Negative margins (R0)	**1/93**	1.08%	1.18%	0.31 (0.04, 2.55)	0.27	**1/81**	1.23%	0.00%	0.32 (0.04, 2.67)	0.29
Positive margins (R1)	**6/173**	3.47%	2.46%			**6/168**	3.57%	2.51%		
Surgical approach following R0 resection in pre-hysterectomy LEEP/conization										
R0 followed by MIS	**1/83**	1.20%	1.30%	NA	NA	**1/60**	1.67%	0.00%	NA	NA
R0 followed by OPEN surgery	0/10	0.00%	0.00%			0/21	0.00%	0.00%		

CI = confidence interval, MIS = minimally invasive surgery, LEEP = loop electrical excision procedure, NA = not assessable.
Subgroups with events displayed in bold.

Table 4

Extrapelvic recurrences by treatment group and surgical approach

	Simple hysterectomy					Radical hysterectomy				
	Events/ subjects	Event rate	3-year outcome	Hazard ratio (95% CI)	*P* value	Events/ subjects	Event rate	3-year outcome	Hazard ratio (95% CI)	*P* value
Surgical approach										
MIS	**6/281**	1.07%	1.94%	1.11 (0.13–9.24)	0.92	**1/243**	0.41%	0.42%	0.34 (0.02–5.53)	0.45
Open	**1/57**	1.75%	1.85%			**1/99**	1.01%	0.00%		
Conization										
Yes	**6/285**	2.11%	1.90%	1.04 (0.13–8.60)	0.97	**1/265**	0.38	0.00%	0.22 (0.01–3.40)	0.29
No	**1/50**	2.00%	2.17%			**1/73**	1.37%	1.45%		
Resection status following LEEP/ conization										
Negative margins (R0)	**0/93**	0.00%	0.00%	NA	NA	0/81	0.00%	0.00%	NA	NA
Positive margins (R1)	**5/173**	2.89%	2.58%			**1/168**	0.06%	0.00%		
Surgical approach following R0 resection in pre-hysterectomy LEEP/conization										
R0 followed by MIS	0/83	0.00%	0.0%	NA	NA	0/60	0.00%	0.00%	NA	NA
R0 followed by OPEN surgery	0/10	0.00%	0.00%			0/21	0.00%	0.00%		

CI = confidence interval, MIS = minimally invasive surgery, LEEP = loop electrical excision procedure, NA = not assessable.
Subgroups with events displayed in bold.

Most recently, a European multicenter cone study SUCCOR retrospectively evaluated disease-free survival following LEEP/conization prior to radical hysterectomy in patients with stage IB1 cervical cancer. In this cohort of 374 patients, a 65% reduction of recurrence risk following LEEP/conization for the overall cohort was estimated and a more than 5 times higher risk for relapse was noted in patients undergoing MIS without prior LEEP/conization compared to patients with open surgery and previous LEEP/conization. On the other hand, similar rates of recurrence for patients with MIS and pre-hysterectomy clear margins compared to patients with open approach without previous LEEP/conization were observed, indicating the potential impact of this approach prior to MIS[12,15].This data could support the identification of an ultra-low-risk group of early-stage cervical cancer within the pathologic SHAPE criteria, with preoperative LEEP/conization and negative margins, who might be able to undergo MIS approach.

Several single center analyses and meta-analyses support the hypothesis, that in early-stage cervical cancer, the vast majority of recurrences occur in patients with tumors larger than two centimeters and without previous clearance of tumor by pre-hysterectomy LEEP/conization[16,23–26].

Although the present study represents the first thorough analysis of the impact of pre-hysterectomy LEEP/conization margins in a prospective phase III trial, it holds potential relevant limitations. At first, this is a strictly exploratory analysis and the statistical calculations and patient numbers were not prospectively powered to answer this specific question. Accordingly, numbers of events are relatively low and, therefore, statistically

Table 5

Cervical cancer related deaths by treatment group and surgical approach

	Simple hysterectomy					Radical hysterectomy				
	Events/ subjects	Event rate	3-year outcome	Hazard ratio (95% CI)	*P* value	Events/ subjects	Event rate	3-year outcome	Hazard ratio (95% CI)	*P* value
Surgical approach										
MIS	**4/281**	1.42%	0.37%	NA	NA	**1/243**	0.41%	0.00%	NA	NA
Open	0/57	0.00%	0.00%			0/99	0.00%	0.00%		
Conization										
Yes	**3/285**	1.05%	0.37%	0.56 (0.06–5.36)	0.61	**1/265**	0.38%	0.00%	NA	NA
No	**1/50**	2.00%	0.00%			0/73	0.00%	0.00%		
Resection status following LEEP/conization										
Negative margins (R0)	0/93	0.00%	0.00%	NA	NA	0/81	0.00%	0.00%	NA	NA
Positive margins (R1)	**3/173**	1.73%	0.61%			**1/168**	0.59%	0.00%		
Surgical approach following R0 resection in pre-hysterectomy LEEP/conization										
R0 followed by MIS	0/83	0.00%	0.00%	NA	NA	0/60	0.00%	0.00%	NA	NA
R0 followed by OPEN surgery	0/10	0.00%	0.00%			0/21	0.00%	0.00%		

CI = confidence interval, MIS = minimally invasive surgery, LEEP = loop electrical excision procedure, NA = not assessable.
Subgroups with events displayed in bold.

insignificant difference may not be reasonably interpreted as without clinically important difference. In addition, specific information regarding tumor volume and correlation with MRI findings are not available and have not been part of this analysis. Since it is more likely that LEEP/conization with negative margins was performed in small or even microscopic tumors within the SHAPE cohort, favorable outcome could also be associated with the selection of smaller tumor sizes. A potential strength however, is the meticulous evaluation of surgical details included in the SHAPE trial. However, given the exploratory nature of this analysis, a prospective validation of our results, for example in a real-world database, is highly desirable.

In conclusion, the results of our analysis support the concept of the potential benefit of pre-hysterectomy LEEP/conization in patients with low risk, early-stage cervical cancer. Although the SHAPE inclusion criteria translate to an oncologically safe approach with SH in these patients, pre-hysterectomy LEEP/conization with clear margins represents an additional objective measure to triage patients. This could help to reliably tailor surgical strategies, including surgical approach, in patients with low-risk cervical cancer.

Ethical approval

The trial was conducted by the Canadian Cancer Trials Group (CCTG) and approved by the institutional review board at each participating institution. Ethical approval was obtained from the Ontario Cancer Research Ethics Board, OCREB# 12-048.

Consent

Written informed consent was obtained from the patient for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Sources of funding

Analyses for this manuscript have been covered by internal resources of the academic institutions. The SHAPE trial was supported in Canada by the Canadian Cancer Society (grant 707213) and the Canadian Institutes of Health Research (grant 119446); in Ireland by Cancer Trials Ireland and the Health Research Board (grant UL-2013-5917); in France by the Programme Hospitalier de Recherche Clinique (PHRC program; grant PHRC 2013-004) from the Institute National du Cancer and the General Directorate for Healthcare Provision (Direction générale de l'offre de soins [DGOS]; grant INCaDGOG-7161); and in the United Kingdom by Cancer Research UK (grant A16363).

Author contributions

S.M., F.T., and M.P.: conceptualization; D.T.: data curation; S.M., F.T., D.T., and M.P.: formal analysis; S.M., F.T., J.S.K., S.E.F., P.B., A.S., Fra. G., T.G., C.D.K., W.V.D., J.T., K.W., Fre.G., S.P., B.E., J.Y.L., P.M., B.S., L.E.S., D.T., and M.P.: resources; S.M. and F.T.: writing – original draft; J.S.K., S.E.F., P.B., A.S., Fra. G., T.G., C.D.K., W.V.D., J.T., K.W., Fre.G., S.P., B.E., J.Y.L., P.M., B.S., L.E.S., D.T., and M.P.: writing – review & editing.

Conflicts of interest disclosure

S.M.: grants and personal fees from Abbvie, AstraZeneca, Daiichi Sankyo, Eisai, GSK, ImmunoGen, MSD, Medac, Novartis, Olympus Europe, PharmaMar, Pfizer, and Roche. F. T.: grants and personal fees from AbbVie, AstraZeneca, Eisai, GSK, ImmunoGen, MSD, Regeneron, Roche, and SAGA diagnostics. S.P.: grants and personal fees from Abbvie, AstraZeneca, Eisai, GSK, MSD. All other authors state no conflicts of interest involved with the present work.

Research registration unique identifying number (UIN)

SHAPE ClinicalTrials.gov number: NCT01658930.

Guarantor

Sven Mahner, Fabian Trillsch, Dongsheng Tu, and Marie Plante.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Data availability statement

None.

Presentation

Data from the analyses of the present manuscript have been presented at the ESGO conference 2024 in Barcelona.

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