GYNECOLOGY

# Analysis of risk factors for recurrence in cervical cancer patients after fertility-sparing treatment: The FERTIlity Sparing Surgery retrospective multicenter study

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**BACKGROUND:** Fertility-sparing treatment in patients with cervical cancer should, in principle, follow identical algorithms to that in patients without future reproductive plans. In recent years, a trend toward nonradical procedures, such as conization or simple trachelectomy, has become apparent in medical literature, because of their associations with better pregnancy outcomes. However, the published reports included small numbers of patients and heterogenous treatment strategies to ascertain the safety of such approaches.

**OBJECTIVE:** This study aimed to collect multi-institutional data regarding the oncological outcomes after fertility-sparing treatment in patients with cervical cancer and to identify prognostic risk factors, including the influence of the radicality of individual cervical procedures.

**STUDY DESIGN:** Patients aged 18 to 40 years with International Federation of Gynecology and Obstetrics 2018 stage IA1 with positive lymphovascular space invasion or ≥IA2 cervical cancer who underwent any type of fertility-sparing procedure were eligible for this retrospective observational study, regardless of their histotype, tumor grade, and history of neoadjuvant chemotherapy. Associations between disease- and treatment-related characteristics with the risk of recurrence were analyzed.

**RESULTS:** A total of 733 patients from 44 institutions across 13 countries were included in this study. Almost half of the patients had stage IB1 cervical cancer (49%), and two-thirds of patients were nulliparous (66%). After a median follow-up of 72 months, 51 patients (7%) experienced recurrence, of whom 19 (2.6%) died because of the disease. The most common sites of recurrence were the cervix (53%) and pelvic nodes (22%). The risk of recurrence was 3 times higher in patients with tumors >2 cm in size than in patients with smaller tumors, irrespective of the treatment radicality (19.4% vs 5.7%; hazard ratio, 2.982; 95% confidence interval, 1.383–6.431; *P*=.005). The recurrence risk in patients with tumors ≤2 cm in size did not differ between patients who underwent radical trachelectomy and patients who underwent nonradical (conization and simple trachelectomy) cervical procedures (*P*=.957), regardless of tumor size subcategory (<1 or 1–2 cm) or lymphovascular space invasion.

**CONCLUSION:** Nonradical fertility-sparing cervical procedures were not associated with an increased risk of recurrence compared with radical procedures in patients with tumors ≤2 cm in size in this large, multicenter retrospective study. The risk of recurrence after any type of fertility-sparing procedure was significantly greater in patients with tumors >2 cm in size.

**Key words:** cervical cancer, conization, fertility-sparing treatment, recurrence, trachelectomy

## Introduction

Cervical cancer is the fourth most common cancer in women worldwide and is the most common cancer with an immediate effect on female fertility. Although the incidence of cervical cancer is steadily declining in high-resource countries because of the effectiveness of organized screening programs, approximately one-third of patients are diagnosed before the age of 40 years, and many have plans to become pregnant in the future.[1] Furthermore, the trend toward a later age at first pregnancy has led to a marked increase in cervical cancer cases among women who have not yet started or completed their family planning.[1,2] Therefore, fertility-sparing treatment (FST) is an emerging topic among patients with early stages of cervical cancer and negative lymph nodes (LNs).

Historically, the algorithms for FST followed the same principles as those used in patients without a fertility-sparing intention. As such, the standard treatment in patients with stage IB cervical cancer should include radical trachelectomy and pelvic lymphadenectomy.[3] However, both procedures are associated with substantial morbidity and, even more importantly, have negative perinatal consequences. In addition, vaginal radical trachelectomy is a technically demanding procedure that is not routinely performed in many institutions.[1] Therefore, nonradial cervical procedures involving simple trachelectomy and conization have been introduced to help overcome these limitations of radical procedures.[2,4,5] Higher pregnancy rates and similar recurrence rates were observed after nonradical cervical procedures, although the published studies involved small numbers of patients, mostly from single institutions, used heterogeneous treatment strategies, and variable selection criteria.[1]

The aims of the observational study FERTIlity Sparing Surgery (FERTISS) in patients with cervical cancer outside controlled trials were to collect robust,

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## AJOG at a Glance

### Why was this study conducted?

This study aimed to collect multi-institutional data from routine clinical practice regarding the treatment and oncological outcomes after fertility-sparing treatment (FST) of patients with cervical cancer.

### Key findings

Nonradical cervical procedures were not associated with a higher risk of recurrence in patients with tumors ≤2 cm in size. Furthermore, the risk of recurrence was not different between nonradical and radical cervical procedures in a subgroup analysis of tumors <1 and 1 to 2 cm (both irrespective of lymphovascular space invasion). Rare tumor types and tumor size >2 cm were important risk factors for recurrence after FST.

### What does this add to what is known?

Nonradical fertility-sparing procedures were not associated with an increased risk of disease recurrence in patients with human papillomavirus–associated cervical cancer, negative regional lymph nodes, and tumors ≤2 cm in size. The omission of parametrectomy, which is associated with a considerable risk of postoperative morbidity, was not associated with a higher risk of recurrence in the International Federation of Gynecology and Obstetrics 2018 stage IA2 and IB1 tumors.

multi-institutional data regarding the oncological outcomes after FST and to identify possible prognostic risk factors, including the influence of the radicality of individual cervical procedures.

## Materials and Methods

### FERTIlity Sparing Surgery study cohort

We retrospectively retrieved data from institutional databases for patients with cervical cancer who underwent FST between January 2001 and December 2020. Only patients aged 18 to 40 years with International Federation of Gynecology and Obstetrics (FIGO 2018) IA1 with (positive lymphovascular space invasion [LVSI]) or ≥IA2 cervical cancer were eligible. Patients were included irrespective of the tumor grade, tumor histotype, or LN staging (including sentinel LN biopsy [SLNB] with any technique for mapping and/or pelvic lymphadenectomy with or without para-aortic lymphadenectomy). All FST procedures were eligible, including conization (any technique), simple vaginal trachelectomy, vaginal radical trachelectomy, and abdominal radical trachelectomy, irrespective of the surgical approach (laparotomy, laparoscopy, robotic surgery, or any combination). Patients who received neoadjuvant chemotherapy (NACT) were also eligible. The only exclusion criterion was hysterectomy when performed as part of the primary treatment.

The study protocol was approved by the institutional review board of the lead institution (General University Hospital in Prague, Czech Republic) in 2018 and by the institutional review boards at the participating sites before study participation. Because of the retrospective nature of the study, the need for informed consent was waived by the institutional review board. The study was conducted as a model A study of the European Network of Gynaecological Oncology Groups (ENGOT; ENGOT Cx14) and was led by the Central and Eastern European Gynaecological Oncology Group (CEEGOG; CEEGOG Cx-03).

### Statistical analysis

Descriptive statistics and frequency tables were used to characterize the data. Continuous variables were described using the mean and standard deviation or the median with 5th and 95th percentiles, together with the total number of nonmissing observations. Categorical variables were described using absolute and relative frequencies. Relative frequencies were calculated on the basis of the number of patients in the relevant subgroup. For subgroup comparisons, baseline data were evaluated, and statistically significant differences were determined (at a level of significance of $\alpha$=.05), using the Kruskal-Wallis test for continuous variables and the Fisher exact test for categorical variables. The difference in the trend toward nonradical cervical procedures over time was tested using the Pearson chi-square test. Overall survival (OS) was defined as the time from diagnosis to death from any cause. Patients who were still alive were censored at the time of database closure. Disease-free interval (DFI) was defined as the time from the cervical procedure to disease recurrence or death. Patients without an event were censored at the time of database closure. OS and DFI were estimated using the Kaplan-Meier method; all point estimates include 95% confidence intervals (CIs). Hazard ratios for DFI were obtained from unidimensional Cox proportional-hazards models. As explanatory variables, we included the known characteristics of patients and their treatment. Sample size calculation or power analysis was not performed before the data analysis. All statistical analyses were performed using IBM SPSS Statistics (version 25.0; IBM Corporation, Armonk, NY) and R software (version 3.5.1; https://cran.r-project.org/bin/windows/base/old/3.5.1/).

## Results

A total of 733 patients treated at 44 centers across 13 countries were eligible for the analyses. The characteristics of these patients are summarized in Table 1. The mean age of the patients was 32.2 years, and two-thirds of patients were nulliparous (66.0%). Nearly half of the cases had FIGO 2018 stage IB1 cervical cancer (356/733, 48.6%). More than two-thirds of the patients (70.3%) had squamous cell cancers; adenocarcinomas and adenosquamous cancers accounted for 28.9% of patients, and 5 patients had another tumor histotype. Half of the patients (49.9%) had evidence of LVSI reported in the specimen. The most frequent diagnostic procedure was conization (61.0%).

**TABLE 1**
**Patient characteristics according to disease stage**

| Characteristic | IA1 L1 (n=208) | IA2 (n=102) | IB1 (n=356) | IB2 (n=41) | IB3 (n=19) | II (n=7) | Any stage (n=733) | *P* value |
|---|---|---|---|---|---|---|---|---|
| Parity | | | | | | | | |
| Nulliparous | 125 (60.1) | 66 (64.7) | 250 (70.2) | 24 (58.5) | 14 (73.7) | 5 (71.4) | 484 (66.0) | .162 |
| Primiparous | 54 (26.0) | 27 (26.5) | 82 (23.0) | 15 (36.6) | 4 (21.1) | 2 (28.6) | 184 (25.1) | |
| Multiparous | 29 (13.9) | 9 (8.8) | 24 (6.7) | 2 (4.9) | 1 (5.3) | 0 (0) | 65 (8.9) | |
| Age (y) | | | | | | | | |
| Mean (SD) | 33.1 (4.7) | 33.2 (4.4) | 31.7 (4.5) | 30.8 (3.4) | 29.4 (5.1) | 33.1 (5.2) | 32.2 (4.6) | <.001[a] |
| Median (IQR) | 32.7 (25.9–40.8) | 33.0 (27.4–40.0) | 31.9 (24.4–39.3) | 30.5 (26.2–36.5) | 28.8 (19.3–38.8) | 31.4 (27.0–42.8) | 32.1 (25.0–39.7) | |
| Diagnostic procedure | | | | | | | | |
| Biopsy | 56 (27.0) | 23 (22.5) | 139 (39.1) | 24 (58.5) | 16 (84.2) | 5 (71.4) | 263 (35.9) | <.001[a] |
| Conization | 138 (66.3) | 78 (76.5) | 213 (59.8) | 16 (39.0) | 3 (15.8) | 2 (28.6) | 450 (61.4) | |
| Papanicolaou test | 14 (6.7) | 1 (1.0) | 4 (1.1) | 1 (2.4) | 0 (0) | 0 (0) | 20 (2.7) | |
| Histologic type | | | | | | | | |
| Adenocarcinoma | 39 (18.8) | 25 (24.5) | 101 (28.4) | 9 (22.0) | 3 (15.8) | 1 (14.3) | 178 (24.3) | .214 |
| Adenosquamous | 7 (3.4) | 4 (3.9) | 20 (5.6) | 1 (2.4) | 2 (10.5) | 0 (0) | 34 (4.6) | |
| Squamous cell | 161 (77.4) | 73 (71.6) | 232 (65.2) | 31 (75.6) | 13 (68.4) | 6 (85.7) | 516 (70.4) | |
| Other | 1 (0.5) | 0 (0) | 3 (0.8) | 0 (0) | 1 (5.3) | 0 (0) | 5 (0.7) | |
| Grade | | | | | | | | |
| G1 | 51 (24.5) | 20 (19.6) | 65 (18.3) | 6 (14.6) | 3 (15.8) | 1 (14.3) | 146 (20.0) | .500 |
| G2 | 86 (41.3) | 39 (38.2) | 151 (42.4) | 17 (41.5) | 8 (42.1) | 2 (28.6) | 303 (41.3) | |
| G3 | 34 (16.3) | 23 (22.5) | 75 (21.1) | 14 (34.1) | 6 (31.6) | 3 (42.9) | 155 (21.1) | |
| Gx | 37 (17.8) | 20 (19.6) | 65 (18.3) | 4 (9.8) | 2 (10.5) | 1 (14.3) | 129 (17.6) | |
| LVSI | | | | | | | | |
| Negative | 0 (0) | 69 (67.7) | 213 (59.8) | 25 (61.0) | 7 (36.8) | 1 (14.2) | 315 (43.0) | <.001[a] |
| Positive | 208 (100.0) | 23 (22.5) | 105 (29.5) | 16 (39.0) | 11 (57.9) | 3 (42.9) | 366 (49.9) | |
| Not specified | 0 (0) | 10 (9.8) | 38 (10.7) | 0 (0) | 1 (5.3) | 3 (42.9) | 52 (7.1) | |

Data are presented as number (percentage), unless otherwise specified.

*IQR*, interquartile range; *L1*, positive lymphovascular space invasion; *LVSI*, lymphovascular space invasion; *SD*, standard deviation.

[a] Statistically significant at $P<.05$.

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**TABLE 2**
**Treatment modalities according to disease stage**

| Variable | IA1 L1 (n=208) | IA2 (n=102) | IB1 (n=356) | IB2 (n=41) | IB3 (n=19) | II (n=7) | Any stage (n=733) | *P* value |
|---|---|---|---|---|---|---|---|---|
| NACT | | | | | | | | |
| No | 207 (99.5) | 102 (100.0) | 330 (92.7) | 34 (82.9) | 11 (57.9) | 2 (28.6) | 686 (93.6) | <.001[a] |
| Yes | 1 (0.5) | 0 (0) | 26 (7.3) | 7 (17.1) | 8 (42.1) | 5 (71.4) | 47 (6.4) | |
| Type of LN staging[b] | | | | | | | | |
| Sentinel LN biopsy | 55 (26.4) | 44 (43.1) | 171 (48.0) | 15 (36.6) | 9 (47.4) | 2 (28.6) | 296 (40.4) | <.001[a] |
| Pelvic lymphadenectomy | 52 (25.0) | 81 (79.4) | 310 (87.1) | 32 (78.0) | 17 (89.5) | 5 (71.4) | 497 (67.78) | <.001[a] |
| Paraaortic lymphadenectomy | 5 (2.4) | 1 (1.0) | 15 (4.2) | 0 (0) | 3 (15.8) | 0 (0) | 24 (3.3) | .054 |
| Type of cervical procedure | | | | | | | | |
| Nonradical procedures | | | | | | | | |
| Conization | 151 (72.6) | 54 (52.9) | 133 (37.4) | 5 (12.2) | 7 (36.8) | 2 (28.6) | 352 (48.0) | <.001[a] |
| Simple vaginal trachelectomy | 19 (9.1) | 7 (6.9) | 27 (7.6) | 5 (12.2) | 3 (15.8) | 1 (14.3) | 62 (8.5) | |
| Radical procedures | | | | | | | | |
| Laparoscopic radical trachelectomy | 1 (0.5) | 13 (12.7) | 30 (8.4) | 3 (7.3) | 0 (0) | 1 (14.3) | 48 (6.5) | |
| Radical abdominal trachelectomy | 18 (8.7) | 17 (16.7) | 93 (26.1) | 21 (51.2) | 5 (26.3) | 3 (42.9) | 157 (21.4) | |
| Radical vaginal trachelectomy | 18 (8.7) | 6 (5.9) | 67 (18.8) | 5 (12.2) | 3 (15.8) | 0 (0) | 99 (13.5) | |
| Robotic radical trachelectomy | 1 (0.5) | 5 (4.9) | 6 (1.7) | 2 (4.9) | 1 (5.3) | 0 (0) | 15 (2.0) | |
| Repeated cervical procedure, n | 69 | 20 | 65 | 4 | 3 | 0 | 161 | |
| Hysterectomy | 2 (2.9) | 0 (0) | 3 (4.6) | 0 (0) | 1 (33.3) | — | 6 (3.7) | .003[a] |
| Laparoscopic radical trachelectomy | 0 (0) | 0 (0) | 1 (1.5) | 0 (0) | 0 (0) | — | 1 (6.3) | |
| Radical abdominal trachelectomy | 5 (7.2) | 6 (30.0) | 3 (4.6) | 0 (0) | 0 (0) | — | 14 (8.7) | |
| Radical vaginal trachelectomy | 1 (1.4) | 1 (5.0) | 4 (6.2) | 2 (50.0) | 0 (0) | — | 8 (5.0) | |
| Reconization | 47 (68.1) | 6 (30.0) | 37 (56.9) | 1 (25.0) | 2 (66.7) | — | 93 (57.8) | |
| Robotic radical trachelectomy | 0 (0) | 0 (0) | 4 (6.2) | 0 (0) | 0 (0) | — | 4 (2.5) | |
| Simple vaginal trachelectomy | 14 (20.3) | 7 (35.0) | 13 (20.0) | 1 (25.0) | 0 (0) | — | 35 (21.7) | |
| Adjuvant chemotherapy | | | | | | | | |
| No | 204 (98.1) | 100 (98.0) | 343 (96.3) | 36 (87.8) | 18 (94.7) | 2 (28.6) | 703 (95.9) | <.001[a] |
| Yes | 4 (1.9) | 2 (2.0) | 13 (3.7) | 5 (12.2) | 1 (5.3) | 5 (71.4) | 30 (4.1) | |

Data are presented as number (percentage).

*L1*, positive lymphovascular space invasion; *LN*, lymph node; *NACT*, neoadjuvant chemotherapy.

[a] Statistically significant at $P<.05$; [b] Some patients underwent multiple procedures.

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All enrolled patients underwent FST. The treatment modalities according to disease stage are summarized in Table 2. Conization was the most common definitive surgical procedure, ranging from 12.2% to 72.6%, depending on the stage. Radical trachelectomy (any type) was performed in 319 of 733 patients (43.5%), ranging from 18.3% to 75.6%, depending on the stage. A second cervical procedure after diagnostic conization was performed in 161 patients (22.0%), predominantly reconization (57.8%) and simple vaginal trachelectomy (21.7%). Over time, there was a significant trend toward nonradical cervical procedures at all centers; they accounted for 46.6% of procedures between 2001 and 2010 and increased to 59.1% between 2011 and 2020 ($P=.005$).

LN staging was part of the surgical treatment in all patients. Approximately two-thirds (67.8%) of patients underwent systematic pelvic lymphadenectomy, and 40.4% of patients underwent SLNB as a solitary procedure (n=106) or combined with systematic lymphadenectomy (n=190). Only 47 patients (6.4%) in the study cohort underwent NACT, followed by surgery; less than half (20/47, 42.6%) of the patients had a tumor >2 cm in size. No patient received adjuvant radiotherapy, and 30 of 733

patients (4.1%) received platinum-based adjuvant chemotherapy after FST.

Over a median follow-up of 72 months (interquartile range, 14−174 months), 51 patients (7.0%) suffered a recurrence of invasive disease (Table 3), of whom 19 died because of the disease and 32 were saved (n=18) or were living with the disease (n=14) at the time of database closure. The risks of recurrence were 5.7% in patients with tumors ≤2 cm in size and 19.4% in patients with tumors >2 cm in size (*P*=.014). The recurrence rates for FIGO 2018 stages IB2 and IB3 were 19.5% and 26.3%, respectively.

The most common sites of recurrence, regardless of stage and type of surgery, were the cervix (53%) and pelvic nodes (22%). Solitary cervical recurrence was found in 14 of 51 patients (27.5%). The median DFI for recurrence was 18 months, and the median time from first diagnosis to death was 32.5 months. The median DFI, estimated using the Kaplan-Meier method, was not reached, but the probability of living without disease recurrence for 3 years was estimated to be 93.9% (95% CI, 92.1%−95.8%) (Figure 1). Recurrence-related symptoms were present at the time of diagnosis in just 9.8% of patients with recurrence. The type of procedure was not significantly associated with disease recurrence (*P*=.845). Of 51 patients with disease relapse, 6 (11.8%) had received NACT.

The following variables were included in the 1-dimensional Cox proportional-hazards model for the risk of recurrence: stage, age, tumor type, tumor size, grade, presence of LVSI, SLNB, pelvic lymphadenectomy, and type of surgery. Only tumor size >2 cm (corresponding to FIGO 2018 stages IB2 and IB3 and tumor size as a continuous variable) and "IB2" and "IB3" stages were significantly associated with recurrence (Table 4).

Of 356 patients with stage IB1 cervical cancer (≤2 cm), 27 (7.6%) experienced disease recurrence. In this group, the recurrence rates did not differ between patients who underwent nonradical procedures and patients who underwent radical procedures (7.5% vs 7.7%; *P*=.957). Furthermore, no difference was found in subgroups divided by tumor size (<1 cm: 5.2% vs 7.4%; *P*=.507; 1−2 cm: 10.9% vs 8%; *P*=.553) or presence of LVSI (11.5% vs 9.4%; *P*=.725) (Table 5; Figure 2).

In addition, 22 patients (3.0%) were diagnosed with precancerous lesions during the follow-up period, all of whom had tumors ≤2 cm in size at initial diagnosis. These patients underwent either reconization (n=16) or simple hysterectomy (n=6).

Of note, 1 patient died during the follow-up because of a second malignancy, and 49 patients underwent hysterectomy for reasons other than recurrence or precancerous cervical lesions (eg, persistent human papillomavirus [HPV] infection, cervical stenosis, other gynecologic malignancies, and other benign conditions).

## Comment

### Principal findings

Fertility preservation in patients with cervical cancer is an important topic

**TABLE 3**
**Risk of recurrence according to disease stage**

| Variable | IA1 L1 (n=208) | IA2 (n=102) | IB1 (n=356) | IB2 (n=41) | IB3 (n=19) | II (n=7) | Any stage (n=733) | *P* value |
|---|---|---|---|---|---|---|---|---|
| Recurrence rate | 9 (4.3) | 2 (2.0) | 27 (7.6) | 8 (19.5) | 5 (26.3) | 0 | 51 (7.0) | <.001[a] |
| Location[b] | | | | | | | | |
| Cervix | 7 (77.8) | 1 (50.0) | 15 (55.6) | 2 (25.0) | 2 (40.0) | — | 27 (52.9) | .246 |
| Distant abdomen | 0 (0) | 0 (0) | 6 (22.2) | 4 (50.0) | 1 (20.0) | — | 11 (21.6) | .149 |
| Distant thorax | 2 (22.2) | 0 (0) | 3 (11.1) | 3 (37.5) | 1 (20.0) | — | 9 (17.6) | .431 |
| Other distant sites | 0 (0) | 0 (0) | 1 (3.7) | 1 (12.5) | 0 (0) | — | 2 (3.9) | .526 |
| Para-aortic LNs | 0 (0) | 1 (50.0) | 4 (14.8) | 3 (37.5) | 0 (0) | — | 8 (15.7) | .117 |
| Parametrium | 0 (0) | 0 (0) | 4 (14.8) | 1 (12.5) | 1 (20.0) | — | 6 (11.8) | .699 |
| Pelvic LNs | 1 (11.1) | 0 (0) | 6 (22.2) | 3 (37.5) | 1 (20.0) | — | 11 (21.6) | .752 |
| Other pelvic structures | 0 (0) | 0 (0) | 1 (3.7) | 1 (12.5) | 2 (40.0) | — | 4 (7.8) | .092 |
| Vagina | 0 (0) | 0 (0) | 3 (11.1) | 0 (0) | 0 (0) | — | 3 (5.9) | .845 |
| Location (clustered) | | | | | | | | |
| Cervix | 7 (77.8) | 1 (50.0) | 15 (55.6) | 2 (25.0) | 2 (40.0) | — | 27 (52.9) | .246 |
| LNs | 1 (11.1) | 1 (50.0) | 7 (25.9) | 4 (50.0) | 1 (20.0) | — | 14 (27.5) | .383 |
| Others | 2 (22.2) | 0 (0) | 13 (48.1) | 5 (62.5) | 3 (60.0) | — | 23 (45.1) | .322 |

Data are presented as number (percentage).

*L1*, positive lymphovascular space invasion; *LN*, lymph node.

[a] Statistically significant at *P*<.05; [b] Some patients had lesions in multiple locations.

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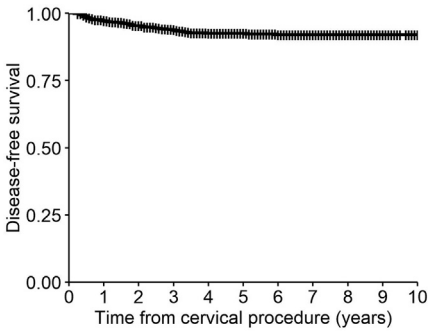
**FIGURE 1**
**Disease-free survival in the whole cohort**

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given the increasing number of women who are delaying pregnancy to a later age.[1,2,6] The primary objective of the FERTISS study was to provide robust data on oncological outcomes in a group of women who underwent FST for early stages of cervical cancer. In addition, the study reflects the current clinical practice of FST in European centers and its evolution over the last 20 years. We observed a low risk of disease recurrence after FST in patients with tumors ≤2 cm in size, negative pelvic LNs, and HPV-associated tumor types. Moreover, the oncological outcomes in patients with tumors ≤2 cm did not differ between those who underwent radical cervical surgery and those who underwent nonradical cervical surgery, regardless of LVSI or tumor size subcategories (<1 cm vs 1−2 cm). Parametrectomy, which may negatively affect the perinatal outcome and increase postoperative morbidity, was not associated with a better prognosis in patients with stage IB1 cervical cancer. FST procedures, regardless of their radicality, were associated with substantially worse oncologic outcomes in FIGO 2018 stages IB2 and higher. Moreover, we refuted the assumption that adenocarcinoma is associated with a worse prognosis than squamous cell carcinoma.

## Results

European clinical practice guidelines recommended that the same treatment algorithms should be followed, irrespective of the fertility-sparing intent.[3] Therefore, the standard FST for cervical cancer stages IA2 and IB1 should include radical trachelectomy.[7] However, we showed that many sites already perform nonradical cervical procedures in higher stages, accounting for 45% of patients with stage IB1 cervical cancer and 33% of patients with stage IB2 or IB3 cervical cancer. When we compared the proportion of nonradical procedures between 2001−2010 and 2011−2020, we found a significant increase over time (46.6% vs 59.1%; *P*=.005). This trend is also reflected in other recent studies.[2,6,8]

One of the key conditions for selecting candidates for FST is a tumor with the largest dimension of ≤2 cm.[1,3] We confirmed that these patients had a very good prognosis with a recurrence rate of just 5.7% and a disease-specific mortality rate of just 1.5%. Moreover, there was no difference in the recurrence rate between patients who underwent radical cervical procedures and patients who underwent nonradical cervical procedures, regardless of further stratification by tumor size subcategories (<1 or 1−2 cm) or presence of LVSI. The low recurrence rate after conization or simple trachelectomy in this well-selected cohort of patients with small tumors was supported by previously published data from smaller cohorts. For example, in a multicenter study of 36 patients, only 1 recurrence (2.7%) was diagnosed after conization.[5] In another study of 43 patients treated by loop excision, the recurrence rate was just 4.6%.[4] In the prospective ConCerv study, which enrolled 44 women who underwent FST for low-risk early cervical cancer, the recurrence rate at 2 years was 3.5%.[9] However, unlike our study, the ConCerv study only included stages IA2 to IB1, and the exclusion criteria were LVSI positivity, depth of invasion >1 cm, or grade III adenocarcinoma.[9]

Furthermore, a systematic literature review documented a reduction in postoperative morbidity and improved reproductive outcomes after nonradical procedures.[6] However, an alarming finding of our study was the 3-fold higher recurrence rate in patients with tumors >2 cm (19.4% vs 5.7%; *P*=.014). The recurrence rate in larger tumors was not related to the type of surgical procedure, tumor type, or administration of NACT.

A substantial proportion of patients with clinically visible tumors underwent conization as a diagnostic procedure. However, adequate margins were not achieved in 22% of those patients who had to undergo a second cervical procedure. The relatively high rate of cervical reoperations shows the need for improving the quality of primary assessment before treatment, including colposcopic examination. It is well established that the risk of preterm birth is significantly higher in women who underwent ≥1 cervical procedure (13% vs 4%) and with increasing depth of excision (7%−10% vs 3%) than in the general population.[10]

Interestingly, the study population consisted of a relatively large proportion (approximately one-third) of patients with adenocarcinoma or adenosquamous carcinoma. An increased incidence of adenocarcinoma, especially in younger patients, was recently shown in other studies,[8,11,12] including a large multicenter study of 4343 patients in which nearly one-third of patients with adenocarcinoma were <40 years old.[13] The frequent endocervical localization of these tumor types may cause limitations for FST, and some authors have reported that adenocarcinomas show a worse prognosis than squamous cell cancers.[12] However, it should be emphasized that adenocarcinoma represents a broad spectrum of tumor types. Data from our study suggested that, at least in the early stages, the prognosis of HPV-associated adenocarcinoma is similar to that of squamous cell carcinoma.

Another prerequisite for FST is regional LN negativity.[3] All of the patients in our study underwent surgical LN staging,[14] which included SLNB in about half of the patients with stage IA2 to IB cervical cancer either as a sole procedure or in combination with systematic lymphadenectomy. It is well established that the absence of SLNB decreases the reliability of nodal staging, particularly the ability to detect low-volume metastases, small

**TABLE 4**
**One-dimensional Cox proportional-hazards model for disease-free interval**

| Variable | HR (95% CI) | *P* value[a] |
|---|---|---|
| Stage (reference: IA1 L1) | | |
| IA2 | 0.429 (0.093–1.985) | .279 |
| IB1 | 1.698 (0.796–3.625) | .171 |
| IB2 | 5.247 (2.024–13.604) | .001[a] |
| IB3 | 4.579 (1.239–16.920) | .023[a] |
| Age at first diagnosis (y) | 0.957 (0.896–1.023) | .198 |
| Histological type (reference: adenocarcinoma) | | |
| Adenosquamous | 1.201 (0.345–4.181) | .773 |
| Squamous cell | 0.771 (0.409–1.454) | .422 |
| Other | 5.348 (0.703–40.695) | .105 |
| Tumor size (mm), continuous[b] | 1.054 (1.023–1.085) | <.001[a] |
| Tumor size of >2 cm (reference: ≤2 cm)[b] | 2.982 (1.383–6.431) | .005[a] |
| Grade (reference: G1) | | |
| G2 | 0.548 (0.231–1.301) | .173 |
| G3 | 1.650 (0.735–3.702) | .225 |
| Gx | 1.118 (0.454–2.750) | .809 |
| LVSI, positive (reference: negative) | 1.542 (0.834–2.851) | .167 |
| Repeated cervical procedure, yes (reference: no) | 1.296 (0.696–2.416) | .414 |
| Sentinel lymph node biopsy, yes (reference: no) | 1.174 (0.663–2.076) | .582 |
| Pelvic lymphadenectomy, yes (reference: no) | 1.213 (0.642–2.294) | .552 |
| Paraaortic lymphadenectomy, yes (reference: no) | 2.317 (0.720–7.459) | .159 |
| Type of cervical procedure (reference: conization) | | |
| Laparoscopic radical trachelectomy | 0.705 (0.165–3.016) | .637 |
| Radical abdominal trachelectomy | 1.760 (0.912–3.397) | .092 |
| Radical vaginal trachelectomy | 1.148 (0.461–2.859) | .767 |
| Robotic radical trachelectomy | — | — |
| Simple vaginal trachelectomy | 1.072 (0.366–3.136) | .899 |
| Type of cervical procedure (clustered) (reference: conization) | | |
| Radical trachelectomy | 1.326 (0.733–2.401) | .351 |
| Simple vaginal trachelectomy | 1.072 (0.366–3.136) | .899 |

*CI*, confidence interval; *HR*, hazard ratio; *L1*, positive lymphovascular space invasion; *LVSI*, lymphovascular space invasion.

[a] Statistically significant at $P<.05$; [b] Largest tumor diameter.

*Slama. Oncological outcomes after fertility-sparing treatment for cervical cancer. Am J Obstet Gynecol 2023.*

macrometastases, and micrometastases that are often missed by standard pathologic examination and can only be detected by ultrastaging.[15] The most recent literature supports the prognostic significance of micrometastases, which carried a similar risk of recurrence to macrometastases, and therefore should be a contraindication to FST.[15,16] LVSI positivity is another important prognostic risk factor that predicts the risk of microscopic regional nodal involvement.[13,15] Although the presence of LVSI was not confirmed as a risk factor for recurrence in our cohort, it should be emphasized that less than half (21/51) of the patients with recurrence underwent SLNB, and LVSI was present in 23 of 30 patients who did not undergo SLNB. It can be hypothesized that some of the recurrences were due to missing information about metastatic involvement of the SLN in the absence of pathologic ultrastaging.

During the postoperative follow-up, precancerous lesions of the cervix were detected in 3.0% of the patients.

**TABLE 5**
**Risk of recurrence in subgroups of patients with stage IB1 cervical cancer**

| | Recurrence | | | | |
|---|---|---|---|---|---|
| | Yes | | No | | |
| Category | Nonradical | Radical | Nonradical | Radical | *P* value |
| IB1 | 12 (7.5) | 15 (7.7) | 148 (92.5) | 181 (92.3) | .957 |
| IB1 L1 | 6 (11.5) | 5 (9.4) | 46 (88.5) | 48 (90.6) | .725 |
| IB L0 | 4 (4.4) | 8 (6.5) | 86 (95.6) | 115 (93.5) | .520 |
| IB1 (<1 cm) | 5 (5.2) | 9 (7.4) | 91 (94.8) | 112 (92.6) | .507 |
| IB1 (1–2 cm) | 7 (10.9) | 6 (8.0) | 57 (89.1) | 69 (92.0) | .553 |

*L0*, negative lymphovascular space invasion; *L1*, positive lymphovascular space invasion.
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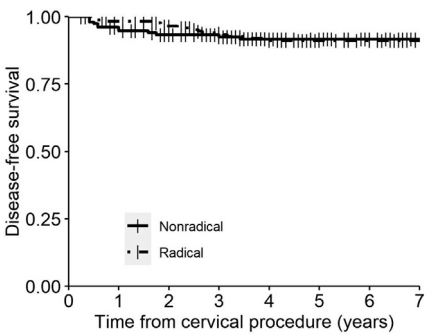
Although these are not invasive tumors, their impact on the patients' fertility may be similar, because treatment in some patients included hysterectomy leading to permanent sterility. However, salvage surgery led to long-term remission in all those patients. Therefore, this fact emphasizes the importance of long-term follow-up by an experienced colposcopist or gynecologic oncologist.[17]

## Clinical implications

Nonradical fertility-sparing procedures represent a safe treatment option for patients with cervical cancer with HPV-associated tumors of ≤2 cm in size and negative regional LNs. In contrast, the risk of recurrence after FST for tumors >2 cm is 3 times higher, and therefore, treatment of such tumors outside clinical trials should not be recommended.

**FIGURE 2**
**Disease-free survival after radical and nonradical procedures in stage IB1 cervical cancer**




*Slama. Oncological outcomes after fertility-sparing treatment for cervical cancer. Am J Obstet Gynecol 2023.*

## Research implications

Although the use of less radical surgery for smaller tumors seems to be an oncologically safe approach, the treatment of larger tumors and the potential benefit of NACT administration in such treatment remain an unanswered question.[6,18] Moreover, our data showed that the indications for NACT administration vary considerably among institutions and that NACT is also used in the treatment of stage IB1 tumors, where there is a disparity between the small cervix in nullipara and the relatively large tumor. In the future, more extensive data from controlled trials (eg, the ongoing CoNteSSa—NEOCON-F trial[6]) are needed to optimally define the indications for NACT and to assess the safety and success of such procedures. Furthermore, we believe that SLNB should be an integral part of surgical staging of LNs in early-stage cervical cancer. However, in our study, this procedure was performed in only half of the patients, although SLNB followed by ultrastaging assessment may reveal a significant number of low-volume metastases. In addition to confirming the value of SLNB in the treatment of FST for early-stage cervical cancer, studies are needed to help verify the safety and sensitivity of SLNB alone without performing subsequent systematic lymphadenectomy during FST.

## Strengths and limitations

The FERTISS study has several strengths, including the registration of a large number of patients across multiple institutions in multiple countries. Thus, the results should reflect the real-world use and outcomes of FST for patients with cervical cancer. The limitations included the retrospective study design with potential selection bias and geolocation bias in procedures and outcomes because of differences in the number of patients registered at each institution.

## Conclusions

To date, the FERTISS study represents the largest cohort of patients who have undergone FST for early-stage cervical cancer. We have demonstrated that the oncological outcomes after FST were excellent in patients with HPV-associated tumors, negative regional LNs, and tumors ≤2 cm in size and that these outcomes were not negatively influenced by nonradical cervical procedures, such as conization or simple vaginal trachelectomy. In patients with tumors >2 cm in size, FST was associated with a significantly higher risk of recurrence, regardless of the tumor type or type of surgery. SLNB, which should be a mandatory procedure in the treatment of FST, was performed in less than half of the patients. The prognosis of FST in patients with the frequently represented HPV-associated adenocarcinoma and adenosquamous carcinoma subtypes did not differ from that of patients with squamous cell carcinomas. However, patients with non—HPV-associated tumor types are not good candidates for FST. ■

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