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Long-term results of fertility-sparing treatment for early-stage cervical cancer

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HIGHLIGHTS

- Cervical conization plus lymph node dissection is a valuable option for early-stage stage cervical cancer.
- About 20% for patients initially submitted to fertility sparing procedure required radical treatments.
- In case of negative margins, cervical conization guarantees a good local disease control rate.

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ABSTRACT

Objective. To evaluate the long-term outcomes of young early stage cervical cancer patients wishing to preserve their childbearing potential.

Methods. Data of young (aged <40 years) patients with early stage cervical cancer were prospectively collected. All patients with stage IA2, IB1 and IB2 cervical cancer were included; they have cervical conization and pelvic node dissection performed via minimally invasive surgery. Survival outcomes were assessed with the Kaplan-Meier model.

Results. Overall, 32 patients met the inclusion criteria. Mean (SD) age of the population included was 33 (±4). According to the FIGO 2018 staging system, the stage of disease was IA2, IB1 and IB2 in 9 (28%), 21 (66%) and 2 (6%) cases, respectively. All patients included had cervical conization and laparoscopic pelvic node assessment, including systematic pelvic lymphadenectomy ($N = 30$, 94%) and sentinel node mapping ($N = 2$, 6%). In six (19%) patients the planned conservative treatment was discontinued. Median follow-up was 75 (range, 12–184) months. No recurrent disease was diagnosed among patients undergoing conservative treatment; while 2 out of 6 patients having definitive surgical or radiotherapy treatments developed recurrent disease. Five-year disease free and overall survivals were 94% and 97%, respectively. Considering reproductive outcomes, 11 (69%) out of 16 patients who attempted to conceive got pregnant.

Conclusions. Cervical conization and pelvic nodes assessment could be considered a valid treatment modality for early-stage cervical cancer patients who are wishing to preserve their childbearing potential.

1. Introduction

In recent years, the implementation of screening programs has led to a reduction in cervical cancer-related morbidity and mortality, especially in high-resource settings. However, although the prevalence of locally advanced disease has been dropping dramatically in developed countries, the prevalence of early-stage disease is slightly increasing [1–3]. Surgery represents the mainstay of treatment for early-stage disease (stage IA2-IB2), and it entails the radical removal of the uterus and the nodal assessment (i.e., lymphadenectomy or sentinel node mapping) [4,5]. Radiotherapy (with or without chemotherapy) is considered as an alternative treatment. However, hysterectomy and radiotherapy lead to permanent sterility. Concerns are arising since it is estimated that approximately 40% of early-stage cervical cancer patients are younger than 40 years old [6–8]. Thus, evaluating the role of conservative strategies for young cervical cancer patients who wish to preserve their childbearing potential is crucial.

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To date several studies investigated various treatment modalities for the conservative management of early-stage cervical cancer [9–15]. The first experiences in the conservative management of early-stage cervical cancer included the execution of radical trachelectomy, which was proposed as an alternative method to radical hysterectomy in young cervical cancer patients [9–22]. However, radical trachelectomy correlates with a postoperative morbidity similar to radical hysterectomy, especially in terms of pelvic floor dysfunction. Interestingly, studies focusing on radical trachelectomy reported that a high proportion of patients have no residual disease on their uterine cervix thus highlighting the need for less radical procedures. Moreover, the execution of trachelectomy (radical or simple) is associated with a high rate of obstetric issues, especially related to infertility and pre-term labor [7,20–23]. For all these reasons, few investigations evaluated the role of simple conization in the management of early-stage cervical cancer. In comparison to trachelectomy, conization is a simpler procedure characterized by a low morbidity rate and lower risk of developing obstetrical issue [7,24].

Our study group and other Authors reported preliminary experiences of early-stage cervical cancer patients managed with cervical conization and pelvic node dissection [23]. Here, we aimed to audit our long-term results of conservative management of early-stage cervical cancer patients who are wishing to preserve their childbearing potential.

2. Materials and methods

After Institutional Review Board (IRB) approval, we prospectively collected data of young patients affected by early-stage cervical cancer and wishing to preserve their childbearing potential, presenting at the Gynecological Oncology Unit of Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy, between May 2003 and June 2017. Inclusion criteria were: (i) young women, aged <40 years; (ii) early stage of disease; (iii) absence of radiological evidence of lymph node metastases; (iv) a strong desire to preserve their childbearing potential; and (v) at least one year of follow-up. Patients affected by neuroendocrine cervical tumors or other rare histologies, as well as patients affected by synchronous cancer, were excluded from the study. All patients included underwent preoperative evaluation including: chest X-ray, electrocardiogram, blood tests, clinical examination, colposcopy and pelvic and abdominal magnetic resonance imaging. Additionally, pelvic ultrasound was carried out in all patients.

Stage of disease and grading were assessed using the International Federation of Obstetrics and Gynecologists (FIGO) system [25]. Histological sub-types were reported according to the World Health Organization (WHO) system [26]. Early stage of disease was defined as FIGO stage IA2, IB1 (with tumor diameter < 20 mm) and IB2 (with tumor diameter between 20 and 40 mm) according to the new FIGO 2018 staging system [24]. Written informed consent was obtained from every patient. Additionally, patients gave consent for data collection and publication. Patients were thoroughly counseled about different treatment modalities. Patients were informed that conservative treatment was an experimental option and that radical hysterectomy or chemoradiation were the two standard treatment modalities for early-stage cervical cancer. Surgical procedure included laser conization plus laparoscopic pelvic lymphadenectomy. During the study period systematic pelvic lymphadenectomy was the standard of care; while only few patients had sentinel node mapping since it was introduced in 2017.

Conization was repeated only when invasive tumor involved margins or minimal free margins (<2 mm free margins). In case of positive lymph nodes at frozen section or at the time of definitive pathological analysis, patients were counseled about the choice between radiochemotherapy or the use of chemotherapy followed by radical hysterectomy. This latter approach is a part of an ongoing clinical trial on the management of cervical cancer. Patients were informed that chemotherapy followed by radical hysterectomy represents an experimental option, while the standard treatment for high-risk cases consists in radiochemotherapy. However, many patients preferred the surgical removal of the tumor, with the aim to reduce the need of local adjuvant radiotherapy in case of optimal response.

Details of surgical procedures as well as intra- and post-operative complications were prospectively collected by trained nurses and residents (not directly involved in the surgery). Postoperative complications were graded as per the Accordion classification system [27]. Follow-up evaluations were scheduled every 4 months for the first 2 years after surgery, every 6 months between 2- and 5-year after surgery and annually thereafter. Survival data were abstracted from a dedicated database prospectively up-dated on a regular basis. Rigorous efforts, including telephone interviews, were done to improve the quality of the follow-up data. Criteria for undergoing adjuvant treatment are described elsewhere [28–29]. Basically, patients received chemoradiotherapy in case of: positive lymph node(s), parametrial and vaginal involvement or positive surgical resection margins (<3 mm). Adjuvant radiotherapy was administered when 2 of the following 3 adverse prognostic factors were present: large tumor diameter, deep cervical stromal involvement and lymph vascular space invasion (LVSI), according to Sedlis' criteria [30]. Presence of lympho vascular space invasion alone was not a criterion for adjuvant therapy.

Basic descriptive statistics were used to report patients' characteristics. Disease-free survival was counted from the date of surgery to the date of recurrence or the last follow-up for non-recurrent patients. Overall survival was counted from the date of surgery to the date of the last follow-up or death. Kaplan-Meier and Cox models were used to assess survival outcomes. Survival outcomes were evaluated within the first five years of surgery. All *p*-values were two-sided. *p*-Values <0.05 were considered statistically significant (see Table 1).

3. Results

Overall, 32 patients met the inclusion criteria and were included in the present study. Fig. 1 shows the flow of patients into the study design. Mean (SD) age of the population included was 33 (±4). 10 (31%), 15 (47%) and 7 (32%) patients were aged <30 years, between 31 and 35 years, and between 36 and 40 years, respectively. One patient had a history of a previous vaginal delivery; while all the remaining 31 (97%) patients were nulliparous. This latter group included four (12%)

Table 1
Patient's characteristics.

Characteristics	Number of patients ($n = 32$)
Age, years	32 (26–40)
Body mass index, Kg/mq	20.7 (±2.0)
Nulliparous	31 (97%)
Prior miscarriage	4 (13%)
2018 FIGO stage	
Stage IA2	9 (28%)
Stage IB1	21 (66%)
Stage IB2	2 (6%)
FIGO grade	
Grade 1	4 (13%)
Grade 2	13 (41%)
Grade 3	13 (41%)
Missing data	2 (6%)
Histology	
Squamous	20 (63%)
Adenocarcinoma	11 (34%)
Adenosquamous	1 (3%)
Presence of LVSI	14 (48%)
Depth of invasion, mm	4.9 (±2.1)
Follow-up, months	75 (12–184)

Data are expressed in median (range), median (SD) or number (%). Abbreviation: FIGO, International Federation of Obstetrics and Gynecologists; LVSI, lymph vascular space invasion.

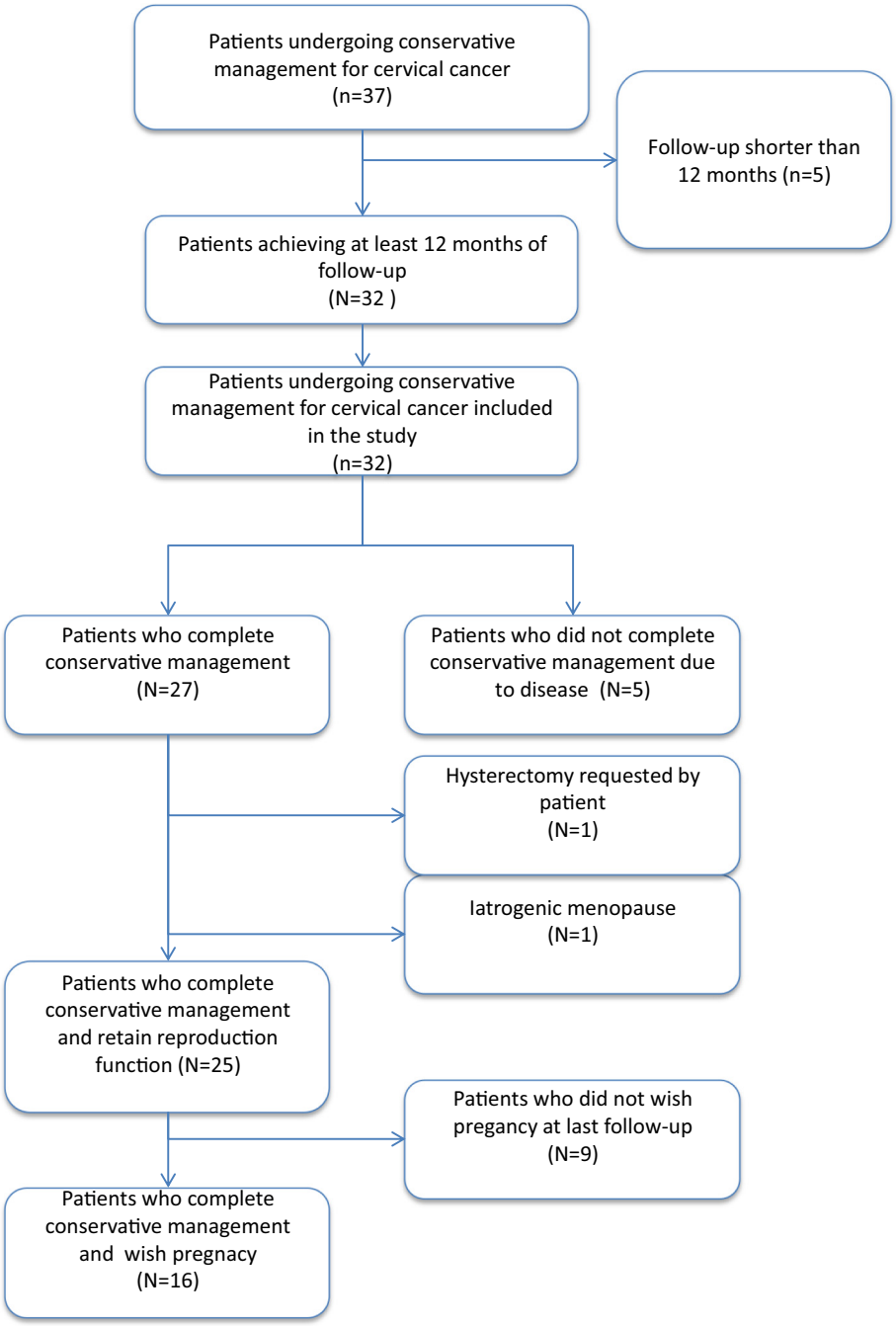

Fig. 1. Study design.

women who had at least one previous miscarriage. Histology included adenocarcinoma, squamous cell and adenosquamous carcinoma in 12 (38%), 19 (59%) and one (3%) patients, respectively. According to the FIGO 2018 staging system, stage of disease included stage IA2, IB1 and IB2 in 9 (28%), 21 (66%) and 2 (6%) cases respectively. Lymph-vascular space invasion was identified in 56% (5 out of 9), 38% (8 out of 21) and 50% (1 out of 2) patients with stage IA2, IB1 and IB2, respectively. Table 1 reports baseline patients' characteristics. All patients included had cervical conization and laparoscopic pelvic node assessment, including systematic pelvic lymphadenectomy ($N = 30$, 94%) and sentinel node mapping ($N = 2$, 6%). Second conization was performed in 12 patients (37.5%). The mean (SD) number of pelvic lymph nodes removed was 25 (± 7). No patients had para-aortic node dissection. No intra-operative complications occurred; however a patient developed a pelvic lymphocele requiring percutaneous drainage via CT-scan about 30 days after systematic pelvic lymphadenectomy. Surgery-related outcomes are listed in Table 2.

In six (19%) patients the planned conservative treatment was discontinued. Four (12%) patients were diagnosed with stage IIIC1p disease, due to the presence of positive nodes at the time of lymph node assessment (three after systematic pelvic lymphadenectomy and one after sentinel node mapping). After counseling three patients received chemotherapy followed by radical hysterectomy. The other patient (the patient who had sentinel node mapping) received radiochemotherapy. Another patient (3%) affected by stage IB2 cervical cancer had diagnostic lymphadenectomy first, and subsequently was submitted to two conization but owing to the persistence of disease on the uterine cervix. She was submitted to radical hysterectomy.

Additionally, one (3%) patient, after the successful execution of the conservative treatment, asked for radical standard treatment, and she

Table 2
Surgical outcomes of patients undergoing conservative management for early-stage cervical cancer.

Operative-related parameters	Characteristics (n = 32)
Operative time, min	100 (45–180)
Estimated blood loss, mL	30 (10−100)
Hospital stay, day	2 (1–4)
Intra-operative complications	0
Postoperative grade 3 or worse complication	1 (3%)
Pelvic node assessment	
- Systematic pelvic lymphadenectomy	30 (94%)
- Sentinel node mapping	2 (6%)
Pelvic nodes yielded	25 (±8)
Patients with positive nodes	4 (13%)

Postoperative complications are graded per the accordion severity system ().

underwent radical hysterectomy. Details of outcomes of those patients are reported in Table 3.

3.1. Oncological outcomes

Median follow-up was 75 (range, 12–184) months. 19 (59%) patients have a follow-up longer than 5 years. Survival curves displaying disease-free and overall survival for the whole population are reported in Fig. 2. No recurrent disease was diagnosed among patients undergoing conservative treatment; while two out of six patients having definitive surgical or radiotherapy treatments developed recurrent disease. One patient affected by stage IA2 cervical cancer was detected with one positive pelvic node at the time of diagnostic lymphadenectomy; she had neoadjuvant chemotherapy plus radical surgery. She developed a supraclavicular lymph node recurrence 4 years after surgery. At the time of last follow-up (88 months), the patient was alive with disease. The second patient developed a recurrence in the para-aortic area 6 months after surgery and died of disease at 24th month of follow-up. For the whole population, five-year disease-free and overall survivals were 94% and 97%, respectively. For patients who complete planned conservative treatment, both five-year disease-free and overall survivals were 100%. One patient who had conservative treatment was diagnosed with a diffuse large B cell non-Hodgkin's lymphoma, 2 years after the treatment for cervical cancer. She had chemotherapy with complete remission of the disease.

3.2. Reproductive outcomes

Among the whole population of 32 patients, 26 patients completed the planned conservative treatment including cervical conization and laparoscopic pelvic nodal assessment. Additionally, one patient developed iatrogenic menopause (after the administration of chemotherapy for non-Hodgkin's lymphoma) thus making possible the evaluation of reproductive outcomes in 25 patients. Among those, nine (36%) did not attempt to conceive. 11 (69%) out of 16 patients who attempted to conceive got pregnant. Eight (50%), one (6%), and one (6%) women had uneventful term pregnancies, preterm delivery (at 32 weeks) and second trimester miscarriage, respectively. Additionally, one patient (6%) had an uneventful ongoing first trimester pregnancy at the time of last follow-up. Two (12%) patients were submitted to prophylactic cerclage. Table 4 presents the reproductive outcomes of women preserving their childbearing potential.

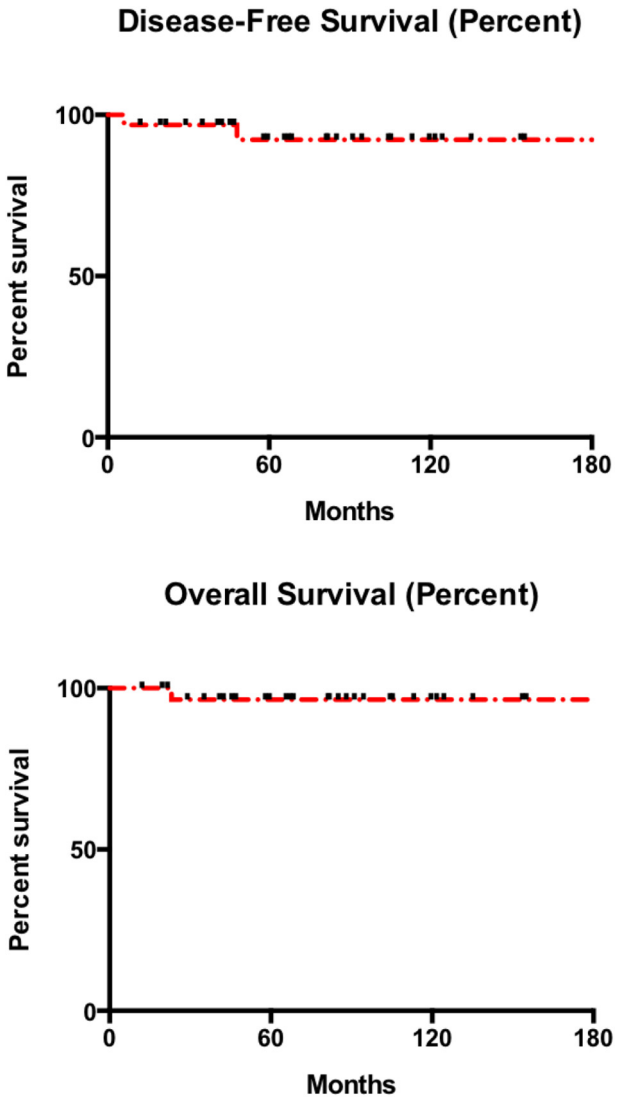

Fig. 2. Survival curves.

4. Discussion

The present paper reports long-term outcomes of conservative management of early-stage cervical cancer patients, thus showing several noteworthy findings. First, our data underlines that young women who wish to preserve their fertility can be submitted to a conservative

Table 3
Characteristics of patients who did not complete planned conservative management.

Patient, age	FIGO stage of disease & histology	Definitive treatment (reason)	Outcomes, mo
Pt1, 35 yrs	IB1, adenocarcinoma	Radical hysterectomy (patient's decision)	Not evidence of disease, 119.5 mo
Pt2, 32 yrs	IB1, adenosquamous carcinoma	Neoadjuvant chemotherapy plus radical hysterectomy (positive nodes)	Not evidence of disease, 85.0 mo
Pt3, 40 yrs	IA2, squamous cell carcinoma	Neoadjuvant chemotherapy plus radical hysterectomy (positive nodes)	Alive with disease, 88 mo
Pt4, 27 yrs	IB2, squamous cell carcinoma	Neoadjuvant chemotherapy plus radical hysterectomy (positive nodes (micrometastasis))	Not evidence of disease, 35 mo
Pt5, 29 yrs	IB1, squamous cell carcinoma	Neoadjuvant chemotherapy plus radical hysterectomy (positive nodes)	Dead of disease, 23 mo
Pt6, 31 yrs	IB2, squamous cell carcinoma	Neoadjuvant chemotherapy followed by radiochemotherapy (tumor size)	Not evidence of disease, 19.5 mo

Abbreviations; Pt, patient; yrs., years; mo, months; FIGO, International Federation of Obstetrics and Gynecologists.

Table 4
Reproductive outcomes of patients willing to preserve their childbearing potential.

Reproductive-related parameters	Characteristics ($n = 25$)
No wishing pregnancy at the moment	9 (36%)
Wishing pregnancy	16 (64%)
Achieving pregnancy	11 (44%) considering all patients preserving fertility potential 11 (69%) considering patients wishing pregnancy
I trimester miscarriage	0
II trimester miscarriage	1 (4%)
Ongoing pregnancy	1 (4%)
Live children[a]	9 (36%)
Uneventful term pregnancies	8 (32%)
Preterm delivery	1 (4%)

Data are expressed in number (%).
[a] Two patients were submitted to prophylactic cervical cerclage.

treatment. Second, in patients with negative nodes, conservative management appears to be a safe procedure. Third, cervical conization, instead of more extensive procedures, seems to achieve an overall good local control of the disease. Additionally, in our series, one patient out of five submitted to conservative treatment required a radical treatment; this point should be paramount in patient counseling.

In recent years, accumulating data underlined the safety and effectiveness of various methods to preserve fertility in young women diagnosed with cervical cancer. Conization is recommended in patients affected by stage IA1 cervical cancer while radical trachelectomy should be considered in stage IA2 and IB1 [7]. However, several retrospective experiences underlined that more conservative approaches including conization are safe and effective in young women [20–23]. Rob et al., reported encouraging outcomes following conization ($n = 10$) or simple trachelectomy ($n = 24$) in early-stage cervical cancer patients with negative nodes [20]. Local recurrence rate was 2.9% [20]. Similarly, Maneo et al., in a multi-institutional study, involving three Italian centers, evaluated the role of conization and pelvic lymphadenectomy in 36 patients affected by stage IB1 cervical cancer [21]. One recurrence occurred in the pelvic area (2.7%), while no local recurrence was observed [21]. Lindsay et al., reported outcomes of 43 patients managed with large loop excision of the transformation zone and laparoscopic pelvic lymph node dissection, reporting a recurrence rate of 4.6% [22]. Our study corroborated these results reporting data on long-term follow-up. In our series, no local recurrence occurred after conization, thus underlining that cervical conization could be consider a safe treatment modality to prevent local recurrence in cervical cancer patients. In our series two distant recurrences occurred in women with disease harboring in the lymph nodes.

In a review on this issue, Plante et al. investigated the role of radical and simple trachelectomy in the management of patients with early-stage cervical cancer who wish to preserve their fertility [6]. The authors reported that, although no mature evidence is still available, conization (in low-risk patients) seems to uphold the oncological safety of trachelectomy, reducing morbidity and improving reproductive results [6].

Five points of the present paper should be addressed: (i) in our experience, hysterectomy was not performed in absence of local recurrence, in patients who complete their reproductive functions. However, the role of completion surgery in those patients is still controversial and deserves further investigation. (ii) In our series the majority of patients had systematic pelvic lymphadenectomy; while sentinel node mapping represents an emerging and more accurate technique for assessing nodal status. (iii) The excellent oncological results achieved in our population reflect an accurate selection of patients for conservative management, thus our data are not projectable on the whole population of young cervical cancer patients. (iv) There is an important correlation between tumor volume and the efficacy of local surgical procedure. Since in our series the majority of patients had low volume disease (<2 cm), cervical conization would be effective. However, trachelectomy would be the preferred treatment modality for patients with large (>2 cm) cervical cancer. Further studies are warranted in order to assess oncologic as well as fertility outcomes in patients with large cervical cancer. (v) in our series, fertility-sparing attempt failed in 2 out of 2 patients affected by stage IB2 cervical cancer. Hence, stage IB2 patients should be counseled about the low probability to preserve their reproductive functions with this type of approach.

The inherent biases of a single-center, single-study design represent the main limitations of the present investigation. Moreover, the relatively low sample size might be a source of additional biases. However, the long-term follow-up of our investigation and the prospective evaluation of consecutive patients managed with conservative surgery are the main strengths of our paper.

In conclusion, the present investigation reported oncological and reproductive outcomes of young patients diagnosed with early-stage cervical cancer, wishing to preserve their reproductive functions. Our data underline that although about one patient in five is not suitable for planned conservative treatment, patients submitted to conization and lymph node assessment have excellent outcomes. Nodal assessment is useful to understand the need of more aggressive treatments. In patients with negative nodes, the execution of conization seems to offer good local control rate. Further prospective studies are needed to improve patients care, decreasing radicality and morbidity without compromising oncological outcomes.

Conflict of interest

The authors report no conflict of interest.

Author contribution

Conceptualization: GB, FR; Methodology: all authors; data collection: VC, DV, ES, FF, GM, FM, AD; Project administration: FR; Supervision: FR; Writing – original draft: GB, DV, GM; writing – review & editing: all authors.

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