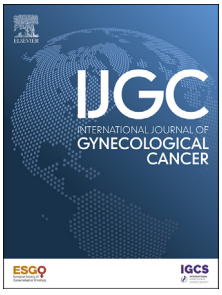
ORIGINAL RESEARCH

Chemo-conization in Early-sTage cERvical caNcer >2 cm scheduled for fertilItY-sparing approach: an analysis of the ETERNITY project



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ABSTRACT

Objective: To investigate the safety of neoadjuvant chemotherapy and conization in early-stage cervical cancer with a tumor size >2 cm using a fertility-sparing approach.

Methods: The ETERNITY project is a retrospective, multi-institutional study that collected data from patients with early-stage cervical cancer undergoing fertility-sparing treatment. In the present study, we report the outcomes of stage IB2 to IB3 cervical cancer undergoing nodal assessment, neoadjuvant chemotherapy, and conization. A propensity-matching algorithm was used to compare patients who underwent upfront radical surgery.

Results: A total of 395 patients were included in the ETERNITY project. Among these, 25 underwent a fertility-sparing attempt with nodal assessment, neoadjuvant chemotherapy, and conization. The median (range) patient age was 37 (24-41) years. Four (16%) patients with positive nodes required definitive chemo-radiation. Twenty-one (84%) patients received neoadjuvant chemotherapy. Two (8%) patients with stable disease underwent radical hysterectomy, whereas the remaining 19 (76%) patients who achieved a clinical response underwent cervical conization. Three (12%) patients underwent radical hysterectomy owing to persistent positive margins, leaving 16 (64%) patients who completed the planned fertility-sparing attempt. After a median (range) follow-up of 36.2 (21.9-88) months, 3 recurrences occurred. Two patients with cervical recurrence underwent hysterectomy, while 1 patient who received definitive chemoradiotherapy owing to the presence of positive nodes developed distant recurrence. Regarding obstetric outcomes, 6 patients attempted to conceive, and 4 (66.7%) pregnancies were achieved (1 was achieved with assisted reproductive technology). In a propensity-matched group of patients who underwent upfront radical surgery, no differences in morbidity or survival rates were recorded.

Conclusions: Neoadjuvant chemotherapy followed by conization should be investigated in selected patients with cervical cancer who wish to preserve their childbearing potential. Further prospective studies are needed to assess the long-term safety and identify predictors of response.

Clinical trial identifier: NCT06351228.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Although growing data supported the execution of fertility-sparing approach in International Federation of Gynecology and Obstetrics stage IA to IB1, only limited data on stage IB2 to IB3 cervical cancer are available.

WHAT THIS STUDY ADDS

Neoadjuvant chemotherapy followed by conization represents a valuable strategy for managing cervical cancers >2 cm in size. Approximately 40% of patients who started a fertility-sparing approach failed the planned treatment. However, initiating fertility-sparing attempts does not expose patients to an increased risk of adverse oncological outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

This study reports useful data for promoting individualized treatment paradigms and improving clinicians' decision-making. Further studies aimed at identifying the predictors of response are needed.

Keywords:
Uterine Cervical Neoplasms; Fertility Preservation; Sentinel Lymph Node Biopsy; Neoadjuvant Chemotherapy; Conization

INTRODUCTION

Cervical cancer is one of the most common gynecological malignancies in women under 40 years of age. It is estimated that cervical cancer is the fifth most common cancer in women aged 30 to 39 years and the sixth most common in women aged 40 to 49 years.[1] Despite the adoption of effective methods to prevent cervical cancer in developed countries, it remains a significant burden on health care systems.[2] In recent years, the number of cervical cancer patients who wish to preserve their fertility has increased, highlighting the need for fertility-sparing surgery as an important unmet need.[3] It is estimated that about 40% of patients diagnosed with cervical cancer are of childbearing age.[3-5]

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According to the 2024 guidelines from European Society of Gynecologic Oncology, European Society of Human Reproduction and Embryology, and European Society of Gynecological Endoscopy guidelines, fertility-sparing treatment can be considered for patients with International Federation of Gynecology and Obstetrics (FIGO) 2018 IA1 to IB1 cervical cancer (tumors less than 2 cm), specifically those with squamous cell carcinoma or HPV-related adenocarcinoma.[4] The role of fertility-sparing approach for patients with tumors greater than 2 cm is not considered standard treatment due to the high risk of recurrence in this subset of patients.[4,5] Nonetheless, accumulating evidence supports the adoption of neoadjuvant chemotherapy followed by conization in patients with tumors between 2 and 4 cm.[6-9] These experiences are limited to series and generally characterized by short-term follow-up.[8] There are several unclear aspects in the conservative management of FIGO 2018 stage IB2 to IB3 cervical cancer (tumor size >2 cm), including the type of neoadjuvant chemotherapy administered, the timing of nodal dissection, the extent of local radicality, and the role of sentinel node mapping.[4] In the present paper, we aim to describe the oncologic and reproductive outcomes of patients with stage IB2 and IB3 cervical cancer who are attempting a fertility-sparing approach with nodal dissection, neoadjuvant chemotherapy, and cervical conization. Additionally, we compared the outcomes of these patients with those of a historical cohort of consecutive patients who underwent a conventional surgical approach.

METHODS

This was a retrospective analysis of data included in the early-stage cervical cancer scheduled for the fertility-sparing (ETERNITY) project. The ETERNITY project is a multicenter retrospective study that collected data from patients with early-stage cervical cancer undergoing conservative surgery between January 1, 2000, and December 31, 2022. Institutional review board (IRB) approval was obtained (IRB #57/20). The ETERNITY project was registered at clinicaltrials.gov under the identifier NCT06351228.[10]

The ETERNITY project collected cases of patients with FIGO 2018 stage IA1 to IB3 cervical cancer who were undergoing fertility-sparing treatment. In this study, we focused only on patients who received neoadjuvant chemotherapy and conization. The inclusion criteria were: (i) histological diagnosis of cervical cancer (squamous cell or adenocarcinoma); (ii) age equal to or greater than 18 years; (iii) 2018 FIGO stage IB2 and IB3 cervical cancer; and (iv) the execution of neoadjuvant chemotherapy. The exclusion criteria were as follows: (i) consent withdrawal and (ii) patients with pre-operative suspicion of nodal disease at the pre-operative workup. In accordance with the journal's guidelines, we will provide our data for independent analysis by a team selected by the Editorial Team for the purpose of additional data analysis or for the reproducibility of this study in other centers if requested.

The primary endpoint of this study was the oncologic and reproductive outcomes of patients undergoing neoadjuvant chemotherapy followed by a fertility-sparing approach. Secondary outcome measures included a comparison of morbidity rates and oncologic outcomes of patients undergoing fertility-sparing and radical surgery. Patients were staged according to the 2018 FIGO staging system.[4,9] Patients who received treatment in the early study period were re-staged according to the 2018 FIGO staging system. Histologic classification and degree of cell differentiation were performed according to the World Health Organization and FIGO classification systems.[4,10]

The pre-operative workup included gynecologic examination, pelvic magnetic resonance imaging, and positron emission tomography/computed tomography. CT tomography and transvaginal ultrasonography were not routinely performed. Multidisciplinary teams discussed options for these patients. All patients were counseled about the experimental nature of fertility-sparing treatment. The patients included in the study received counseling about their fertility potential. According to international guidelines, all patients underwent a nodal evaluation in the first surgical step.[5] Nodal evaluation allowed the identification of patients requiring definitive chemoradiotherapy. At the beginning of the study period, the standard care was systematic pelvic lymphadenectomy. During the study period, there was an increase in the adoption of sentinel node mapping plus systematic pelvic lymphadenectomy.[10] All removed lymph nodes were placed in formalin and subsequently embedded in paraffin. The sentinel nodes underwent ultra-staging according to institutional protocols. Non-sentinel lymph nodes were traditionally evaluated using hematoxylin and eosin staining. According to the American Joint Committee on Cancer classification, macro-metastasis, micro-metastasis, and isolated tumor cells are defined by the presence of clusters of neoplastic cells >2 mm, between 0.2 and 2 mm, and <0.2 mm.[9] No intra-operative frozen section of the nodes was carried out. Patients with negative lymph nodes received platinum-based neoadjuvant chemotherapy. Three cycles of paclitaxel and platinum (with or without ifosfamide) were administered every 21 days. Patients who achieved a clinical response underwent cervical conization/simple trachelectomy. Pathological response to chemotherapy was classified as optimal [no residual tumor (complete response) or residual disease with ≤ 3 mm stromal invasion (PR1)] or suboptimal response.[11] Pathological characteristics of the cervical specimens were used to tailor the need for adjunctive surgical procedures or medical/radiation treatments (using Peters' criteria).[12]

The Clavien-Dindo severity system was used to classify severe complications, and the Martin criteria were used to improve the quality of reporting.[13] of reported data on 90-day severe morbidity (starting from the day of nodal evaluation). Grade 1 events were considered mild. Grade 2+ events were collected. Grade 2 events were characterized by moderate complications. Grade 3+ events were characterized as severe complications.[13] Martin criteria were used to improve the quality of complication reporting.[14] Medical records were used to collect data regarding obstetrical details. Similarly, details regarding follow-ups were updated regularly by trained nurses and residents. Patients were regularly evaluated in an outpatient setting according to the institutional protocols. Briefly, patients were followed up, including pap smear, colposcopy, and colposcopy-guided biopsy if clinically indicated, every 6 months for the first 5 years, and annually thereafter. Imaging was performed as clinically indicated. A dedicated team of gynecologists performed all the clinical and colposcopic examinations. The dates and sites of recurrence were recorded. Recurrence was assessed using

imaging techniques and histological assessment was performed (when feasible) to confirm the presence of recurrent disease.

Statistical Methods

This retrospective study was characterized by the potential risk of allocation bias. To improve the quality of reporting and interpretation of the results, we applied a propensity score analysis. Propensity score analysis aims to reduce the biases arising from different covariates. A multivariate logistic regression model was developed. Age, histology (squamous vs non-squamous), disease stage (FIGO IB2 vs IB3), tumor size, and lymphovascular space invasion (yes vs no) were included in the model. Propensity score matching analysis was used to minimize the inherent biases of the retrospective study design. The description of propensity score matching is reported in detail elsewhere.[15] Patients scheduled for a fertility-sparing attempt were matched 1:1 to a group of patients who underwent radical hysterectomy (included in the single-center data set of the Fondazione IRCCS Istituto Nazionale dei Tumori di Milano). Only patients who underwent open radical hysterectomies were included in this study. We used a caliper width $\leq$0.1 standard deviations of the logit odds of the estimated propensity score. Basic descriptive statistics were used to compare the 2 populations. Differences in categorical variables were analyzed using the Fisher exact test. The *t* test and Mann-Whitney *U* test were used to compare continuous variables, as appropriate. Disease-free and overall survival rates were estimated using the Kaplan-Meier model. The log-rank test was used to compare the risk of recurrence and death between the 2 groups over time. Hazard ratios (HR) and 95% were calculated using univariate and multivariate models as appropriate. Only variables with a $p < .20$ were included in the multivariate analysis. Statistical significance was set at $p < .05$ significant. Statistical analyses were performed using GraphPad Prism version 6.0 (GraphPad Software) and IBM Microsoft SPSS version 20.0 (SPSS Statistics. International Business Machines Corporation IBM 2013) for Mac.

RESULTS

Overall, 395 patients were included in the ETERNITY trial. Among these, 25 patients with 2018 FIGO stage IB2 to IB3 had a fertility-sparing attempt at chemo-conization. The patient characteristics are shown in Table 1. Figure 1 shows the flow of patients starting the fertility-sparing attempt with chemo-conization. All 25 patients underwent nodal dissection. The median (range) of patients was 37 (24-41) years. Nineteen (76%), 4 (16%), and 2 (8%) patients underwent pelvic lymphadenectomy, sentinel node mapping plus backup lymphadenectomy, and sentinel node mapping alone, respectively. Four (16%) patients had positive nodes (3 with macrometastases and 1 with micro-metastasis detected through sentinel node mapping) and required definitive chemo-radiation. Twenty-one (84%) patients received neoadjuvant chemotherapy. Two (8%) patients with stable disease underwent radical hysterectomy, whereas the remaining 19 (76%) patients who achieved a clinical response underwent cervical conization. An optimal pathological response was observed in 8 (42%). Five (20%) patients with positive surgical margins at conization underwent reconization or trachelectomy. Three patients (12%) underwent hysterectomy because of persistently positive margins, leaving 16 patients (64%) who completed the planned fertility-sparing attempt. Three recurrences occurred after a median (range) follow-up of 36.2 (21.9-88) months. Two patients with cervical recurrence underwent hysterectomy, while 1 patient who received definitive chemo-radiotherapy owing to the presence of positive nodes developed distant recurrence. Regarding obstetric outcomes, 6 patients attempted to conceive. Four (66.7%) were successful. One pregnancy was achieved by using assisted reproductive technology. Two prophylactic cerclages (50% each) were used. All women had term deliveries without complications.

Using propensity score matching, we selected 25 controls from a historical cohort of patients who underwent upfront open radical hysterectomy. Table 2 presents details of the study groups. Regarding operative parameters, no patients received transfusions

Table 1 Baseline Patient Characteristics

Characteristics	*N* = 25
Age, yrs	37 (24-41)
BMI, kg/m^2	22 (17-35)
HPV vaccination	
No	23 (92)
Yes	2 (8)
Previous pregnancies	
No	22 (88)
Yes	3 (12)
Histology	
Squamous cell carcinoma	17 (68)
Adenocarcinoma	8 (32)
2018 FIGO stage at presentation	
Stage IB2	20 (80)
Stage IB3	5 (20)
FIGO grade	
G1 and G2	16 (64)
G3	9 (36)
Tumor diameter, cm	3.5 (2.5-5.5)
LVSI	
No	15 (60)
Yes	10 (40)
Nodal dissection	
Sentinel node mapping	2 (8)
Sentinel node mapping plus lymphadenectomy	4 (16)
Lymphadenectomy	19 (76)
Number of nodes	25 (2-34)
Positive nodes	
No	21 (84)
Yes	4 (16)
Follow-up, mo	36 (21.9-88)

Abbreviations: BMI, body mass index; HPV, human papillomavirus; FIGO, International Federation of Obstetrics and Gynecology; G, grade; LVSI, lymphovascular space invasion.
Data are reported as number (%) or median (range).

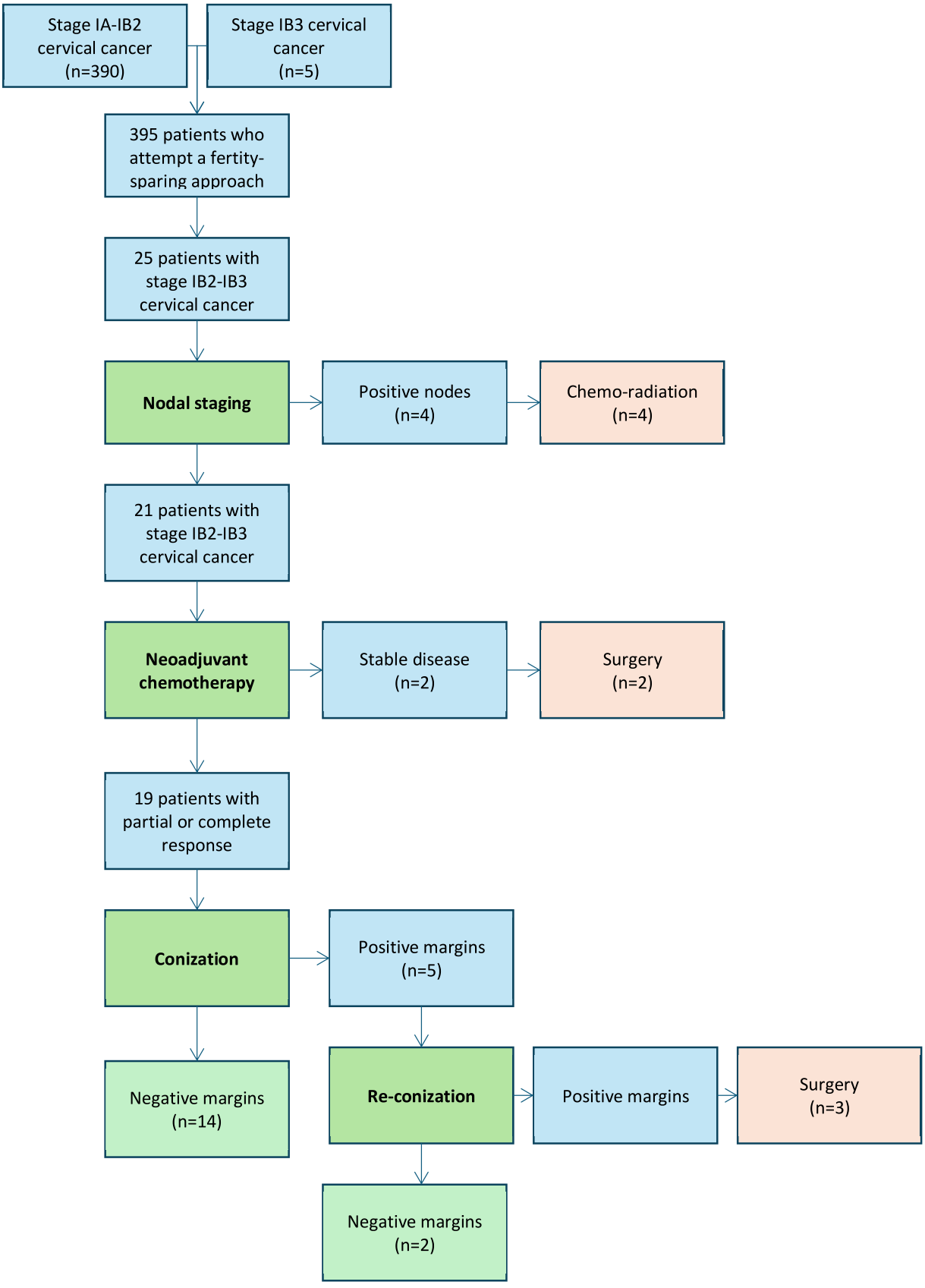

Figure 1 Study design.

Table 2 Characteristics of the Propensity Score-Matched Population

Characteristics	Fertility-sparing attempt $N = 25$	Upfront radical hysterectomy $N = 25$	*p*-Value
Age, yrs	37 (24-41)	38 (25-40)	.65
BMI, kg/m^2	22 (17-35)	22.5 (18-37)	.76
Histology			1.0
Squamous cell carcinoma	17 (68)	17 (68)	
Adenocarcinoma	8 (32)	8 (32)	
2018 FIGO stage at presentation			1.00
Stage IB2	20 (80)	21 (84)	
Stage IB3	5 (20)	4 (16)	
FIGO grade			1.00
G1 and G2	16 (64)	17 (68)	
G3	9 (36)	8 (32)	
Tumor diameter, cm	3.5 (2.5-5)	3.5 (2.5-5.5)	.78
LVSI			1.00
No	15 (60)	16 (64)	
Yes	10 (40)	9 (36)	
Positive nodes			1.00
No	21 (84)	20 (80)	
Yes	4 (16)	5 (20)	
Follow-up, mo	36 (21.9-88)	62.2 (2.6-103.8)	<.001

Abbreviations: BMI, body mass index; HPV, human papillomavirus; FIGO, International Federation of Obstetrics and Gynecology; G, grade; LVSI, lymphovascular space invasion. Data are reported as number (%) or median (range).

in the fertility-sparing group, whereas 2 patients received transfusions in the radical hysterectomy group. No intra-operative complications were observed in either group. Four 90-day complications were recorded in the fertility-sparing group: 3 patients had grade 1 pelvic lymphoceles and 1 patient had post-operative bleeding requiring re-intervention. In the radical hysterectomy group, 5 complications were recorded: 2 cases of post-operative anemia requiring blood transfusions (grade 2), 1 lymphocele requiring percutaneous drainage (grade 3), 1 urinary tract fistula requiring ureter catheterization (grade 3), and 1 case of post-operative bleeding requiring surgery for hemostasis (grade 3). Table 3 shows the transfusion and complication rates. Figure 2 shows the disease-free survival ($p = .60$, log-rank test) and overall survival ($p = .73$, log-rank test). No differences in recurrence (HR 1.59, 95% CI 0.272 to 9.340) and survival (HR 0.66, 95% CI 0.065 to 6.858) rates were recorded.

DISCUSSION

Summary of Main Results

The present study reports the data of patients who began a fertility-sparing attempt for stage IB2 to IB3 cervical cancer. Therefore, an accurate patient selection is necessary. Identifying patients with negative nodes and those who respond to chemotherapy allows for tailored treatment. More than 6 out of 10 patients completed the planned fertility-sparing attempt. Additionally, we observed that, compared with radical surgery, starting a fertility-sparing approach did not influence the risk of developing 90-day morbidity or survival outcomes.

Results in the Context of Published Literature

Accumulating data support the safety and effectiveness of the fertility-sparing approach in early-stage cervical cancer.[16,17] Several reports describe encouraging long-term data in patients with cervical tumors <2 cm undergoing cervical conization with or without nodal dissection.[10,16,17] Recently, the retrospective data from the ETERNITY project (NCT06351228) corroborated these results, supporting the adoption of sentinel node mapping instead of pelvic lymphadenectomy.[10] However, data on conservative attempts for cervical tumors larger than 2 cm are limited to anecdotal series.[8,9,18] Chemotherapy downstages cervical tumors, allowing less extensive cervical procedures and preserving the anatomical function of the uterine cervix. In 2006, Plante and colleagues[19] reported the first case series of 3 patients undergoing neoadjuvant chemotherapy followed by conization. Few series have been published with encouraging results.[18] De Vincenzo and colleagues,[18] reported a series of women undergoing pelvic node dissection, neoadjuvant chemotherapy, and cervical conization. Starting from a sample of 25 women who received counseling for a fertility-sparing attempt, 17 women started a fertility-sparing journey. Four patients had screening failure (3 for positive nodes and 1 for menopause), leaving 13 patients available for the fertility-sparing approach. The authors reported a recurrence rate of 7.7% and a pregnancy rate of 66.7% (2 of 3 patients wished to conceive).[18] Of note, those data are in line with the data included in the ETERNITY trial reported in this paper. However, it is essential to highlight that neoadjuvant chemotherapy followed by conization is not the only strategy adopted for managing cervical tumors larger than 2 cm.

Table 3 Surgery-Related Complications

Characteristics	Fertility-sparing attempt *N* = 25	Upfront radical hysterectomy *N* = 25	*p*-Value
Intra-operative transfusions	0	0	>.99
Intra-operative complications	0	2 (8)	.49
Post-operative transfusions	0	2 (8)	.49
Post-operative complications	3 (12)	5 (20)	.70
Grade 1 post-operative complications	2 (8)	0	.49
Grade 2 post-operative complications	0	2 (8)	.49
Grade 3 post-operative complications	1 (4)	3 (12)	.61
Grade 4 post-operative complications	0	0	>.99
Grade 5 post-operative complications	0	0	>.99
Post-operative complications directly related to nodal dissection	2 (8)	1 (4)	1.00
Post-operative complications directly related to the treatment of cervical tumor	0	1 (4)	1.00

Data are reported as numbers (%).

Independent study groups have described outcomes for vaginal, minimally invasive, and abdominal radical trachelectomies.[16,17] To date, no comparative data exist, and it is not possible to determine the optimal fertility-sparing approach for managing stage IB2 to IB3 cervical cancer. The ongoing CoNteSSa trial (NCT04016389) is recruiting patients with FIGO 2018 stage IB2 cervical cancer (tumor size >2 and ≤4 cm) treated with neoadjuvant chemotherapy followed by a fertility-sparing approach.[20] This prospective study plans to enroll 90 patients receiving platinum-based chemotherapy followed by trachelectomy.[20]

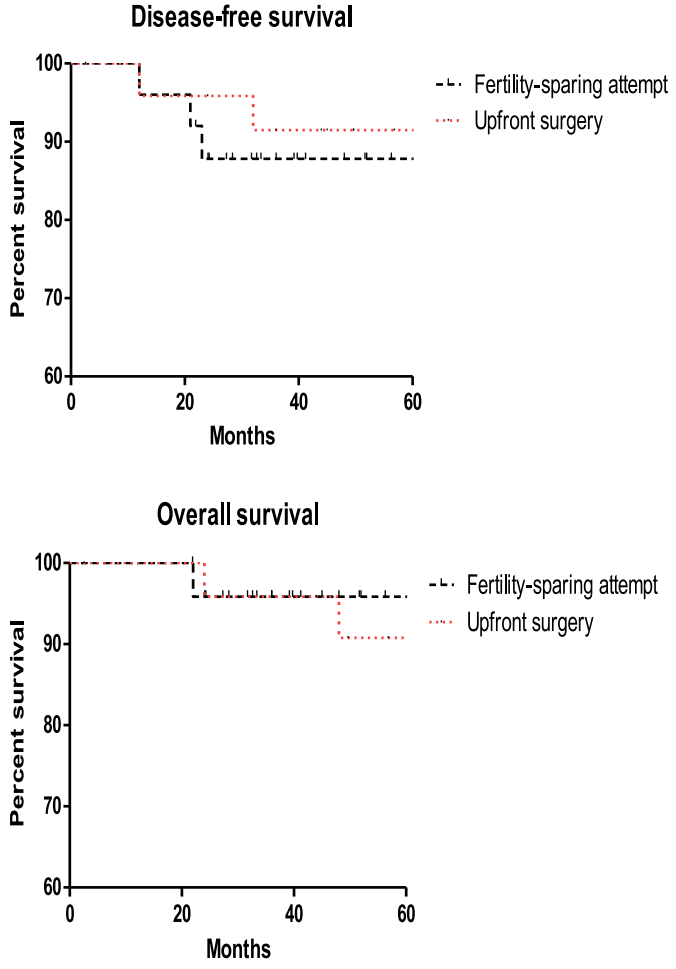

Figure 2 Survival outcomes.

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Strengths and Weaknesses

The main strength of the present investigation was the evaluation of long-term data on chemo-conization in stage IB2 to IB3 cervical cancer. Additionally, this is the first study to compare the outcomes of patients who underwent a fertility-sparing approach with those who underwent upfront radical hysterectomy. The main limitation of this study is the inherent bias of the retrospective study design. Several points in the present study deserve further comment. First, although 16 patients completed the planned fertility-sparing attempt in our series, only 6 (37.5%) patients attempted to conceive. This finding supports the importance of pre-operative counseling for patients with cervical cancer. Second, all patients were managed by multidisciplinary tumor boards in referral centers. Hence, our results may not be generalizable to settings that lack adequate oncological experience. Third, the administration of neoadjuvant chemotherapy followed by conization might represent a win-to-win scenario to avoid the need for extensive cervical procedures (ie, trachelectomy). Compared to conization, radical trachelectomy is more challenging, requires specific surgical skills, and is associated with a non-negligible risk of pre-term delivery.[21] Fourth, further studies are necessary to validate these findings. Finally, although the propensity score attempts to reduce possible bias, it cannot provide a fair comparison between patients undergoing fertility-sparing and radical surgery. Several measurable and non-measurable characteristics might affect patient selection, and thus affect the interpretation of our results.

Implications for Practice and Future Research

The results from a cohort of patients with stage IB2 and IB3 cervical cancer included in the ETERNITY project support the execution of prospective trials testing neoadjuvant chemotherapy followed by conization in this setting. Strict criteria (including accurate counseling) should be implemented to identify appropriate patients for conservative attempts.

CONCLUSIONS

In the present study, we report data regarding the execution of nodal dissection, neoadjuvant chemotherapy, and conization in patients with stage IB2 and IB3 cervical cancer who wished to preserve their childbearing potential.

In our experience, nodal dissection and careful evaluation of clinical response to neoadjuvant chemotherapy are of paramount importance in identifying patients who can complete fertility-sparing attempts. Therefore, more effective neoadjuvant treatments must be tested. The advantages (efficacy) and disadvantages (risk of ovarian failure) of immune checkpoint inhibitors (ICI) adoption of immune checkpoint inhibitors in this setting must be carefully considered. Further prospective, multi-institutional studies are required.

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Author Contributions Conceptualization: GB, GS, and FR; Methodology: All authors; Project administration: GB and FR. GS; supervision: MM, FG, GS, FR; writing — original draft: all authors; writing — review and editing: all authors.

Declaration of Competing Interests Not declared.

Appendix

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