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# Conservative management of cervical cancer: Current status and obstetrical implications

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A B S T R A C T

Recent advances in screening and early diagnosis have decreased cervical cancer incidence and mortality rates in high-resource settings. The postponement of childbearing, combined with an increased number of cervical cancer survivors, has yielded new paradigms in patient care. In recent years, radical surgery has been challenged as the standard of care for early-stage cervical cancer owing to its significant morbidity and fertility impairment. Attention has been directed to assessing more conservative procedures that can reduce treatment-induced morbidity without compromising oncologic safety and reproductive potential of patients with early-stage disease. In those with more advanced disease, neoadjuvant chemotherapy followed by conservative surgery has also been considered. These conservative treatment modalities including cervical conization, simple trachelectomy, and simple hysterectomy have been studied in various settings. In this chapter, we discuss the role of conservative surgery in the management of cervical cancer and the resulting obstetrical outcomes.



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## The need for a more conservative approach in the surgical management of cervical cancer

### *A growing concern about the benefit of radical surgery in early-stage disease*

The standard treatment for early-stage cervical cancer has traditionally been radical hysterectomy to minimize residual tumor and prevent relapse of disease [1]. Despite excellent oncologic outcomes, radical hysterectomy is associated with several complications, primarily owing to the removal of the parametria [2]. These include bladder and rectal dysfunction, sexual dysfunction, and fistula formation [3–7]. While morbidity induced by parametrectomy can significantly alter the quality of life of patients, it is unclear whether parametrial resection in women with early-stage cervical cancer is beneficial. Several studies have reported a low rate of parametrial spread in selected groups of patients with early-stage disease (Table 1) [8–21]. In patients with favorable prognostic features such as a lesion size <2 cm, depth of invasion <10 mm, and negative pelvic nodes, rates of parametrial spread have been found to be less than 1% in most reports [22]. These findings have challenged the necessity of radical hysterectomy in the management of early-stage cervical cancer.

### *An evolving profile of cervical cancer survivors*

Over the past decades, most high-resource countries have achieved a significant reduction in overall mortality from cervical cancer with 5-year survival rates for localized disease surpassing 90% [23]. Cervical cancer screening access and uptake have notably increased in these settings because of the introduction of the Papanicolaou (Pap) test and organized screening programs. Moreover, recent advances in the development of diagnostic and prognostic tools – including magnetic resonance imaging

**Table 1**
Prognostic factors used to identify patients with a low risk of parametrial spread and rate of parametrial spread.

| Study author, year | N | Prognostic Factors | | | | | Rate of parametrial spread (%) |
|---|---|---|---|---|---|---|---|
| | | Tumor size ≤ 2 cm | SCC, AC, or AS histology | DOI | Absence of LVSI | Absence of PLN metastasis | |
| Kinney, 1995 [8] | 83 | x | x | | x | | 0.0 |
| Covens, 2002 [9] | 536 | x | | ≤10 mm | | x | 0.6 |
| Stegeman, 2007 [10] | 103 | x | x[a] | <10 mm | x | x | 0.0 |
| Wright, 2007 [11] | 270 | x | | | x | x | 0.4 |
| Strnad, 2008 [13] | 80 | x | x | <1/2 SI | | x | 0.0 |
| Frumovitz, 2009 [14] | 125 | x | x | | x | | 0.0 |
| Smith, 2010 [19] | 53 | x | x | | x | | 0.0 |
| Kim, 2010 [20] | 140 | | x | ≤5 mm[b] | | | 0.0 |
| Kamimori, 2011 [15] | 58 | x | x | | | | 0.0 |
| Al-Kalbani, 2012 [16] | 36 | x | x | | | | 0.0 |
| Gemer, 2013 [21] | 107 | x | x | | x | x | 0.0 |
| Kato, 2015 [17] | 323 | x | x | | | | 1.9 |
| Vranes, 2016 [18] | 211 | x | x | | x | x | 0.9 |

N: number in the study meeting to defined prognostic criteria, SCC: squamous cell carcinoma, AC: adenocarcinoma, AS: adenosquamous, DOI: depth of stromal invasion, LVSI: lymphovascular space invasion, PLN: pelvic lymph node, <2/3 SI: less than 2/3 stromal invasion.

[a] This study also included clear cell carcinoma.

[b] Negative endocervical resection margin on LEEP specimen also used in this study.

(MRI), ultrasound volumetry, minimally invasive surgery, lymphatic mapping with sentinel lymph node biopsy, and frozen section analysis – have refined the early detection and management of cervical cancer [24–28]. Consequently more women with cervical cancer are being diagnosed at an earlier stage and at a younger age, and the post-treatment survival rate has significantly increased. In the United States, cervical cancer is currently most frequently diagnosed among women aged 35–44 years [23] compared with those aged 45–54 years in the 1990s [29]. Meanwhile, the average age of women at first birth has increased over the past decades, thus reflecting the increase in first birth rates in women aged 35 years and older (Fig. 1) [30]. Furthermore, many women of reproductive age with cervical cancer have a desire for fertility in the future, and loss of fertility due to cancer treatment may lead to grief, stress, sexual dysfunction, and depression [31,32]. These concerns among survivors and scientific advances have highlighted the need to find ways to preserve fertility in patients with cancer of childbearing age, without compromising oncologic outcomes [33].

*A first alternative but still limited surgical modality*

Radical trachelectomy was initially proposed as an alternative to radical hysterectomy in patients with early-stage disease who desired fertility in the future [34]. A number of studies have reported on the feasibility and safety of radical trachelectomy, with perioperative morbidity and oncologic outcomes comparable to radical hysterectomy [35–38]. Similar to radical hysterectomy, radical trachelectomy involves removal of the parametria and related morbidity. Furthermore, many reports have found that after diagnostic Loop Electrosurgical Excision Procedure (LEEP)/conization procedures, 62–67% of patients undergoing radical trachelectomy do not have residual disease in their surgical specimen, thereby suggesting that they could be offered less radical procedures [39,40]. In this context, more conservative modalities to manage early-stage cervical cancer have emerged [22,41]. Several studies have explored less radical surgical options including simple hysterectomy, simple trachelectomy, and cervical conization with or without sentinel lymph node biopsy and pelvic lymph node dissection. In this chapter, we examine the current state of conservative management of cervical cancer, assess the reproductive outcomes of patients treated with this approach, and identify areas of future research.

## Emerging surgical modalities for the conservative management of cervical cancer

*Cervical conization*

Cervical conization is defined as the excision of a cone-shaped or cylindrical wedge of the uterine cervix involving the transformation zone. It has been widely accepted for the treatment of patients

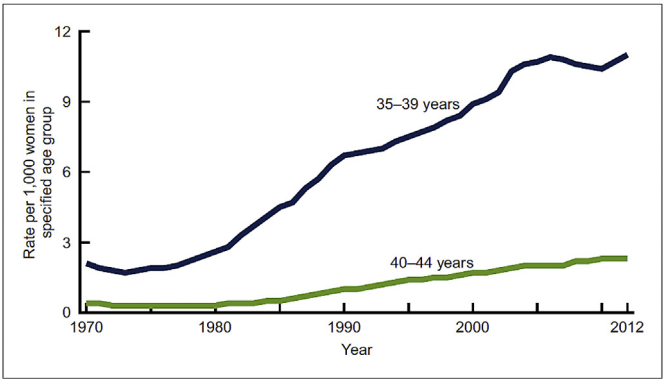


**Fig. 1.** First birth rates by selected age of mother: United States, 1970–2012.
Source: CDC/NCHS, National Vital Statistics System [30].

with International Federation of Gynecology and Obstetrics (FIGO) stage IA1 disease [42]. In patients with lymphovascular space invasion (LVSI), pelvic lymph node dissection or sentinel lymph node mapping is recommended in addition to conization. This consensus was reached following an analysis of the US Surveillance, Epidemiology, and End Results (SEER) database of women age ≤40 years with stage IA1 cervical cancer where no difference was found in the 5-year survival rate between those who underwent conization alone versus hysterectomy (98% versus 99%) [43].

Although radical trachelectomy is recommended in women of reproductive age with stage IA2 and stage IB1 disease who desire fertility in the future, data from retrospective studies suggest that conization with lymph node dissection could be safe in these patients, providing accurate tumor measurement is available, and the margins are negative on the conization specimen [44,45]. Table 2 summarizes the oncologic outcomes of patients with cervical cancer treated conservatively reported in the literature [42,46–57].

In a pilot study evaluating the safety of conservative management of cervical cancer, Rob et al. evaluated 40 patients with early-stage cervical cancer with tumor size <2 cm and <50% infiltration of cervical stroma [47]. Disease was stage IA1 in 3 patients, IA2 in 10 patients, and IB1 in 27 patients. All patients had laparoscopic sentinel lymph node identification with frozen section analysis, and if negative, a complete pelvic lymphadenectomy was performed. In six patients (15%) whose frozen sections were positive, a radical hysterectomy was performed. Of the remaining 34 patients with negative pelvic lymph nodes, pelvic lymphadenectomy was performed followed by a large conization in 10 women with stage IA2 disease and a simple trachelectomy in 24 women with stage IB1 disease. After a mean follow-up of 47 months, one recurrence has been reported in a patient with a stage IB1 tumor with 8 mm of cervical stromal invasion and presence of LVSI. The patient was treated with chemoradiation and was reported to be free from disease 62 months following treatment [47].

A subsequent study by Maneo et al. [50] aimed to evaluate the role of simple conization and pelvic lymphadenectomy in patients with stage IB1 disease. The study included 36 patients with a median age of 31 years and a median tumor size of 11.7 mm. Five patients (14%) had LVSI. All patients had undergone a prior conization, and eight patients also underwent a reconization. Margins of all the final surgical specimens were free from disease. After a median follow-up time of 66 months, one patient had a recurrence in the pelvis 34 months after initial therapy.

Another series of 17 patients with stage IA2 to IB1 cervical cancer was reported in 2011 by Fagotti et al. [49]. The authors explored the value of conization instead of radical trachelectomy for fertility preservation. All patients had negative pelvic lymph nodes on MRI before surgery and underwent laparoscopic pelvic lymphadenectomy and simple conization. In case of positive lymph nodes at frozen section or definitive pathologic analysis, patients were treated with radical hysterectomy and pelvic and para-aortic lymphadenectomy. The median age was 33 years, and the stage was IA2 in four patients (24%) and IB1 in 13 patients (76%). Four patients (23%) required radical hysterectomy: three for positive margins and one for a positive lymph node. Two patients required additional treatment owing to positive resection margins. After a median follow-up time of 16 months, no recurrences were observed. The authors concluded that patients with low-risk early-stage cervical cancer could be safely treated by conization.

*Simple trachelectomy*

Simple trachelectomy refers to the surgical removal of the uterine cervix, without parametrial resection. This procedure, usually associated with pelvic lymph node dissection or lymphatic mapping, has been studied as an alternative to radical surgery for the treatment of patients with stage IA2 to IB1 cervical cancer who wish to preserve their fertility (Table 2).

In 2012, Palaia et al. [52] reported on the feasibility of simple trachelectomy plus pelvic lymphadenectomy in 14 patients diagnosed with early-stage cervical cancer. Inclusion criteria included age ≤38 years, desire to maintain fertility, ≤stage IB1 disease, tumor size <2 cm, no LVSI, and no evidence of nodal metastasis. All patients underwent a laparoscopic bilateral pelvic lymphadenectomy with frozen section analysis. If the pelvic nodes were positive for disease, standard abdominal radical hysterectomy was performed. In the absence of nodal metastasis, a simple vaginal trachelectomy was

**Table 2**
Oncologic outcomes of conservative surgery for cervical cancer.[a]

| Study author, year | Number of patients eligible | Conservative surgical modality | Number of recurrences (%) | Time to recurrence (months) | Number of disease-related deaths (%) | Time to death (months) | Median follow-up in months (range) |
|---|---|---|---|---|---|---|---|
| Bisseling, 2007 [42] | 18 | 18 cone | 0 (0.0) | | 0 (0.0) | | 72[b] |
| Landoni, 2007 [46] | 11 | 11 cone | 0 (0.0) | | 0 (0.0) | | 20 (7–29) |
| Rob, 2008 [47] | 34 | 24 ST10 cone | 1 (4.2) | 14 | 0 (0.0) | | 47 (12–102) |
| Pluta, 2009 [48] | 55 | 55 SH | 0 (0.0) | | 0 (0.0) | | 47 (12–92) |
| Fagotti, 2011 [49] | 17 | 17 cone | 0 (0.0) | | 0 (0.0) | | 16 (8–101) |
| Maneo, 2011 [50] | 36 | 36 cone | 3 (8.3) | 20, 34, 36 | 1 (2.8) | 72 | 66 (18–168) |
| Raju, 2012 [51] | 15 | 15 ST | 0 (0.0) | | 0 (0.0) | | 96 (12–120) |
| Palaia, 2012 [52] | 14 | 14 ST | 0 (0.0) | | 0 (0.0) | | 38 (18–96) |
| Biliatis, 2012 [53] | 62 | 35 cone<br>27 SH | 0 (0.0) | | 0 (0.0) | | 56 (13–132) |
| Andikyan, 2014 [54] | 10 | 9 cone<br>1 biopsy | 0 (0.0) | | 0 (0.0) | | 17 (1–83) |
| Bouchard-Fortier, 2014 [55] | 29 | 29 cone | 0 (0.0) | | 0 (0.0) | | 21 (1–112) |
| Salihi, 2015 [56] | 11 | 11 cone | 1 (40) | 40 | 0 (0.0) | | 58 (13–122) |
| Plante, 2017 [57] | 35 | 35 ST | 1 (2.9) | NR | 0 (0.0) | | 42 (1–100) |
| Total (crude rates)[c] | 347 | 176 cone<br>88 ST<br>82 SH | N = 6 (1.7) | | N = 1 (0.3) | | |

Abbreviations: ST simple trachelectomy, SH simple total hysterectomy, NR not reported.
[a] This summary table excludes case reports and patients treated conservatively after neoadjuvant chemotherapy (NACT).
[b] The range is not reported in this study.
[c] Crude recurrence and mortality rates among those who underwent conservative surgery despite adjuvant treatment received.

performed. After a median follow-up of 38 months, 13 patients were alive without evidence of disease. One patient died from unrelated causes, and no recurrences were observed.

In another series, Raju et al. [51] evaluated 66 patients who underwent either a simple vaginal trachelectomy (n = 15) with pelvic lymphadenectomy or radical vaginal trachelectomy (n = 51) with pelvic lymphadenectomy for stage IA2 or IB1 cervical cancer. The criteria for performing a simple vaginal trachelectomy were a LEEP or cone biopsy specimen with tumor-free margins, tumor not larger than 1 cm, no evidence of LVSI, and tumor grade 1 or 2. Of the 15 patients who underwent simple vaginal trachelectomy, 5 had stage IA2 disease and 10 had stage IB1 disease. No patient had LVSI. There was no residual disease in the surgical specimen in 8 of the 15 patients (53%) who underwent simple vaginal trachelectomy (compared with 29% of the patients who underwent radical vaginal trachelectomy). After a median follow-up time of 96 months, no recurrences were observed.

A recent report by Plante et al. [57] evaluated the safety of simple vaginal trachelectomy and nodal assessment in 35 patients with low-risk early-stage cervical cancer (<2 cm). All patients underwent a simple vaginal trachelectomy preceded by laparoscopic sentinel node mapping plus pelvic node dissection. Patients' median age was 29 years, and 24 (69%) were nulliparous. Eight had stage IA1 disease with LVSI, 9 had stage IA2 disease, and 18 stage IB1 disease. On final pathology, lymph nodes were negative in all patients, except in two patients who had lymph nodes with isolated tumor cells. Twenty-two patients (63%) had either no residual disease in the trachelectomy specimen (n = 15) or residual dysplasia only (n = 7). With a median follow-up of 42 months, one patient had a local recurrence and was treated with chemoradiation. She developed a second recurrence and underwent a pelvic exenteration. The authors concluded that simple trachelectomy and lymph node evaluation seems to be a safe alternative in well-selected patients with low-risk early-stage cervical cancer.

*Simple hysterectomy*

Hysterectomy refers to the surgical removal of the uterus. Unlike radical hysterectomy, simple hysterectomy does not involve parametrial resection. This procedure, usually coupled with pelvic lymphadenectomy, has also been assessed as an alternative to radical hysterectomy in patients with cervical cancer with low risk of parametrial spread who do not wish to preserve fertility. We identified two relevant studies in the literature (Table 2).

The first study reported on 60 women with stage IA1 to IB1 cervical cancer with favorable prognostic characteristics (tumor size <2 cm and <50% stromal invasion) who did not desire fertility in the future [48]. MRI and ultrasound volumetry were performed after biopsy (wide excision, large loop excision of the transformation zone or needle cone) to identify residual disease. If the tumor was ≥20 mm in the largest diameter or stromal invasion was more than half of stroma, women were excluded from the study and underwent radical hysterectomy. All eligible patients underwent laparoscopic sentinel lymph node identification with frozen section. Of the 60 patients enrolled, five had positive sentinel lymph nodes on frozen section and underwent radical hysterectomy. In the remaining 55 patients, a simple vaginal hysterectomy was performed. With a median follow-up of 47 months, no recurrences were reported [48].

A subsequent study by Biliatis et al. [53] evaluated 62 patients with stage IB1 cervical cancer. Patients were eligible for conservative surgery if the tumor volume estimated by volumetry was less than 500 $mm^3$. After a first loop biopsy, patients underwent MRI and examination under anesthesia (EUA) to exclude advanced disease and retroperitoneal lymphadenopathy. All women with histology of the first conization showing incompletely excised invasive or high-grade preinvasive disease had a second conization during EUA to obtain additional information on tumor volume. In the absence of residual tumor in the second loop, conservative management was offered. Patients with residual cancer in the second loop specimen were excluded. Twenty-seven eligible women did not desire fertility and underwent simple hysterectomy. After a median follow-up of 56 months, no recurrences were noted. The authors concluded that simple hysterectomy with pelvic lymph node dissection is safe and feasible in select women with early-stage cervical cancer who do not desire fertility in the future.

*Oncologic and reproductive outcomes of conservative surgery for cervical cancer*

In this review, we identified a total of 347 women with early-stage cervical cancer treated solely with conservative surgery (Table 2). Despite inconsistencies in the inclusion criteria across studies, most patients had lesion size <2 cm in diameter. Eighty-two patients underwent simple hysterectomy, 88 underwent simple trachelectomy, and 176 underwent conization. Among these cases, the crude recurrence rate was 1.7% and the crude mortality rate was 0.3%. When compared to women who underwent radical surgery, oncology outcomes tend to be better after conservative surgery [58]. However, this result, which is not derived from controlled trials, should be interpreted with caution, as patients who were treated with radical surgery in most studies may have had poorer prognostic factors than those selected for conservative surgery.

Table 3 summarizes the reproductive outcomes of patients with cervical cancer managed conservatively. Among 190 women where fertility preservation was successful, we identified 103 pregnancies with a live birth rate of 72.8% (Table 3). Similar to the oncologic outcomes, pregnancy rates after conservative surgery seem to be higher than findings in women who underwent radical trachelectomy [58]. However, given the variability in eligibility criteria, the fact that selection criteria are not as restrictive for patients treated radically as for those treated conservatively, and the lack of clinical trials comparing outcomes among both groups, further study is needed to confirm these findings.

## Neoadjuvant chemotherapy and conservative management of cervical cancer

The role of neoadjuvant chemotherapy (NACT) in the treatment of early-stage cervical cancer is being explored. Indications for NACT are to reduce tumor size to later facilitate surgical resection and to

**Table 3**
Reproductive outcomes of conservative surgery for cervical cancer.[a]

| Study author, year | Conservative surgical modality | Completed fertility-sparing treatment (%)[b] | Pregnancies[c] | T1/T2 losses (%)[d] | Ongoing pregnancies (%) | Live births (%) | Median follow-up in months (range) |
|---|---|---|---|---|---|---|---|
| Bisseling, 2007 [42] | 18 cone | 18 (100) | 18 | 5 (27.8) | 0 (0.0) | 13 (72.2) | 72[e] |
| Landoni, 2007 [46] | 11 cone | 11 (100) | 3 | 0 (0.0) | 0 (0.0) | 3 (100) | 20 (7–29) |
| Rob, 2008 [47] | 24 ST 10 Cone | 32 (94.1) | 23 | 8 (34.8) | 3 (13.0) | 12 (52.2) | 47 (12–102) |
| Fagotti, 2011 [49] | 17 cone | 13 (76.5) | 2 | 0 (0.0) | 0 (0.0) | 2 (100) | 16 (8–101) |
| Maneo, 2011 [50] | 36 cone | 31 (86.1) | 21 | 6 (28.6) | 1 (4.7) | 14 (66.7) | 66 (18–168) |
| Raju, 2012 [51] | 15 ST | 15 (100) | 4 | 0 (0.0) | 0 (0.0) | 4 (100) | 96 (12–120) |
| Palaia, 2012 [52] [f] | 14 ST | 14 (100) | 8 | NR | NR | NR | 38 (18–96) |
| Biliatis, 2012 [53] | 35 cone | 35 (100) | 7 | 0 (0.0) | 0 (0.0) | 7 (100) | 56 (13–132) |
| Plante, 2017 [57] | 35 ST | 35 (100) | 25 | 5 (20.0) | 0 (0.0) | 20 (80) | 42 (1–100) |
| Total (crude rates) | | 190 | 103 | 24 (23.3) | 4 (3.9) | 75 (72.8) | |

Abbreviations: T1: first trimester, T2: second trimester, ST: simple trachelectomy, NR: not reported.

[a] This summary excludes case reports, studies where simple hysterectomy was performed, and patients treated conservatively after neoadjuvant chemotherapy (NACT).

[b] Excludes patients who had complete hysterectomy or received fertility-compromising.

[c] Number of pregnancies regardless of how many times a woman has conceived.

[d] Number T1/T2 terminations without living births.

[e] The range was not reported.

[f] Not included in the total because of insufficient data.

minimize prognostic factors associated with a poor response, thereby eliminating the need for post-operative adjuvant radiotherapy [59]. In patients with stages IB1 and IIA disease with tumor size of 2–4 cm, NACT has been shown to reduce nodal metastases, parametrial infiltration, and tumor size, making initially nonoperable cases amenable to fertility-preserving surgery [60–62]. Although meta-analysis of the available data has yet to show an oncologic benefit of NACT in early cervical cancer, its use in the context of fertility preservation has been gaining attention [62].

In this review, we identified 47 cases of stage IB1–IIA cervical cancer who underwent NACT before conservative surgery (Table 4) [56,61,63]. This allowed us to calculate a crude recurrence rate of 8.5% (4/47) and a crude mortality rate of 2.1% (1/47). Some authors recommend the use of NACT before surgery to downstage tumors >2 cm to follow more conservative cervical resection, thus reducing the risk of relapse and improve the fertility results [59]. In patients with complete clinical response to NACT, with a normal clinical examination and normal pelvic MRI, the probability of finding occult parametrial infiltration could be very low, and a radical procedure could be avoided. However, there is no consensus on this issue at this point, and further studies are needed.

Among selected studies, the use of NACT before conservative surgery in a total of 37 patients has resulted in 28 pregnancies with a 78.6% live birth rate (Table 5). In a recent review of the outcomes of NACT followed by conservative surgery for patients with early-stage cervical cancer, Pareja et al. [64] reported that the pregnancy rate appeared to be higher for patients with tumors ≥2 cm in size who underwent NACT followed by conservative surgery (30.6%) than for those who underwent immediate vaginal radical trachelectomy (24.0%) or abdominal radical trachelectomy (16.5%). However, reproductive outcomes after surgery have not been sufficiently assessed in this group of patients.

The preferred timing of nodal assessment with regard to NACT remains unclear. In a series of patients treated with NACT and surgery, higher rates of recurrence among women with positive nodes were reported versus women with negative nodes [65]. The authors concluded that nodal assessment before NACT could help select a subset of patients ineligible for fertility-sparing surgery. Furthermore, others support that NACT before lymph node assessment may lower the risk of nodal invasion, which could result in an increased rate of fertility-sparing surgery for patients [66]. While nodal involvement is a major negative prognostic factor in early-stage cervical cancer, it is hypothesized that initial lymph node assessment could be more helpful in determining the appropriate NACT regimen for patients [66].

**Table 4**
Oncologic outcomes of conservative surgery for cervical cancer after neoadjuvant chemotherapy.[a]

| Study author, year | Number who received NACT | Timing of LN assessment (number of positive LN) | NACT regimen | Surgical modality | Number of recurrences (%) | Time to recurrence (months) | Number of disease-related deaths (%) | Time to death (months) | Median follow-up (range) |
|---|---|---|---|---|---|---|---|---|---|
| Maneo, 2008 [61] | 21 | After (2) | TIP/TEPx3 | Cone | 0 (0.0)[b] | | 0 (0.0) | | 69 (10–124) |
| Robova, 2010 [63] | 15 | After (1) | TI/TAx3 | ST | 3 (20.0) | NR | 1 (6.7) | NR | 76.5 (17–142) |
| Salihi, 2015 [56] | 11 | Before (1) | 2 TIP x3<br>4 ddCP x3<br>5wCP x3 | Cone | 1 (9.1) | 40 | 0 (0.0) | | 58 (13–122) |
| Total (crude rates)[c] | N = 47 | | | 32 cone<br>15 ST | N = 4 (8.5) | | N = 1 (2.1) | | |

Abbreviations: NACT neoadjuvant chemotherapy, LN lymph node, ST simple trachelectomy, TP cisplatin + paclitaxel, TI cisplatin + ifosfamide, TA cisplatin + doxorubicin (for adenocarcinoma), TIP cisplatin + paclitaxel + ifosfamide, TEP cisplatin + paclitaxel + epirubicin (for adenocarcinoma), ddCP dose-dense carboplatin + paclitaxel, wCP weekly carboplatin + paclitaxel, NR not reported.

[a] Case reports are excluded from this summary.

[b] Three patients developed CIN after the procedure.

[c] Crude recurrence and mortality rates among those who successfully underwent conservative fertility-sparing surgery despite adjuvant treatment received.

**Table 5**
Reproductive outcomes of conservative procedures for cervical cancer after neoadjuvant chemotherapy.[a]

| Study author, year | Successful sparing surgery[b] | Pregnancies[c] | T1/T2 losses (%)[d] | Ongoing Pregnancies (%) | Live births (%) | Median follow-up in months (range) |
|---|---|---|---|---|---|---|
| Maneo, 2008 [61] | 16 | 10 | 1 (10.0) | 0 (0.0) | 9 (90.0) | 69 (10–124) |
| Robova, 2010 [63] | 12 | 7 | 0 (0.0) | 1 (14.3) | 6 (85.7) | 76.5 (17–142) |
| Salihi, 2015 [56] | 9 | 11 | 4 (36.4) | 0 (0.0) | 7 (63.6) | 58 (13–122) |
| Total (crude rates) | 37 | 28 | 5 (17.9) | 1 (3.5) | 22 (78.6) | |

Abbreviations: T1 first trimester, T2: second trimester.
[a] This summary excludes case reports and studies where simple hysterectomy was performed.
[b] Excludes patients who had complete hysterectomy or received fertility-compromising adjuvant treatment.
[c] Number of pregnancies regardless of how many times a woman has conceived.
[d] Number of T1/T2 terminations without living births.

## Future directions

There remain several unanswered questions regarding the safety of conservative management in early-stage cervical cancer.

### *The definition of criteria for low-risk of parametrial spread*

Various retrospective studies have attempted to identify the patients who are at low risk for parametrial involvement. Although still unclear, small tumor size, limited depth of stromal invasion, negative lymph node status, and absence of LVSI are some of the prognostic factors associated with low-risk of parametrial involvement [9,11,14,67]. The limitation of these criteria is that pathologic assessment of the surgical specimens is required to confirm depth of invasion, lymph node status, and the presence of LVSI. To address this limitation, models to predict parametrial involvement preoperatively have been assessed [68,69]. An analysis of 317 patients with stage IB1 cervical cancer found that tumor size >3 cm and serum squamous cell carcinoma antigen (SCC Ag) level >1.40 ng/mL were significantly associated with parametrial spread [68]. In another study of 115 patients with stage IB1 cervical cancer, Yamazaki et al. [69] sought to identify preoperative factors that could help guide clinicians in the choice of radical versus nonradical surgery. They reported that conservative surgery may be a treatment option for patients with stage IB1 cervical cancer with MRI-based tumor diameter <25 mm, MRI-based volume index <5000 $mm^3$, and negative results for SCC-Ag and CA-125. Although conservative procedures have been performed in patients with small (<2 cm) cervical lesions with no evidence of radiological lymph node involvement, it remains unclear in which patients we may safely avoid parametrectomy.

### *The indications for conization versus simple trachelectomy*

Many studies have assessed cervical conization and simple trachelectomy as alternatives to radical surgery. While some authors have offered cervical conization to patients with stage IA2 disease and simple trachelectomy to patients with stage IB1 disease [47], the indications of conization versus trachelectomy were not clearly defined in most studies. Conization may be the method of choice for smaller and localized cervical lesions. In addition, when performed with laser or electrosurgical loop, conization may not require general anesthesia [70]. However, if there is too little cervix to excise because of previous excisions, then conization may not be possible and simple trachelectomy is preferred. Trachelectomy may be recommended in cases of more extensive lesions or in patients at risk of lost to follow-up. However, trachelectomy is more difficult to perform than conization. Despite these considerations, studies with an aim of determining the circumstances under which either procedure should be carried out are necessary.

*The accountability of adverse obstetric outcomes to conservative management*

While many cervical cancer survivors treated conservatively have conceived and delivered, some cases of adverse obstetric outcomes including premature delivery, spontaneous abortion, fetal demise, and ectopic pregnancy have occurred (Tables 3 and 5). A meta-analysis showed that conization is associated with an increase in preterm delivery rate and preterm premature rupture of membranes [71]. However, it is not certain that adverse obstetrical outcomes observed after conservative surgery in these series are solely explained by the surgery. Studies have reported more favorable obstetric outcomes for women treated with radical trachelectomy followed by cerclage [72]. However, there is no consensus regarding the most appropriate method and type of cerclage. While some authors propose the use of a permanent monofilament O-polypropylene suture, which may reduce the risk of infection [40], others use Mersilene tape [73] or the Saling procedure [74]. However, the benefits of each method in cervical cancer survivors managed with conservative modalities should be balanced with its limitations.

## Ongoing trials

To provide stronger evidence on the efficacy of conservative management for early-stage cervical cancer, larger prospective trials are currently ongoing. These include an international trial (*ConCerv*) led by our team at the University of Texas MD Anderson Cancer Center [22,75]. Started in 2009, *ConCerv* is a multi-institutional trial evaluating the safety of conservative surgery in women with early-stage cervical cancer with favorable prognostic features. Patients desiring fertility in the future undergo cervical conization and pelvic lymph node dissection with lymphatic mapping. Patients not desiring fertility in the future undergo a simple hysterectomy and pelvic lymph node dissection with lymphatic mapping. At this time, we have accrued 88 of the planned 100 patients from 16 collaborating sites including MD Anderson Cancer Center, other sites in the USA (Nebraska, New York, and Texas), and globally (Argentina, Australia, Brazil, Colombia, Italy, Mexico, Peru, and Thailand).

Another ongoing trial is Gynecologic Oncology Group 278, “Evaluation of physical function and quality of life before and after conservative surgical therapy for stage early cervical cancer” [76]. This trial is led by Dr. Alan Covens and aims to assess the effect of conservative surgery on bladder, bowel, and sexual function. Other objectives are to investigate whether conservative surgery is associated with better physical function and less toxicity and to determine reproductive outcomes after conservative surgery. Another study, the SHAPE trial, led by Dr. Marie Plante, is a randomized trial comparing radical hysterectomy with simple hysterectomy in patients with low-risk early-stage cervical cancer [77]. Accrual is ongoing for both these studies.

## Summary

Conservative surgery is being investigated as an alternative to radical surgery in the management of early-stage cervical cancer. Because of the effective implementation of cervical cancer screening and early detection programs in high-resource settings, a growing number of women are diagnosed with small-volume disease. Given the increased survival and the low risk of parametrial spread observed in this population, less radical surgery will likely gain wider attention in the coming years. While preliminary results from small series of selected patients with favorable prognostic factors are promising, conservative surgery warrants further investigation to assess its oncologic safety in larger prospective cohorts. Because of the growing rate of cervical cancer survivors of reproductive age and the increasing childbearing age among women, the obstetrical outcomes of conservative surgery, which seem to be higher than those of radical surgery, will also need to be further studied. Moreover, a consensus on selection criteria that can be assessed preoperatively and easily measurable should be reached. The concept of neoadjuvant chemotherapy (NACT) is being considered in this context for patients with tumor size greater than 2 cm and requires further investigation. NACT followed by conservative surgery could provide greater hope of fertility preservation and better obstetrical outcomes than radical modalities. However, this issue will need to be addressed in larger studies. Ongoing trials will provide additional information on the safety and reproductive impact of conservative surgery in the management of cervical cancer.

**Practice points**

- Conservative management of cervical cancer can reduce the morbidity associated with radical surgery in selected patients with a low risk of parametrial spread without compromising the oncologic safety of the treatment.
- Patients with early-stage disease (stage IA1 with LVSI, stage IA2 to IB1) and favorable prognostic features (tumor size <2 cm; no lymph node metastases) are potential candidates for conservative surgery.
- In young patients with further fertility desire, conservative modalities offer the possibility to maintain their reproductive potential.
- Nearly 75% of conceptions after conization and simple trachelectomy in cervical cancer survivors have resulted in the delivery of a living newborn.
- Neoadjuvant chemotherapy may play a role in patients with more advanced disease (tumor size of 2–4 cm) by allowing less radical surgery if response to NACT occurs.

**Research agenda**

- More reproducible criteria that could be widely used preoperatively to accurately predict the risk of parametrial spread need to be determined and validated.
- The indications of cervical conization versus simple trachelectomy in this context have not yet been elucidated.
- The suitable timing of NACT with regard to nodal assessment in patients that might benefit from conservative surgery should be further investigated.
- The impact of conservative fertility-sparing modalities on the occurrence of adverse obstetric outcomes following the procedure should be clearly determined.

## Conflicts of interest

KMS is the PI of the *ConCerv* trial.
JFD has no conflict of interest to disclose.

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