Fertility-sparing surgery after neo-adjuvant chemotherapy in women with cervical cancer larger than 4 cm: a systematic review

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HIGHLIGHTS

- After neo-adjuvant chemotherapy for tumors >4 cm, 65% of patients had successful fertility-preserving surgery.
- A complete pathological response occurred in 56% of patients.
- The 4.5-year disease-free survival and overall survival rates were 92.3% and 100%, respectively.

ABSTRACT

Objective The objective of this systematic review was to assess the oncologic and fertility outcomes of patients with cervix-confined cancer >4 cm who underwent neo-adjuvant chemotherapy followed by fertility-sparing surgery.

Methods This study was registered in PROSPERO (registration number CRD42021254816). PubMed/MEDLINE, ClinicalTrials, EMBASE, Cochrane Central Register of Controlled Trials, SCOPUS, and OVID databases were searched from inception to July 2021. The included patients were those with cancer confined to the cervix and tumor diameter >4 cm (International Federation of Gynecology and Obstetrics (FIGO) 2018 stage IB3) with squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma who underwent intra-venous neo-adjuvant chemotherapy followed by successful fertility-sparing surgery.

Results The initial search identified 2990 articles. A total of 40 patients from 11 studies had attempted fertility preservation surgery (conization, simple or radical trachelectomy) and in 26 patients (65%) it was successful. All patients received platinum-based chemotherapy. A complete pathological response occurred in 56% of patients and two patients (7.7%) had a recurrence. The 4.5-year disease-free survival was 92.3% and the 4.5-year overall survival rate was 100%. Of six patients who tried to conceive, four (67%) achieved at least one pregnancy and three of the five pregnancies (60%) were pre-term deliveries (all after radical trachelectomy). All patients with recurrence received cisplatin and ifosfamide instead of cisplatin and paclitaxel, underwent non-radical surgery, and had residual disease in the final specimen.

Conclusions Evidence for fertility-sparing surgery after neo-adjuvant chemotherapy in patients with cervical cancer and tumors >4 cm is limited, and this approach should be considered as an experimental intervention. As the use of non-radical surgery could be a risk factor, if neo-adjuvant chemotherapy is used, patients should undergo fertility-sparing radical surgery.

INTRODUCTION

Cervical cancer is the fourth most frequent malignancy in women worldwide. According to the data from GLOBOCAN 2020, 604 127 new cases were estimated with an age-standardized mortality rate of 7.3 per 100 000 women for 2020.[1] Approximately 35% of patients diagnosed are <45 years of age and, due to a delay in childbearing, a growing number of women of reproductive age desire fertility-sparing treatment.[2 3] Fertility preservation may be considered in select cases through conization, simple trachelectomy, or radical trachelectomy depending on the risk factors for International Federation of Gynecology and Obstetrics (FIGO) 2018 stage IA1 + lymphovascular space invasion, IA2, and IB1 stages,[2 4] and the lymph node evaluation may be performed through systematic pelvic lymph node dissection or in some cases by sentinel lymph node (SLN) detection, or a combination of both procedures.[5 6] For tumors of 2–4 cm there is the option of upfront abdominal radical trachelectomy[7–9] or the use of neo-adjuvant chemotherapy followed by conization or trachelectomy according to the response.[10–12] Unfortunately, for tumors >4 cm, fertility-preserving options are limited as the standard of treatment is chemoradiotherapy.[5] Patients with cervical tumors >4 cm have been included in previous retrospective studies although they have never been analyzed as a separate sub-group.

The objective of this systematic review was to assess the oncologic and fertility outcomes of patients with cervical cancer >4 cm (FIGO 2018 stage IB3) who underwent neo-adjuvant chemotherapy followed by fertility-sparing surgery.

METHODS

A systematic literature review was conducted following the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) checklist. PubMed/

MEDLINE, ClinicalTrials, EMBASE, Cochrane Central Register of Controlled Trials, SCOPUS, and OVID databases were searched from inception to July 2021. The overall search strategy is shown in the supplementary material (online supplemental file 1). In addition, we searched the reference lists of all eligible study reports and undertook forward citation tracking (using Google Scholar). This study was registered in PROSPERO (registration number CRD42021254816).

We included English language articles reporting all types of studies including case reports and commentaries. Abstracts and unpublished studies were excluded. The included patients were those with cervical cancer confined to the cervix and tumor diameter >4 cm (FIGO 2018 IB3 stage) with squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma who underwent neo-adjuvant chemotherapy (only intra-venous route, any agent, at any concentration, frequency, and duration) followed by successful fertility-sparing surgery (conization, simple or radical trachelectomy, any route). Exclusion criteria were patients under 18 years of age, with FIGO 2018 stage IIA, IIB stage or higher, pregnancy, evidence of extra-uterine disease on pre-surgical imaging (any modality accepted), previous pelvic radiotherapy, or any form of adjuvant radiotherapy (brachytherapy and/or external beam radiotherapy).

If two or more papers were published either by the same author/institution or using the same primary data source, only the most recent paper was included in the review. The measured outcomes were disease-free survival, overall survival, clinical response (as defined by trial authors), residual disease in the pathology report, and chemotherapy-related toxicity. We also evaluated fertility outcomes as pregnancy rate after treatment and pregnancy results.

Study selection

Two authors (JR, DV-C) independently assessed all titles and abstracts of records retrieved from the search strategy for inclusion. The final selection of trials for inclusion was undertaken independently by three authors (RP, JR, DV-C) and any disagreement was resolved through discussion. For eligible studies, two authors (JR, DV-C) extracted the data independently using the form. Any disagreement about extracted data was resolved through discussion until a consensus was reached. Individual data were extracted from each study. Where necessary, the main investigators of included studies were contacted by email for further information in cases where not all relevant information was available.

The information was presented as median or mean (according to its normal distribution) and percentages with absolute frequencies for quantitative or qualitative variables, respectively. Survival analysis was performed to estimate disease-free survival and overall survival using Kaplan–Meier survival curves. The statistical analysis was performed in SPSS 21.0 According to local regulation, no institutional review board agreement was required for this type of study. Ethical approval was not required as only data from previously published studies were retrieved and analyzed. In accordance with the journal's guidelines, we will provide our data for the reproducibility of this study in other centers if requested.

RESULTS

The search identified 2990 articles and, after duplicates were removed, 2676 were evaluated and the title and abstract screening of these references identified 21 studies as potentially eligible for this review. The full-text screening excluded 10 studies: six did not include tumors >4 cm,[13–18] two had duplication of information,[19 20] one included a patient with lymph node metastases on pre-surgical PET-CT,[21] and in one fertility-preserving surgery was not possible in any patient. Finally, 11 studies met the selection criteria[12 22–31] (see Figure 1).

A total of 40 patients from 11 studies with tumors measuring >4 cm were scheduled for intra-venous neo-adjuvant chemotherapy followed by fertility-preserving surgery and, in 26 (65%), successful fertility preservation was achieved. All studies were retrospective cohorts, case series, or case reports. Table 1 shows a detailed description of the included patients. In the 21 patients for which age was available, the median age was 28 (range 23–37) years. For the other five patients the individual data were not available,[29 30] and a median age of 28 years (four patients) and 31 years (one patient) was published for the whole cohorts of each publication (19 patients and 28 patients, respectively). All included patients met the criteria to be classified as FIGO 2018 stage IB3. The most common histological sub-type was squamous cell carcinoma in 16 patients (61.5%), eight patients (30.8%) had adenocarcinoma and two patients (7.7%) had adenosquamous carcinoma.

The median tumor size was 4.6 cm (range 4.1–6.0) measured either clinically or using at least one imaging method: ultrasound, magnetic resonance imaging (MRI), computed tomography (CT), or positron emission tomography-CT (PET-CT). All patients received platinum-based chemotherapy in different combinations and doses: 22 (84.6%) patients received cisplatin and 4 (15.4%) received carboplatin. Twenty-one (80.1%) patients received paclitaxel and 10 (38.5%) received three combined chemotherapy agents. None of the included patients received monotherapy and the doses and schedule for each agent were not homogenous. For 22 of the 26 patients (84.6%) information about the complete chemotherapy regimen was available. Twelve patients (54.5%) received chemotherapy every 3 weeks, seven (58.3%) with three agents and five (41.7%) with two agents. Six (27.3%) of these 22 patients received chemotherapy weekly and the other four patients (18.2%) received chemotherapy in 10-day cycles. Complete information about the chemotherapy schemes is shown in Table 2. No chemotherapy-related toxicity was reported in 12 patients (46.2%) and, for the remaining patients, alopecia was the most common adverse event in eight patients (30.1%) followed by hematologic toxicity in five patients (details about the severity were not reported and there were no reports of suspension of chemotherapy regimen).

For 20 of the 26 patients (77%), information about clinical or imaging response was available (definition of response was variable among studies): nine (45%) patients had a complete response and 11 (55%) had a partial response. All patients had lymph node evaluation. Seven patients (26.9%) underwent evaluation through laparoscopic lymphadenectomy before chemotherapy administration and in two patients sentinel lymph node biopsy was also performed; the other 19 patients (73.1%) underwent pelvic lymphadenectomy after neo-adjuvant chemotherapy, two with sentinel lymph node biopsy.

Surgical management of the primary tumor was a radical trachelectomy in 20 patients (76.9%), seven (35%) via an abdominal approach, five (25%) via a vaginal approach, four (20%) laparoscopic-assisted vaginal, three (15%) total laparoscopic, and in one patient (5%) a robotic-assisted approach was used. Four

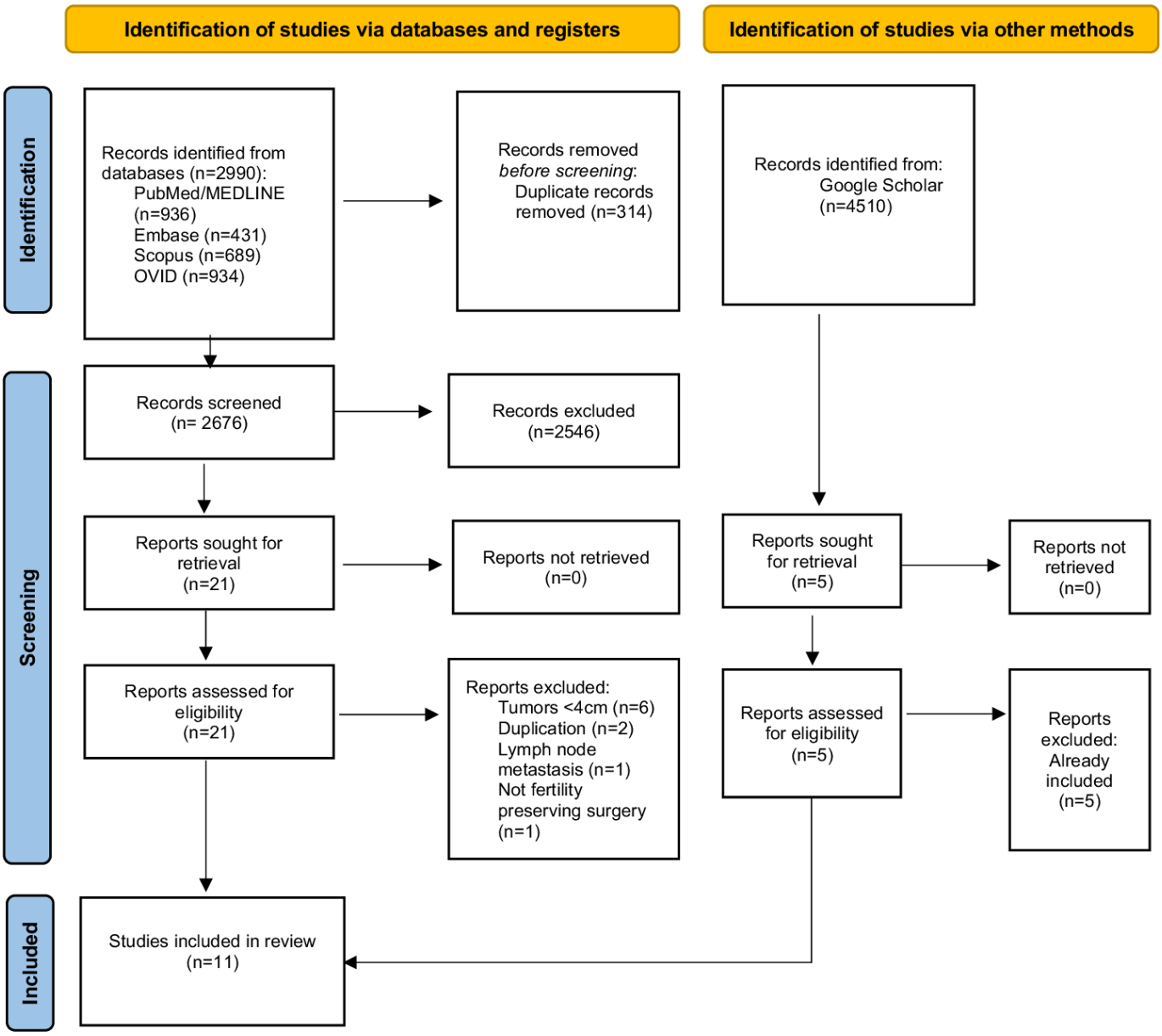

Figure 1 PRISMA flow diagram for study selection.

patients (15.4%) underwent simple trachelectomy and two (7.7%) underwent conization. Information about the pathologic cervical specimen was available for 25 patients (96.2%), of whom 14 (56%) had a complete pathological response and 11 (44%) had a partial response (range 3–39 mm of residual invasive disease). All 26 patients had negative lymph nodes. A detailed description of surgical procedures is shown in Table 3. Given the nature of the studies and the intervention, with only single-arm studies we did not evaluate the risk of bias for the included studies as this would not provide reliable information.

Survival analyses were performed to estimate disease-free survival and overall survival. Kaplan–Meier curves were constructed. According to the data provided by the original studies, the median follow-up was 55 months (range 6–119). The 4.5-year disease-free survival was 92.3%, median was not reached, and the 4.5-year overall survival was 100%. Two patients had recurrence (7.7%), one with squamous cell carcinoma and one with adenosquamous carcinoma. Both received cisplatin and ifosfamide chemotherapy every 10 days for three cycles and underwent non-radical surgery (one conization and one simple trachelectomy) with systematic pelvic lymphadenectomy and had residual disease (7 mm and 39 mm). Conversely, no patients with a complete pathological response had a recurrence. The recurrences were pelvic (endocervical and cervix/parametrium) and were detected at 6 months of follow-up (see Table 3). One patient underwent radical hysterectomy for recurrence and was free of disease at 62 months of follow-up; the other patient was treated with concomitant chemoradiation and was free of disease 71 months after the definitive treatment. No patient died during the follow-up.

Information on obstetric and perinatal outcomes was available for 20 patients (76.9%); six (30%) tried to conceive and four of these achieved at least one pregnancy during follow-up. Five pregnancies were reported: three pre-term deliveries, two term deliveries, and

Table 1 Major characteristics of studies included in the systematic review

No	Author/year	Total no	No scheduled with tumor >4 cm and NACT	No with successful fertility-preserving surgery	Age (years)	Maximum tumor size (cm)	Histologic subtype
1	Palaia 2011[27]	1	1	1	24	5.5	S
2	Hamed 2012[22]	1	1	1	31	6	S
3	Vercellino 2012[31]	18	6	2	27	4.2	AS
4					37	4.2	A
5	Lanowska 2014[24]	20	2	2	30	5	S
6					26	4.1	A
7	Robova 2014[12]	28	7	2	31	4.2	S
8					27	4.3	S
9	Van Gent 2014[30]	28	1	1	31*	4.2	S
10	Hauerberg 2015[23]	120	1	1	28	4.5	A
11	Slama 2016[28]	44	2	2	29	4.2	AS
12					33	5.9	S
13	Marchiole 2018[25]	19	5	4	25	4.2	A
14					28	4.5	A
15					32	4.5	A
16					29	4.4	S
17	Tesfai 2020[29]	19	7	4	28*	5	S
18					28*	4.5	S
19					28*	5	A
20					28*	5	S
21	Rendón 2021[26]	25	7	6	26	5	S
22					30	4.5	S
23					27	5	S
24					27	4.3	A
25					23	4.1	S
26					25	4.3	S

*Mean or median age for the whole cohort.
A, adenocarcinoma; AS, adenosquamous; NACT, neo-adjuvant chemotherapy; S, squamous cell carcinoma.

no miscarriages. All patients with pre-term deliveries had undergone a radical trachelectomy as primary treatment.

DISCUSSION

Summary of Main Results

In this systematic review of patients diagnosed with cervical cancer FIGO 2018 stage IB3 who underwent neo-adjuvant chemotherapy followed by fertility-preserving surgery, we found a rate of successful fertility preservation of 65%. All patients received platinum-based chemotherapy and most (80.1%) in combination with paclitaxel; 73% had lymph node evaluation after neo-adjuvant chemotherapy and 76.9% underwent a radical procedure. A complete pathological response was reported for 56% in the final specimen. The 4.5-year disease-free survival rate was 92.3% and the 4.5-year overall survival rate was 100%. Of those who tried to conceive, 67% achieved at least one pregnancy and 60% were pre-term deliveries (all after radical trachelectomy).

Results in the Context of Published Literature

Previous reviews have evaluated the outcomes for fertility-preserving surgical management in cervical cancer. For low-risk tumors up to 2 cm, conization or trachelectomy through vaginal, abdominal, or minimally invasive surgery has shown favorable results.[2 4 32 33] Recently, a prospective trial of 100 patients evaluating less radical surgery for low-risk cervical cancer included 42 women with squamous cell carcinoma and adenocarcinoma who underwent conization with negative lymph node evaluation for fertility preservation.[32] The authors showed that only one patient had a recurrence (2.4%). Fourteen pregnancies were reported in 11 of 40 women (27.5%); 13 (92.9%) delivered at term and one (7.1%) resulted in fetal death. These results are more favorable than those in our review with a recurrence rate of 7.7% but a similar global pregnancy rate of 20%, reflecting the difference in risk factors for our population.

Patients with tumors between 2 cm and 4 cm could be treated by upfront surgery or neo-adjuvant chemotherapy followed by

Table 2 Information on chemotherapy treatment

No	Chemotherapy regimen	Schedule	Cycles	Toxicity
1	Cisplatin 75 mg/m^2 + paclitaxel 175 mg/m^2 + ifosfamide 5 g/m^2	Every 3 weeks	3	Moderate hematologic and extra-hematologic toxicity
2	Cisplatin 50 mg/m^2 + paclitaxel 135 mg/m^2	Not reported	4	Not reported
3	Cisplatin 100 mg/m^2 + paclitaxel 200 mg/m^2	Every 3 weeks	2	The acute toxicity of chemotherapy did not exceed grade 3 hematologic and grade 2 non-hematologic toxicities according to standard criteria. No late toxicity was noted
4	Cisplatin 100 mg/m^2 + paclitaxel 200 mg/m^2 + ifosfamide 5 g/m^2	Every 3 weeks	2	
5	Cisplatin 100 mg/m^2 + paclitaxel 200 mg/m^2 + ifosfamide 5 g/m^2	Not reported	3	None
6	Cisplatin 100 mg/m^2 + paclitaxel 200 mg/m^2 + ifosfamide 5 g/m^2	Not reported	2	None
7	Cisplatin 75 mg/m^2 + ifosfamide 3 g	10 days interval	3	G1 neutropenia
8	Cisplatin 75 mg/m^2 + ifosfamide 3 g	10 days interval	3	None
9	Cisplatin 70 mg/m^2 + paclitaxel 70 mg/m^2	Weekly	6	None
10	Cisplatin + ifosfamide + 5-fluorouracil (doses not specified)	Not reported	Not reported	Not reported
11	Cisplatin + ifosfamide (doses not specified)	10 days interval	3	G1 neutropenia
12	Cisplatin + ifosfamide (doses not specified)	10 days interval	3	None
13	Cisplatin 75 mg/m^2 + paclitaxel 175 mg/m^2 + ifosfamide 5 g/m^2	Every 3 weeks	4	Alopecia, no other
14	Cisplatin 75 mg/m^2 + paclitaxel 175 mg/m^2 + epirubicin 75 mg/m^2	Every 3 weeks	3	Alopecia, no other
15	Cisplatin 75 mg/m^2 + paclitaxel 175 mg/m^2 + epirubicin 75 mg/m^2	Every 3 weeks	3	Alopecia, no other
16	Cisplatin 75 mg/m^2 + paclitaxel 175 mg/m^2	Every 3 weeks	4	Alopecia, no other
17	Cisplatin 70 mg/m^2 + paclitaxel 70 mg/m^2	Weekly	5	The most common neo-adjuvant chemotherapy-related toxicity observed was hair loss (alopecia). Gastrointestinal side effects such as anorexia and nausea were also frequently described. Other side effects such as renal failure or bone marrow depression were rare
18	Cisplatin 70 mg/m^2 + paclitaxel 70 mg/m^2	Weekly	6	
19	Cisplatin 70 mg/m^2 + paclitaxel 70 mg/m^2	Weekly	3	
20	Cisplatin 70 mg/m^2 + paclitaxel 70 mg/m^2	Weekly	6	
21	Carboplatin 290 mg + paclitaxel 800 mg	Every 3 weeks	3	None reported
22	Carboplatin + paclitaxel (doses not specified)	Every 3 weeks	3	None reported
23	Carboplatin + paclitaxel (doses not specified)	Every 3 weeks	3	None reported
24	Cisplatin 75 mg/m^2 + paclitaxel 175 mg/m^2 + ifosfamide 5 g/m^2	Every 3 weeks	3	None reported
25	Cisplatin 50 mg/m^2/days 2–3 + paclitaxel 175 mg/m^2/day 1 + 5 fluorouracil 800 mg/m^2 /days 1-2-3	Every 3 weeks	3	None reported
26	Carboplatin 2AUC + paclitaxel 175 mg/m^2	Weekly	6	None reported

fertility-preserving surgery. In this population vaginal radical trachelectomy has worse oncological outcomes than the abdominal route and the pregnancy rate was higher in patients who receive neo-adjuvant chemotherapy than among those who underwent laparotomic radical trachelectomy (69% vs 49%).[33] A recent review[10] evaluating neo-adjuvant chemotherapy and including 205 patients showed that, of the patients who received neo-adjuvant chemotherapy, 87.8% underwent successful fertility-sparing surgery. This proportion is larger than the result of our review which included only patients with tumors >4 cm, possibly reflecting a population with higher risk disease. The global recurrence and death rates were 12.8% and 2.8%, respectively and, of 112 women who tried to conceive after surgery, 84.8% achieved a pregnancy. These results are similar to the results of our review. Unfortunately, in previous reviews[33 34] patients with tumors >4 cm (FIGO 2018 stage IB3) were not analyzed as a separate sub-group. Lymphadenectomy prior to chemotherapy could select a proportion of patients with lymph node disease not detected in the images and reduce the number of women eligible for fertility preservation. However, the rate of lymph node disease in post-chemotherapy lymphadenectomy is between 4.6% and 8.3%,[26 29] which could indicate that the lymph node status is susceptible to downstaging with chemotherapy.

Recently, a systematic review was published of 15 studies including 48 patients which assessed outcomes for patients with cervical cancer and tumors ≥4 cm undergoing fertility-sparing surgery.[35] Three risk factors for disease-free survival were identified in this review: adenocarcinoma and glassy cell histotypes, grade 3 tumors, and tumor size >5 cm. This systematic review is different from our review in several ways. First, the authors did not present individual data and patients with FIGO 2018 stage IB2 were included as well as those with high-risk histologies. Additionally, the study included patients who underwent surgery without neo-adjuvant chemotherapy and patients who received intra-arterial neo-adjuvant chemotherapy, representing a different population.

The CONTESSA study[36] is a prospective trial already recruiting patients to assess the safety and efficacy of neo-adjuvant chemotherapy and fertility-sparing surgery by simple trachelectomy/conization in women with FIGO 2018 stage IB2 cervical cancer. Patients with tumors >4 cm are not included and unfortunately it will not provide additional information for this population.

Table 3 Surgical procedure and clinical/pathological response

No	Cervical surgery after NACT	LND	LND timing	Clinical/ imaging response*	Pathological response*	Follow-up time (months)	Recurrence	Death
1	Simple trachelectomy	Laparoscopic pelvic lymphadenectomy	Post NACT	Complete	Complete	18	No	No
2	Robotic-assisted RT	Pelvic and para-aortic lymphadenectomy	Post NACT	Complete	Complete	16	No	No
3	VRT	Laparoscopic pelvic and para-aortic lymphadenectomy	Pre NACT	Partial (<20 mm)	Partial (20 mm)	70	No	No
4	VRT	Laparoscopic pelvic and para-aortic lymphadenectomy	Pre NACT	Partial (<20 mm)	Partial (20 mm)	15	No	No
5	VRT	Laparoscopic pelvic lymphadenectomy	Pre NACT	Not reported	Complete	79	No	No
6	VRT	Laparoscopic pelvic lymphadenectomy	Pre NACT	Not reported	Complete	6	No	No
7	Simple trachelectomy	Laparoscopic SLN biopsy + pelvic lymphadenectomy	Post NACT	Not reported	Complete	71	No	No
8	Simple trachelectomy	Laparoscopic SLN biopsy + pelvic lymphadenectomy	Post NACT	Not reported	Partial (7 mm)	62	Yes (endocervical) 6 months	No
9	ART	Open pelvic lymphadenectomy	Post NACT	Not reported	Partial (5 mm)	6.2	No	No
10	VRT	Laparoscopic pelvic lymphadenectomy	Post NACT	Not reported	Not reported	68	No	No
11	Simple trachelectomy	Laparoscopic SLN biopsy + pelvic lymphadenectomy	Pre NACT	Complete	Partial (4 mm)	104	No	No
12	Conization	Laparoscopic SLN biopsy + pelvic lymphadenectomy	Pre NACT	Partial	Partial (39 mm)	77	Yes (cervix, parametrium) 6 months	No
13	LARVT	Laparoscopic pelvic lymphadenectomy	Post NACT	Partial (10 mm)	Partial (24 mm)	100	No	No
14	LARVT	Laparoscopic pelvic lymphadenectomy	Post NACT	Complete	Complete	84	No	No
15	LARVT	Laparoscopic pelvic lymphadenectomy	Post NACT	Partial (10 mm)	Partial (3 mm)	47	No	No
16	LARVT	Laparoscopic pelvic lymphadenectomy	Post NACT	Complete	Complete	6	No	No
17	ART	Open pelvic lymphadenectomy	Post NACT	Partial (15 mm)	Complete	65	No	No
18	ART	Open pelvic lymphadenectomy	Post NACT	Partial (35 mm)	Complete	26	No	No
19	ART	Open pelvic lymphadenectomy	Post NACT	Complete	Complete	45	No	No
20	ART	Open pelvic lymphadenectomy	Post NACT	Complete	Complete	64	No	No
21	ART	Open pelvic lymphadenectomy	Post NACT	Partial	Partial (14 mm)	48	No	No
22	LRT	Laparoscopic pelvic lymphadenectomy	Post NACT	Partial	Partial (15 mm)	42	No	No

Continued

Table 3 Continued

No	Cervical surgery after NACT	LND	LND timing	Clinical/ imaging response*	Pathological response*	Follow-up time (months)	Recurrence	Death
23	Conization	Laparoscopic pelvic lymphadenectomy	Post NACT	Complete	Complete	96	No	No
24	LRT	Laparoscopic pelvic lymphadenectomy	Pre NACT	Partial	Partial (17 mm)	46	No	No
25	ART	Open pelvic lymphadenectomy	Post NACT	Partial	Complete	119	No	No
26	LRT	Laparoscopic pelvic lymphadenectomy	Post NACT	Complete	Complete	45	No	No

*There were different definitions for clinical and pathological response among studies.
ART, abdominal radical trachelectomy; LARVT, laparoscopic-assisted radical vaginal trachelectomy; LND, lymph node dissection; LRT, laparoscopic radical trachelectomy; NACT, neo-adjuvant chemotherapy; RT, radical trachelectomy; VRT, vaginal radical trachelectomy.

Strengths and Weaknesses

A strength of our review is that it includes individual patient data through contact with the authors of the article in cases of missing information, and we present detailed information about treatment schemas, surgical outcomes, and follow-up. We have a registered protocol with specified selection criteria and a rigorous process for data analysis. However, we recognize that it is limited by several factors. We restricted the search to published data in the English language so we could have missed some relevant references published in other languages. Also, the retrospective nature of all the studies included in the review is a limitation, with potential selection and publication bias, and it is possible that patients with adverse results or those who were not considered candidates for fertility preservation were not included in the publication. As there was no standard method for evaluation of tumor size including clinical and imaging (MRI, CT, or PET-CT) methods, there could be clinically relevant differences between patients. Also, there were no standard schemes and doses of the chemotherapy agents, clinical and pathological analysis of the response to chemotherapy, or the follow-up protocol. Even though we contacted the authors of the original articles to obtain additional information, it was not possible to access all relevant outcomes, particularly for fertility outcomes and clinical response rates, so these results may underestimate or overestimate the findings reported.

Implications for Practice and Future Research

This systematic review shows that the evidence for fertility-sparing surgery after neo-adjuvant chemotherapy in patients with cervical cancer and tumors >4 cm is limited and this approach should be considered an experimental intervention. Proper and extensive counseling to patients is recommended during discussion of treatment choices. The most common chemotherapy scheme used was platin-based in combination with paclitaxel used concomitantly, and most patients underwent lymph node dissection after neo-adjuvant chemotherapy. Doses and chemotherapy schemes, pre-surgical studies, and follow-up were different for all patients. All patients with recurrence received cisplatin and ifosfamide, underwent non-radical surgery, and had residual disease. We encourage clinicians and other authors to collect prospective information on this population and to standardize the management through multi-institutional collaboration.

CONCLUSION

Fertility-sparing surgery after neo-adjuvant chemotherapy in patients with cervical cancer and tumors >4 cm is feasible, although the evidence is limited and this approach should be considered as an experimental intervention. Non-radical surgery and residual disease are risk factors for recurrence.

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Supplement 1. Search strategy

Database	Search strategy	Field search	Filters
PubMed	((((patient*[Title/Abstract] AND ("cervical cancer*"[Title/Abstract] OR "cervix cancer*"[Title/Abstract] OR "uterine cervical neoplasm*"[Title/Abstract] OR "uterine cervical cancer"[Title/Abstract] OR "cervix neoplasm*"[Title/Abstract] OR "early-stage cervical cancer"[Title/Abstract] OR "early cervical cancer") AND Title/Abstract)) AND ("neoadjuvant chemotherapy"[Title/Abstract] OR "neo-adjuvant chemotherapy"[Title/Abstract] OR "neoadjuvant therapy"[Title/Abstract] OR "preoperative chemotherapy"[Title/Abstract] OR "conservative surgery"[Title/Abstract] OR "fertility-sparing surgery"[Title/Abstract] OR surgery[Title/Abstract] OR trachelectom*[Title/Abstract] OR "radical trachelectomy"[Title/Abstract] OR "abdominal trachelectomy"[Title/Abstract] OR "abdominal radical trachelectomy"[Title/Abstract])) OR ("laparoscopic trachelectomy"[Title/Abstract] OR "laparoscopic radical trachelectomy"[Title/Abstract] OR "robotic trachelectomy"[Title/Abstract] OR "robotic radical trachelectomy"[Title/Abstract] OR "vaginal trachelectomy"[Title/Abstract] OR "vaginal radical trachelectomy"[Title/Abstract] OR conization*[Title/Abstract] OR "cone resection*"[Title/Abstract])) AND ("fertility preservation*" OR "fertility-preserving" OR fertility OR fecundity OR fertilization OR pregnanc* OR "pregnancy attempted" OR recurrence* OR neoplasm* OR "neoplasm recurrence*" OR death OR survival) AND ((Case Reports[ptyp] OR Observational Study[ptyp] OR Randomized Controlled Trial[ptyp]) AND English[lang])	Title/Abstract And All Fields	Article types Languages
Embase	((patient*:ab,ti AND ('cervical cancer*':ab,ti OR 'cervix cancer*':ab,ti OR 'uterine cervical neoplasm*':ab,ti OR 'uterine cervical cancer':ab,ti OR 'cervix neoplasm*':ab,ti OR 'early-stage cervical cancer':ab,ti OR 'early cervical	Title/Abstract And All Fields	Study types Publication types Languages

	cancer':ab,ti) AND ('neoadjuvant chemotherapy':ab,ti OR 'neo-adjuvant chemotherapy':ab,ti OR 'neoadjuvant therapy':ab,ti OR 'preoperative chemotherapy':ab,ti OR 'conservative surgery':ab,ti OR 'fertility-sparing surgery':ab,ti OR surgery:ab,ti OR trachelectom*:ab,ti OR 'radical trachelectomy':ab,ti OR 'abdominal trachelectomy':ab,ti OR 'abdominal radical trachelectomy':ab,ti) OR 'laparoscopic trachelectomy':ab,ti OR 'laparoscopic radical trachelectomy':ab,ti OR 'robotic trachelectomy':ab,ti OR 'robotic radical trachelectomy':ab,ti OR 'vaginal trachelectomy':ab,ti OR 'vaginal radical trachelectomy':ab,ti OR conization*:ab,ti OR 'cone resection*':ab,ti) AND ('fertility preservation*' OR 'fertility-preserving' OR fertility OR fecundity OR fertilization OR pregnanc* OR 'pregnancy attempted' OR recurrence* OR neoplasm* OR 'neoplasm recurrence*' OR death OR survival) AND ('case report'/de OR 'observational study'/de OR 'randomized controlled trial'/de OR 'retrospective study'/de) AND 'article'/it AND [english]/lim		
Scopus	(TITLE (patient* AND ("cervical cancer*" OR "cervix cancer*" OR "uterine cervical neoplasm*" OR "uterine cervical cancer" OR "cervix neoplasm*" OR "early-stage cervical cancer" OR "early cervical cancer")) AND TITLE-ABS-KEY ("neoadjuvant chemotherapy" OR "neo-adjuvant chemotherapy" OR "neoadjuvant therapy" OR "preoperative chemotherapy" OR "conservative surgery" OR "fertilitysparing surgery" OR surgery OR trachelectom*) OR TITLE-ABS-KEY ("radical trachelectomy" OR "abdominal trachelectomy" OR "abdominal radical trachelectomy" OR "laparoscopic trachelectomy") OR TITLE-ABS-KEY ("laparoscopic radical trachelectomy" OR "robotic trachelectomy" OR "robotic radical trachelectomy" OR "vaginal trachelectomy" OR "vaginal radical trachelectomy" OR conization* OR "cone resection*") AND TITLE-ABS-KEY ("fertility preservation*" OR "fertility-preserving" OR fertility OR fecundity OR fertilization OR pregnanc* OR "pregnancy attempted" OR recurrence* OR neoplasm* OR "neoplasm recurrence*" OR death OR survival)) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (LANGUAGE , "English"))	Article title, Abstract, Keywords	Document type Publication stage (final) Language

Ovid	1 (((patient* and ("cervical cancer*" or "cervix cancer*" or "uterine cervical neoplasm*" or "uterine cervical cancer" or "cervix neoplasm*" or "early-stage cervical cancer" or "early cervical cancer") and ("neoadjuvant chemotherapy" or "neo-adjuvant chemotherapy" or "neoadjuvant therapy" or "preoperative chemotherapy" or "conservative surgery" or "fertility-sparing surgery" or surgery or trachelectom* or "radical trachelectomy" or "abdominal trachelectomy" or "abdominal radical trachelectomy")) or ("laparoscopic trachelectomy" or "laparoscopic radical trachelectomy" or "robotic trachelectomy" or "robotic radical trachelectomy" or "vaginal trachelectomy" or "vaginal radical trachelectomy" or conization* or "cone resection*")) and ("fertility preservation*" or "fertility-preserving" or fertility or fecundity or fertilization or pregnanc* or "pregnancy attempted" or recurrence* or neoplasm* or "neoplasm recurrence*" or death or survival)).ab. 2 limit 1 to english language [Limit not valid in Books@Ovid,Journals@Ovid,Your Journals@Ovid,ACP Journal Club,CDSR,CCA,CLCMR,DARE; records were retained] 3 limit 2 to (case report or randomized controlled trial) [Limit not valid in Books@Ovid,Journals@Ovid,Your Journals@Ovid,ACP Journal Club,CDSR,CCA,CLCMR,DARE,CLHTA,CLEED,Global Health,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] 5 remove duplicates from 4	Abstract	Publication years Language Publication types Remove duplicates