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Radical vaginal trachelectomy: long-term oncologic and fertility outcomes in patients with early cervical cancer

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ABSTRACT

Objective Radical vaginal trachelectomy is a fertility-preserving treatment for patients with early cervical cancer. Despite encouraging oncologic and fertility outcomes, large studies on radical vaginal trachelectomy are lacking.

Method Demographic, histological, fertility, and follow-up data of consecutive patients who underwent radical vaginal trachelectomy between March 1995 and August 2021 were prospectively recorded and retrospectively analyzed.

Results A total of 471 patients of median age 33 years (range 21–44) were included. 83% (n=390) were nulliparous women. Indications were International Federation of Gynecology and Oncology (FIGO, 2009) stages IA1 with lymphovascular space involvement (LVSI) in 43 (9%) patients, IA1 multifocal in 8 (2%), IA2 in 92 (20%), IB1 in 321 (68%), and IB2/IIA in 7 (1%) patients, respectively. LVSI was detected in 31% (n=146). Lymph node staging was performed in 151 patients (32%) by the sentinel node technique with a median of 7 (range 2–14) lymph nodes and in 320 (68%) by systematic lymphadenectomy with a median of 19 (range 10–59) lymph nodes harvested. Residual tumor was histologically confirmed in 29% (n=136). In total, 270 patients (62%) were seeking pregnancy of which 196 (73%) succeeded. There were 205 live births with a median fetal weight of 2345 g (range 680–4010 g). Pre-term delivery occurred in 94 pregnancies (46%). After a median follow-up of 159 months (range 2–312), recurrences were detected in 16 patients (3.4%) of which 43% occurred later than 5 years after radical vaginal trachelectomy. Ten patients (2.1%) died of disease (five more than 5 years after radical vaginal trachelectomy). Overall survival, disease-free survival, and cancer-specific survival were 97.5%, 96.2%, and 97.9%, respectively.

Conclusion Our study confirms oncologic safety of radical vaginal trachelectomy associated with a high chance for childbearing. High rate of pre-term delivery may be due to cervical volume loss. Our long-term oncologic data can serve as a benchmark for future modifications of fertility-sparing surgery.

INTRODUCTION

Cervical cancer remains a relevant problem, even in higher income countries.¹ When nulliparous women

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Several case series of radical vaginal trachelectomy with <200 patients and mainly 5 years of follow-up have been reported and show oncological results similar to radical hysterectomy, with pregnancy rates comparable to the general population but increased risk of prematurity.

WHAT THIS STUDY ADDS

⇒ This is the largest and longest case series of patients undergoing radical vaginal trachelectomy (n=471) with the longest follow-up (median 13 years) reported to date. Disease-free survival (96%) and overall survival (98%) are equivalent to results following radical hysterectomy. Recurrence occurred after a median of 52 months and, in 43% of patients, after 5 years and up to 9 years. Pregnancy rates were high (73%). Despite placement of permanent cerclage during radical vaginal trachelectomy, the rate of pre-term delivery (46%) remains a challenge.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The current therapeutic trend for patients with early-stage cervical cancer seeking future fertility is reduction of surgical radicality to decrease the rate of premature delivery, but appropriate criteria for this tailored approach are needed. We present long-term oncologic data of radical vaginal trachelectomy which can serve as a benchmark for a new fertility-preserving strategy. Moreover, we consider that, given the significant number of patients recurring after 5 years, surveillance should be extended to 10 years.

are diagnosed with cervical cancer, fertility-sparing treatment becomes a major issue.² Radical vaginal trachelectomy, introduced by Daniel Dargent in 1994,³ was the first fertility-sparing therapy for patients with early cervical cancer^{4,5}; however it has failed to gain worldwide acceptance.⁶ To date there have been approximately 1500 radical vaginal trachelectomies reported with decreasing frequency, whereas publications on abdominal or robotic radical trachelectomy have increased.^{7–9}



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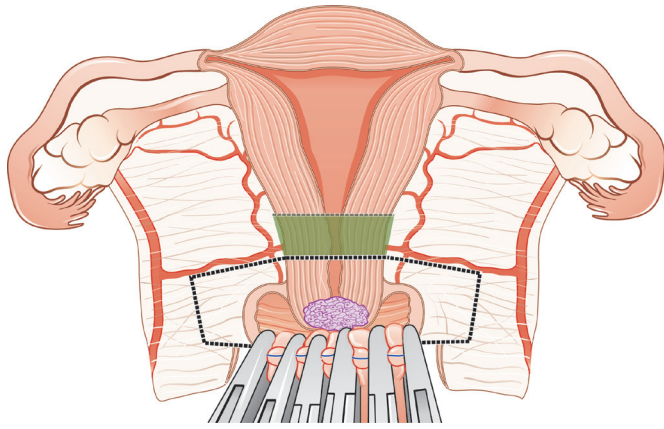


Figure 1 Schematic illustration of radical vaginal trachelectomy. The vaginal cuff is closed with a continuous suture under tension with six clamps. Residual tumor is marked in purple and the extent of the surgical resection is indicated by the black dotted line. The preserved part of the cervix is shown in green.

The risk for pre-term delivery correlates directly with the volume loss of the uterine cervix and, thus, the radicality of the procedure. Volume loss is lowest with conization, higher with simple trachelectomy, and highest with radical trachelectomy where part of the parametrium is also resected. Given the low incidence of parametrial spread in small volume cervical cancer without lymph node metastases, a tendency towards less radical cervical resection is seen.^{10–12} Conization and simple trachelectomy are alternatives for patients with low-risk disease. However, inclusion criteria for these tailored fertility-sparing treatments vary considerably and long-term oncologic results are not available. Moreover, conization also can significantly increase the risk of intra-amniotic infection, premature rupture of membranes, and neonatal intensive care unit stay in a subsequent pregnancy depending on the number and size of conization(s), as reported in several meta-analyses on the treatment of dysplasia.^{13 14} The goal of this study was to evaluate the long-term oncologic and fertility outcomes of 471 consecutive

patients who underwent radical vaginal trachelectomy by the same team over a 26-year period.

METHODS

All patients with tumor stages IA1 with lymphovascular space involvement (LVSI) to IB1 <2 cm, human papillomavirus-related histologic type, tumor-free lymph nodes on frozen section, age <45 years, and a desire for fertility preservation were included. The primary endpoint was the rate of recurrences and therefore disease-free survival, secondary overall survival, cancer-specific survival, and pregnancy rate. The technique of radical vaginal trachelectomy has been previously described^{15 16} (Figure 1). All surgeries have been performed according to the original description by the same team of gynecologic oncologists between March 1995 and August 2021 at Friedrich-Schiller-University Jena, Charité University Berlin, and Asklepios Clinic Hamburg (Figure 2) from October 2018 with slight modification in ureteral dissection.⁶ In all patients a permanent cerclage was placed using monofilament suture material.

Demographic, surgical, and histological data were continuously monitored from the patients' clinical records. Follow-up and fertility data were obtained using questionnaires and telephone calls. The data of this cohort have been reported previously.¹⁷ Disease-free survival, overall survival, and cancer-specific survival were analyzed using the Kaplan–Meier method. This retrospective study was approved by local ethical committee.

RESULTS

A total of 471 patients underwent radical vaginal trachelectomy. Their median age was 33 years (range 21–44) (Table 1). At the time of surgery 390 patients (83%) were nulliparous. Histology was squamous carcinoma in 320 patients (68%), adenocarcinoma in 146 patients (31%), and adenosquamous in five patients (1%). Grading was G1, G2 and G3 in 62 (13%), 313 (67%), and 96 (20%) tumors, respectively. Tumor stage was International Federation of

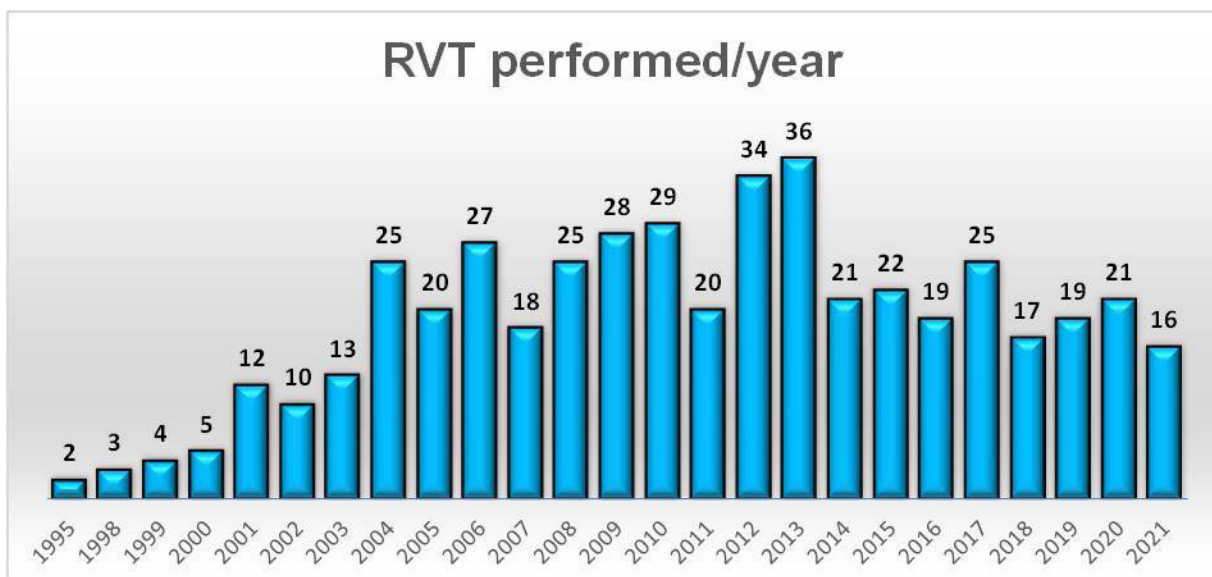


Figure 2 Number of patients per year undergoing radical vaginal trachelectomy (RVT).

Table 1 Demographic, histologic, surgical, fertility, and follow-up data

Patients	n=471
Age, median (range)	33 (21–44)
Nulliparous	390 (83%)
Histology	SCC: n=320 (68%) Adeno: n=146 (31%) AS: n=5 (1%)
Stage (FIGO 2009)	IA1 (multifocal): n=8 (2%) IA1 with LVSI: n=43 (9%) IA2: n=92 (20%) IB1: n=321 (68%) IB2: n=5 (1%) IIA: n=2
Grading	G1: n=62 (13%) G2: n=313 (67%) G3: n=96 (20%)
LVSI	Positive: n=146 (31%) Negative: n=325 (69%)
Type of lymph node assessment	Sentinel: n=151 (32%) Complete LND: n=320 (68%)
No of removed lymph nodes, median (range)	Sentinel: 7 (2–14) Complete: 19 (10–59)
Residual tumor in trachelectomy specimen	Yes: n=136 (29%) No: n=335 (71%)
Adjuvant therapy following RVT	n=29 (6%) Adjuvant chemotherapy: n=4 Adjuvant chemoradiation: n=12 Radical hysterectomy (±RCTX): n=13
Seeking motherhood	Yes: n=270/439 (62%) No: n=169/439 (38%) Not able due to adjuvant therapy: n=29 Lost to follow-up: n=3
Pregnancy rate	196/270 (73%) 4 pregnancies: n=2 3 pregnancies: n=7 2 pregnancies: n=41 1 pregnancy: n=146
Fertility results	205 live births Fetal weight (median): 2345 (680–4010)g 33 first trimester miscarriages 13 second trimester miscarriages 4 ongoing pregnancies 2 ectopic pregnancies
Median follow-up (months)	159 (2–312) Recurrences: n=16 (3.4%) Death: n=10 (2.1%) Death from other cause: n=2 (breast cancer, traffic accident)

adeno, adenocarcinoma; AS, adenosquamous carcinoma; LND, lymph node dissection; LVSI, lymphovascular space invasion; RCTX, chemoradiation; RVT, radical vaginal trachelectomy; SCC, squamous cell carcinoma.

Gynecology and Obstetrics (FIGO) 2009 IA1 (multifocal) in eight patients (2%), IA1 LVSI positive in 43 patients (9%), IA2 in 92 patients (20%), IB1 in 321 patients (68%), and IB2 or IIA in five and two patients (1%), respectively. LVSI was diagnosed in 146 patients (31%).

The type of lymph node assessment was sentinel node mapping in 151 patients (32%) and complete lymphadenectomy in 320 (68%) patients with a median number of seven harvested lymph nodes (range 2–14) in the sentinel procedure and 19 (range 10–59) in complete lymphadenectomy. Residual tumor was detected in 136 (29%) trachelectomy specimens. According to tumor board

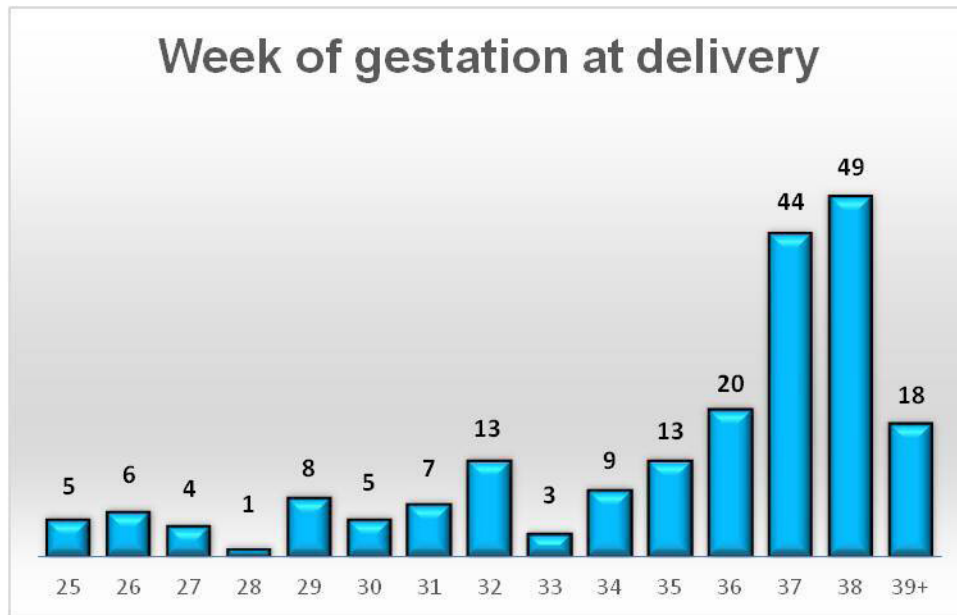


Figure 3 Distribution of week of gestation at delivery of 205 children following radical vaginal trachelectomy.

recommendations, 29 (6%) patients underwent adjuvant therapy such as chemotherapy (n=4), chemoradiation (n=12) or radical hysterectomy (\pm chemoradiation) (n=13) due to lymph node metastases on final pathology, classified as tumor-free on frozen section, or close/tumor-involved resection margins.

Following radical vaginal trachelectomy, 270 of the 439 patients (62%) tried to become pregnant. Of these, 196 patients (73%) succeeded, with four pregnancies in two women, three pregnancies in seven, two pregnancies in 41, and one pregnancy in 146 women. In total, 205 children with a median fetal weight of 2345 g (range 680–4010 g) and normal Apgar scores and pH values were delivered by cesarean section. Considering 257 documented pregnancies, two ectopic pregnancies (0.1%), 33 first trimester miscarriages (13%), 13 second trimester miscarriages (5%) and four ongoing pregnancies were reported. Premature delivery occurred in 94 (46%) women, with severe, moderate, and mild prematurity in 15 (16%), 21 (22%), and 58 (62%), respectively. All 15 newborns before 28 weeks were without any permanent handicap (Figure 3). Twelve of the 15 very early pre-term deliveries (weeks 24 to 27 6/7) occurred between 1995 and 2008 within the first radical vaginal trachelectomies. The average birth weights of the babies increased from the first to the second to the third study period (trachelectomy numbers: 1–150, 151–300, 301–471) from 2406 g to 2604 g to 2779 g.

Three patients were lost to follow-up. After a median follow-up of 159 months (range 2–312), 16 recurrences were detected (3.4%) and 10 (2.1%) patients died of disease, two from other causes. Overall survival, disease-free survival, and cancer-specific survival were 97.5%, 96.2%, and 97.9%, respectively. Recurrences occurred after a median of 52 months (range 9–117), and in 43% of patients these occurred beyond 5 years with the longest interval being >9 years. In evaluating histologic sub-types, five patients who recurred were diagnosed with adenocarcinoma and 11 patients with squamous carcinoma. The initial stage was IA2 in two patients, IB1 in 13 patients, and IB2 in one patient. LVSI positivity was found in five of 16 patients. In eight of 16 patients residual tumor was detected

in the trachelectomy specimen. Recurrences in patients who died were distant in five, pelvic in four, and not specified in one patient. All six patients alive had pelvic recurrence.

DISCUSSION

Summary of Main Results

Radical vaginal trachelectomy is oncologically safe. The pregnancy rate was high (73%), with 46% of pregnancies ending in pre-term labor. The overall recurrence and death rates were low at 3.4% and 2.1%, respectively. Of note, 43% of recurrences occurred more than 5 years after radical vaginal trachelectomy.

Results in Context of the Literature

Radical vaginal trachelectomy was introduced as the first fertility-sparing alternative to radical hysterectomy with a similar oncologic outcome.^{2,3} Under strict inclusion criteria, the majority of centers confirmed low recurrence and death rates of 0–6.8% and 0–5.2%, respectively.^{7, 18–21} The demographic, histologic, and oncologic results in our study are in concordance with other single institution series; however, our median follow-up interval is the longest reported to date.^{22–25} Of note, 43% of recurrences and 50% of deaths in our study occurred more than 5 years after radical vaginal trachelectomy. Thus, studies with 5 years of follow-up may underestimate the oncologic safety of fertility-sparing therapy.

The oncologic results of radical vaginal trachelectomy in the reviews by Smith et al²⁰ of 1491 women (recurrence rate 3.8%, death rate 1.7%), Nezhat et al¹⁹ of 1387 women (recurrence rate 3.7%, death rate 1.1%), and Morice et al⁷ of 1977 women (recurrence rate 4.7%) are in the same range as abdominal radical trachelectomy and slightly better than total laparoscopic trachelectomy.^{7–9} High-volume centers achieve better results than those who perform one procedure per year.²⁶ Since 2002 our team has performed at least 10 (up to 36) radical vaginal trachelectomies per year (Figure 2).

An interesting observation is that up to 40% of women who underwent radical vaginal trachelectomy ultimately did not try to conceive,^{22 24 25} which is consistent with 38% in our cohort. More research should be focused on this topic in the future.

Parametrial resection can cause peri- and post-operative morbidity. In a study of 18 patients, Froding et al reported persistent bladder emptying problems and lymphedema after radical vaginal trachelectomy comparable to abdominal radical hysterectomy.²⁷ Shepherd et al²² reported peri-operative and post-operative complication rates of 4.9% and 19.5%, respectively. These results are similar to Mathevet et al who reported 29% urinary, 26% lymphovascular, and 14% neurologic post-operative complications.²⁸ We have not systematically analyzed peri- and post-operative complications, but no bladder, ureter, bowel, or vascular injuries occurred with the last 200 procedures.

Besides the oncologic outcome, the ability to get pregnant is important following radical vaginal trachelectomy. Pregnancy rates following radical vaginal trachelectomy are consistently high at 53–76%.^{7 19 22 24 25} Our pregnancy rate of 73% is in the upper range. In their reviews, Smith et al and Nezhat et al concluded that radical vaginal trachelectomy offers the highest pregnancy rates among different radical trachelectomy techniques.^{19 20}

Pre-term delivery following radical vaginal trachelectomy is mainly due to shortening of cervical length and competence and, thus, increases the risk of infection and consecutive premature rupture of membranes. Whereas the pre-term delivery rate in the general population is 10.6%,²⁹ the pre-term rate following radical vaginal trachelectomy is 30–45%.^{7 19 20 22} Our rate of 46% is in the upper range. We agree with the comment by Netzhat et al that, in the beginning of radical vaginal trachelectomy, obstetricians delivered patients by planned cesarean section at week 34 of gestation before any onset of labor and we followed a similar strategy. Zusterzeel et al reported a pre-term delivery rate at 24–28 weeks, 28–32 weeks, and >37 weeks of 6.3%, 8.5% and 53%, respectively.²⁴ Similar results were obtained by Hauerberg et al with 5.6%, 9.4%, and 38%, respectively.²⁵ The respective rates of 7.8%, 10%, and 54% in our study are in the same range without any permanent handicap for any infant following very early pre-term delivery. Increased surgical experience and improved antenatal care can postpone delivery later on in the pregnancy.³⁰ Indeed, in our series 12 out of 15 very early pre-term deliveries (24–27 6/7 weeks) occurred within the first 150 radical vaginal trachelectomies, and the average birth weights of babies born in the first, second, and third study periods (2406 g, 2604 g, and 2779 g, respectively) continued to increase.

Given the abovementioned main drawbacks of radical vaginal trachelectomy—that is, pre-term delivery, possible surgical morbidity, and missing residual tumor in trachelectomy specimens—there has been a tendency towards less radical cervical surgery for fertility-sparing treatment during the last few years. Conization and simple trachelectomy have gained increasing acceptance as fertility-sparing treatment in women with low-risk early cervical cancer.^{7 10–12 18 20} Plante and co-workers reported on 50 patients (52% with stage Ib1 tumors, 16% with G3 tumors, and 30% with LVSI).¹⁰ After a mean follow-up of 76 months only one recurrence occurred resulting in a progression-free survival of 97.9% and overall survival of 97.6%. The pre-term delivery rate was 9%. Martinelli et al reported on 39 patients who underwent

conization and lymph node assessment. The study cohort comprised 64% with stage Ib1 tumor and 39% with LVSI. The recurrence rate was 6.1% after 51 months of follow-up and the pre-term delivery rate was 10%.³¹ Tomao et al reported on conization as fertility-sparing therapy in 54 patients. Stage Ib1 was diagnosed in 76%, G3 in 20%, and LVSI in 22%. The median follow-up was 55 months with a recurrence rate of 13%.³² In a large international multicenter trial of 733 patients the recurrence rate was 5.7%. No difference in the recurrence rate was seen between radical trachelectomy and non-radical procedures regardless of LVSI involvement.¹¹

In their recent systematic review, Morice et al summarized the data of 649 patients following conization/simple trachelectomy and 1977 patients following radical vaginal trachelectomy and found recurrence rates, pregnancy rates, and live birth rates of 4.1% vs 4.7%, 56.3% vs 58.7%, and 88% vs 71%, respectively.⁷ Comparing these findings with their review from 2016,³³ the recurrence rate of conization/simple trachelectomy increased from 2.5% to 4.1% and is now in the same range as radical vaginal trachelectomy (4.7%). The difference in the rate of premature delivery fell from 24% to 12%, mainly related to less frequent pre-term deliveries following radical vaginal trachelectomy. The validity of this meta-analysis is limited by the lack of data on LVSI, deep stromal involvement, and MRI findings. Given the small number of patients and different inclusion criteria in the few studies on conization/simple trachelectomy, comparison with radical vaginal trachelectomy studies is unreliable. Statements from the new European Society of Gynecological Oncology guideline³⁴ on the treatment of patients with cervical cancer reflect our uncertainties with respect to fertility-sparing treatment rather than evidence-based knowledge.

Strengths and Weaknesses

The strengths of this study are the largest number of patients uniformly treated by one experienced gynecologic oncology team, the prospective recording of consecutive data, the longest follow-up period, and the high rate of complete follow-up data. Limitations of the study are its retrospective nature, the lack of information on radiologic assessment prior to surgery, the lack of data on the initial depth of cervical stroma invasion and resected parametrial size, and the absence of a detailed record on peri- and post-operative morbidity. Moreover, the follow-up status was obtained by telephone or survey and not by medical assessment.

Implications for Practice and Future Research

Oncologic as well as fertility data of our retrospective study can be used as a comparison with any modification of fertility-sparing therapy. The ongoing tendency towards less radical procedures is justified in the background of no residual tumor in the trachelectomy specimen in 71%. However, additional predictive markers (eg, proliferation index, PDL status, molecular genetic profile, mRNA analysis in removed lymph nodes and circulating tumor cells)³⁵ have to be evaluated. In addition, a two-step protocol may be advantageous. In the first step conization and sentinel node biopsy followed by analysis of tumor biology and resection margins should be performed. If histology reveals tumor-free lymph nodes on ultrastaging and a low risk early cervical cancer in conization with negative margins, no further fertility-sparing treatment is needed. The remaining patients will be advised on a second fertility-sparing treatment or even to abstain from fertility-preserving treatment

and to undergo radical hysterectomy or primary chemoradiation. Antenatal care of patients following radical trachelectomy has to be improved to decrease the pre-term delivery rate.

CONCLUSION

Radical vaginal trachelectomy for patients seeking parenthood and being diagnosed with low-risk or intermediate-risk early cervical cancer <2 cm performed in a referral center is oncologically safe and achieves high fertility rates. Long-term follow-up is mandatory because 43% of recurrences occurred more than 5 years after radical vaginal trachelectomy. Pregnancy following radical vaginal trachelectomy requires obstetric attention due to the increased risk of pre-term labor. Well-designed trials are urgently needed to define the criteria for either tailored or radical procedures of fertility-sparing therapy in order to avoid over-treatment or under-treatment for these young patients.

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Data availability statement Data are available upon reasonable request. We will provide our data for independent analysis by a selected Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

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