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Original Article

Fertility-sparing surgery for women with stage I cervical cancer of 4 cm or larger: a systematic review

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ABSTRACT

Objective: To investigate current evidence on oncological, fertility and obstetric outcomes of patients with stage I cervical cancer of 4 cm or larger undergoing fertility-sparing surgery (FSS).
Methods: Systematic review of studies including women affected by stage I cervical cancer ≥4 cm who underwent FSS. Main outcome measures: disease-free survival (DFS), overall survival (OS), pregnancy rate, live birth rate, premature delivery rate.
Results: Fifteen studies met all eligibility criteria for this systematic review, involving 48 patients affected by cervical cancer ≥4 cm who completed FSS. Three patients (6.3%) experienced a recurrence and one of them (2.1%) died of disease. The 5-year DFS rate was 92.4%. The 5-year OS rate was 97.6%. A significantly shorter 5-year DFS was reported for high-risk patients (G3, non-squamous histotype, diameter ≥5 cm) compared with low-risk (74.7% vs. 100%; log-rank test, p=0.024). Data about fertility outcomes were available for 12 patients. Five patients out of 12 (41.7%) attempted to conceive with an estimated pregnancy rate of 80%, a live birth rate of 83.3% and a premature delivery rate of 20%.
Conclusion: Women with high tumor grade, aggressive histology and tumor size ≥5 cm have a higher risk of recurrence. Oncologic outcomes are encouraging among low-risk patients; however, the lack of high-quality studies makes it difficult to draw any firm conclusions. Prospective multicentric clinical trials with a proper selection of inclusion/exclusion criteria should be conducted in women with low-risk factors, strong desire to preserve their fertility and high likelihood to conceive.

Keywords: Fertility Preservation; Cervical Cancer; Conservative Treatment; Fertility; Neoadjuvant Chemotherapy

INTRODUCTION

Cervical cancer is the fourth cancer for both incidence and mortality among the female population worldwide and the second cause of cancer death in women aged 20 to 39 years.

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Synopsis

Fertility-sparing surgery (FSS) in women with stage I cervical cancer ≥4 cm is considered experimental. This systematic review collected data of 48 patients affected by stage I cervical cancer ≥4 cm who underwent FSS. A shorter 5-year disease-free survival was reported for high-risk patients compared with low-risk. The estimated pregnancy rate was 80%, live birth rate 83.3% and premature delivery rate 20%. Prospective clinical trials with a proper selection of inclusion/exclusion criteria should be conducted.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: D.D.V.; Data curation: D.D.V., C.G., S.C.M., S.G.; Formal analysis: D.D.V., C.G., S.C.M., S.G.; Funding acquisition: D.D.V.; Investigation: D.D.V., C.G., S.C.M., S.G.; Methodology: D.D.V., C.G., S.C.M., S.G., B.G., P.F., S.F., P.G., P.I., T.G.; Project administration: M.L.; Resources: D.D.V.; Software: D.D.V.; Supervision: A.R., B.P.P., M.L.; Validation: D.D.V., C.G., S.C.M., S.G., B.G., P.F., S.F., P.G., P.I., T.G., A.R., B.P.P., M.L.; Visualization: D.D.V., C.G., S.C.M., S.G.; Writing - original draft: D.D.V., C.G., S.C.M., S.G.; Writing - review & editing: D.D.V., C.G., S.C.M., S.G., B.G., P.F., S.F., P.G., P.I., T.G., A.R., B.P.P., M.L.

Since the peak of incidence occurs before the fourth decade of life, merely 40% of cervical cancer diagnosis occurs during the childbearing age of a woman, and so the issue of conservative surgery to preserve fertility is a key factor in their management [1]. Indeed, in the last decades, fertility-sparing surgery (FSS) has emerged as an alternative treatment in young women with early-stage cervical cancer who strongly desire to preserve their childbearing potential [2,3]. Different FSS procedures have been proposed so far in order to preserve the fertility potential without affecting oncologic outcomes. According to current guidelines, FSS can be offered to patients with early International Federation of Gynecology and Obstetrics (FIGO) 2018 stage (IA1–IB1) cervical cancer (greatest diameter <2 cm) and favorable histology (i.e., squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma) [4,5]. Moreover, according to recent studies, FSS might be carefully considered in well-selected patients with FIGO 2018 stage IB2 carcinomas (greatest diameter between 2 and 4 cm) [6,7]. Conversely, the role of FSS in tumors of 4 cm or larger limited to the cervix uteri is still controversial and considered to be experimental. Indeed, the impact that the FSS has on oncological and reproductive outcomes of patients with stage I cervical cancer of 4 cm or larger is often not acknowledged or assessed in the few published studies on FSS in cervical cancer with diameter >2 cm [8,9].

The present systematic review aims to assess the impact of FSS in young women with stage I cervical cancer of 4 cm or larger, not merely in terms of survival outcomes but also concerning fertility and obstetric outcomes.

MATERIALS AND METHODS

1. Search strategy

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were used for this study [10]. A search was performed up to September 30, 2020 by three authors (C.G., S.C.M., S.G.) independently within several database (MEDLINE, Embase, Cochrane Library, Google Scholar) to ensure all relevant studies evaluating the impact of FSS for stage FIGO 2018 IB3, FIGO 1994–1997 stage IB1–IB2 or FIGO 2009 stage IB1–IB2 cervical cancer on oncological and reproductive outcomes.

The process of evidence acquisition combined the following MeSH terms: “cervical cancer,” “cervix,” “conservative surgery,” “conservative treatment,” “fertility-sparing surgery,” “trachelectomy,” “conization,” “cone resection,” and “fertility.” Article abstracts, full text of articles and cross-referenced studies identified from retrieved articles were screened for pertinent information. All duplicate records were removed.

2. Selection of studies and methodologic quality assessment

Key criteria for inclusion were: 1) original studies published in English, in peer-reviewed journals studies; 2) stage I cervical cancer of 4 cm or greater in size at the time of initial diagnosis; 3) desire of the patients to preserve their fertility and refusal of radical treatment to be stated; and 4) completed FSS (i.e., trachelectomy, conization).

Exclusion criteria were: 1) editorials, review articles and conference abstracts; 2) studies with incomplete or absent data on obstetric outcomes; and 3) studies not reporting surgical and fertility outcomes of the cohort of patients with cervical cancer of 4 cm or larger separately from the study population.

The selected studies were comprehensively examined, and relevant data extracted for each paper and inputted to the spreadsheet. The information selected included: journal, authors, year of publication, age, race, histotype, grading, tumor size at diagnosis, lymphovascular space invasion (LVSI), neoadjuvant chemotherapy (NACT), tumor dimension after NACT and response rate, type of FSS (abdominal radical trachelectomy [ART], vaginal radical trachelectomy [VRT], vaginal simple trachelectomy [VST], and conization), surgical approach (surgical access route: abdominal versus vaginal), type of nodal assessment (sentinel lymph node, pelvic and/or paraaortic lymphadenectomy) and approach used (laparotomy, laparoscopy, robotic), number of resected lymph nodes, number of positive lymph nodes, follow-up schedule, number of pregnancies (including miscarriages) for each patient, type of conception (spontaneous conception vs assisted reproduction), type of delivery (term vs preterm), recurrence rate, disease-free survival (DFS), and overall survival (OS). The three authors (C.G., S.C.M., S.G.) carried out data extraction and quality assessment from all the retrieved studies based on full-text articles. Discrepancies between the investigators were resolved by consensus.

3. Outcomes

The primary outcome of interest was the impact of FSS on oncological and fertility outcomes. In particular, for each eligible study cohort, the following outcomes were considered:

- DFS: the time from surgery until first relapse.
- OS: the time from surgery until death.
- Pregnancy rate: the ratio of the number of patients who had at least one pregnancy to the total number of patients wishing to conceive.
- Live birth rate: the ratio of the number of live-birth deliveries to the total number of pregnancies achieved.
- Premature delivery rate: the ratio of the number of premature deliveries (before 37 weeks of pregnancy) to the total number of pregnancies resulting in live births.

4. Statistical analysis

Survival curves were estimated for each group, considered separately, using the Kaplan-Meier method and compared statistically using the log rank test. As studies differed for different follow-up time frame, in order to reduce the risk of survival bias, a 5-years landmark analysis technique was applied by manually excluding patients with follow-up durations below or above the landmark's threshold.

RESULTS

1. Primary studies included in the literature review

A search of the MEDLINE (PubMed) database resulted in 766 relevant articles and further search in the Embase, Cochrane Library, Google Scholar databases yielded no additional articles. No additional eligible studies were retrieved by hand-searching bibliographies. Fifteen studies fulfilled the inclusion criteria for this systematic review, involving a total 48 patients (**Fig. S1**).

2. Study characteristics

The characteristics of included studies are detailed in **Table 1**. Among the 15 studies included, 9 studies (60%) were prospective [9,11,14-20], 2 (13.3%) were retrospective [8,21], and 4 (26.7%) were case reports [22-25]. No randomized controlled trials were found. Eight studies

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Table 1. Characteristics of included studies

Study characteristics	Studies (n=15)	Patients (n=48)
Publication years		
2005–2010	3 (20.0)	7 (14.6)
2011–2019	12 (80.0)	41 (85.4)
Study design		
Prospective	9 (60.0)	31 (64.6)
Retrospective	2 (13.3)	13 (27.1)
Case report	4 (26.7)	4 (8.3)
Institutional setting		
Monocentric*	8 (53.3)	24 (50.0)
Multicenter	7 (46.7)	24 (50.0)

Values are presented as number (%).
*Four studies were case reports [22-25].

(53.3%) were monocentric [8,16-18,22-25] and seven (46.7%) were multicentric [9,11,14,15,19-21]. Three studies (20%) were published between 2005 and 2010 [14,22,23], while 12 studies (80%) were published between 2011 and 2019 [8,9,11,15-21,24,25]. The definition of inclusion/exclusion criteria for FSS were available for 11 studies (73.3%) [8,9,11,14-21] (**Table S1**). Of note, one study reported as inclusion criteria for VRT tumors with stage IA1 with LVSI, IA2, and IB1 with no more than 2 cm; however, it reported also the case of one patient with 45-mm stage IB2 cervical cancer treated with VRT after NACT [18]. Four studies (26.7%) did not report exclusion criteria as they were case reports [22-25]. The most reported exclusion criteria were nodal metastases (10/11; 90.9%) followed by positive margins (5/11; 45.5%), distant metastasis (3/11; 27.3%), age >40 years (2/11; 18.2%), and aggressive histotypes (2/11; 18.2%).

Details regarding preoperative instrumental and laboratorial assessment were available for 13 studies (86.7%) [8,9,11,15-21,23-25] (**Table S2**). Pre-treatment evaluation consisted of magnetic resonance imaging (MRI) in the vast majority of the studies (12/13; 92.3%) followed by computed tomography (CT) (6/13; 46.2%), positron emission tomography (PET) (6/13; 46.2%), and colposcopy (5/13; 38.5%). Six (40%) out of 15 studies described the specific purpose of imaging. MRI [2,15,18,21,25] was used to determine tumor size and parametrial involvement, while CT [15,17,21,25] and PET [17,21] scans were carried out to evaluate the presence of lymph node or distant metastases. Of the 11 authors who included patients undergoing NACT, 3 did not report evaluation methods after NACT [17,18,22], while 2 others evaluated the response to NACT through imaging but did not specify the technique [8,25]. The criteria for defining the response to NACT were not unanimous throughout the included studies: 4 studies [8,11,17,22] reported the pathological response to NACT, while 6 [9,16,19,23-25] the radiological one. The most adopted assessment tools were MRI and colposcopy (5/6, 83.3%), followed by ultrasound (3/6, 50%).

The follow-up schedule was tailored individually for 34 patients (70.8%) with a weighted mean±standard deviation of 56.15±38.75 months. The remaining 14 patients (29.2%) were extracted from 3 cohorts who reported a median follow up of 90 months [20], 90 months [15], and 32 months [14], respectively.

3. Patient characteristics and surgical data

The characteristics of included patients are summarized in **Table 2**. For each variable, missing data are reported in **Table 2**.

Precise age was provided for 18 patients (37.5%) with a weighted mean of 28.61 years (median age: 28 years; 25th–75th percentile: 25.75–31.25 years). The remaining 30 patients (62.5%)

Table 2. Characteristics of patients selected (n=48)

Characteristics	Results*	Missing data
Age (yr)	28.61±4.12	30/48 (62.5[ND])
Lesion size at diagnosis (mm)	44.59±5.71	16/48 (29.2[ND])
Histotype		9/48 (8.7[NR])
Squamous cell carcinoma	25 (64.1)	
Adenocarcinoma	10 (25.6)	
Glassy cell carcinoma	3 (7.7)	
Adenosquamous carcinoma	1 (2.6)	
Grading		32/48 (66.7) (56.3[NR], 10.4[ND])
1	3 (18.8)	
2	8 (50)	
3	5 (31.2)	
LVSI		38/48 (79.2) (45.8[NR], 33.4[ND])
Positive	5 (50)	
Negative	5 (50)	
Lymphadenectomy		1/48 (2.1[ND])
Pelvic	40 (85.1)	
Pelvic and para-aortic	7 (14.9)	
NACT		1/48 (2.1[ND])
Yes	33 (70.2)	
No	14 (29.8)	
Lesion size post NACT† (mm)	7.25±10.87	1/33 (3[NR])
Response rate†		1/33 (3[NR])
Complete response	17 (53.1)	
Partial response	12 (37.5)	
Stable disease	3 (9.4)	

Results data are presented as mean±standard deviation or number (%). Missing data are presented as patients/total with (%).
LVSI, lymphovascular space invasion; NACT, neoadjuvant chemotherapy; NR, not reported; ND, not deducible from the cohorts synopsis.
*The percentage was calculated excluding missing data; †Reported for cohort of patients submitted to NACT before surgery (n=33) [8,9,11,16-19,22-25].

were extracted from cohorts who reported median age ranging between 28 and 32 years [8,20] and mean age ranging from 30.5 and 32.5 years [14,15,17,21], respectively.

Data about histology were reported for 39 patients (81.3%): 25 (64.1%) presented with squamous cell carcinoma, 10 (25.6%) with adenocarcinoma, 3 (7.7%) with glassy cell carcinoma, and 1 (2.6%) with adenosquamous carcinoma. Tumor grading was available for 16 patients (33.3%): 8 patients (50%) had grade 2 tumor, 5 (31.2%) grade 3, and 3 (18.8%) grade 1.

Thirty-three patients underwent NACT and 14 did not. The maximum tumor diameter at diagnosis was reported in exact millimeters for 34 patients (70.8%), whereas it was only known to be ≥4 cm for the remaining 14 patients (29.2%). The weighted mean tumor maximum diameter at diagnosis was 44.59±5.71 mm (median: 42 mm; 25th–75th percentile: 40–50 mm) (NACT group [n=33]: 44.42±5.7 mm [median: 42 mm; 25th–75th percentile: 42–47.5 mm]; non-NACT group [n=1]: 50 mm). The LVSI was specified for 10 patients (20.8%), being positive in 5 patients (50.0%) and negative in 5 patients (50.0%).

Among the 33 patients who underwent NACT, data about post-NACT tumor size were reported for 32 patients. The weighted mean post-NACT tumor size was 7.25±10.87 mm (median: 0 mm; 25th–75th percentile: 0–14.25 mm). Seventeen patients (53.1%) had a complete response (11 pathological [8,11,17,22] and 6 radiological [16,19,25]), 12 (37.5%) a partial response (4 pathological [8] and 8 radiological [9,16,19,23,24]) and 3 (9.4%) a stable disease (pathological [8]).

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All 48 patients underwent trachelectomy as fertility-sparing surgery. The most adopted surgical route was open abdominal (31 out of 48 procedures; 64.6%), followed by vaginal (17/48; 35.4%). Among the 17 patients who underwent vaginal trachelectomy, one was robotic-assisted (5.9%), 5 (29.4%) were laparoscopic-assisted, while 11 (64.7%) were exclusively vaginal. Furthermore, among patients who underwent vaginal trachelectomy, 14 (82.4%) were radical (1 robotic-assisted and 13 purely) and 3 (17.6%) were simple.

Data about lymphadenectomy were available for 47 patients. Forty (85.1%) patients underwent pelvic lymphadenectomy, 7 (14.9%) women had both pelvic and para-aortic lymphadenectomy. The most used surgical approach for lymphadenectomy was laparoscopy (60.4%), followed by open abdominal surgery (37.5%) and robotic surgery (2.1%). Lymphadenectomy was performed in all patients: before FSS in 8 patients (16.7%) and during FSS in 40 patients (83.3%). Of note, the timing of lymphadenectomy among patients receiving NACT differed between the studies: lymphadenectomy was the first-step during FSS in 27 (81.8%) patients [8,11,17-19,23-25], while it was performed before NACT in 6 (18.2%) patients [9,16,22]. The exact number of removed lymph nodes was available for 30 patients (62.5%) with a weighted mean of 22.4±9.58 (median: 19; 25th–75th percentile: 17–25.5). The remaining 18 patients (37.5%) were extracted from three cohorts that reported a median of 24 [15,21] and a mean of 32.2 lymph nodes being removed [14].

4. Oncological outcomes

Three women (6.3%) experienced a recurrence and one of them (2.1%) died of disease. Therefore, the occurrence of a relapse was fatal in 33% of cases. The median DFS was not reached and the 5-year DFS rate was 92.4%. The 5-year OS rate was 97.6%.

There was no statistically significant difference between patients who received NACT before FSS and those who underwent upfront FSS in terms of 5-year DFS (91% vs. 92.9%, respectively; p=0.946) and 5-year OS (100% vs. 92.9%, respectively; p=0.173).

Although lacking the statistical significance, a trend towards worse 5-year DFS rate was reported for adenocarcinoma (71.4%) and glassy cell (66.7%) histologies compared with squamous cell (log-rank test, p=0.070) (**Fig. 1A**), for grade 3 (50%) compared with grade 1–2 (100%) (log-rank test, p=0.060) (**Fig. 1B**), and for tumors ≥5 cm (74.1%) compared with those <5 cm (94.4%) (log-rank test, p=0.131).

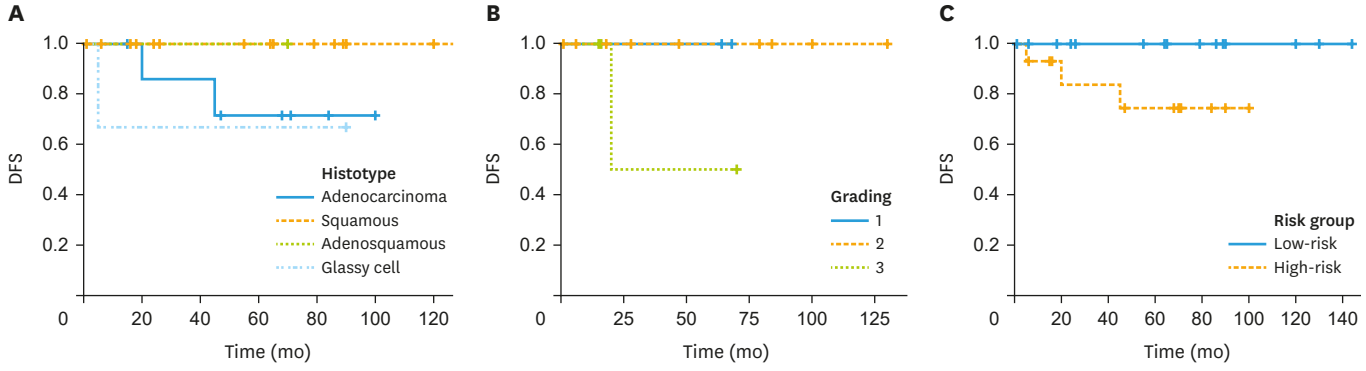

Fig. 1. Survival outcomes, Kaplan-Meier plots for patients with early-stage cervical cancer ≥4 cm treated with FSS. (A) DFS according to histotype; log-rank (Mentel-Cox), p=0.070. (B) DFS according to histologic grading; log-rank (Mentel-Cox), p=0.060. (C) DFS according to risk group; log-rank (Mentel-Cox), p=0.024.
DFS, disease-free survival; FSS, fertility-sparing surgery.

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Given the strict interdependency between these three factors, patients were classified into 2 subgroups: 1) "high-risk" if they had at least one of the following factors: adenocarcinoma/glassy cell histology, G3, or diameter ≥5 cm; 2) "low-risk", if none of these risk factors was present. A significantly lower 5-year DFS was reported for high-risk patients compared with low-risk (74.7% vs. 100%; log-rank test, p=0.024) (**Fig. 1C**).

Moreover, concerning the three patients who reported a recurrence, the first patient had a diagnosis of 5-cm glassy cell carcinoma and underwent ART plus pelvic lymphadenectomy. A pelvic side-wall recurrence occurred 5 months after primary treatment and, due to the failure of chemo-radiotherapy, a pelvic exenteration was performed. The patient died of disease 16 months after FSS [20]. The second recurrence occurred in a 37-year-old patient affected by G3 adenocarcinoma of the cervix. The patient underwent laparoscopic staging plus lymphadenectomy and 2 cycles of NACT with a partial response (62.5%). Twenty months after VRT, the patient had a pelvic recurrence successfully treated with posterior exenteration and chemoradiation [16]. The third patient had a 5-cm tumor (adenocarcinoma) and underwent NACT with a complete response. A recurrence was diagnosed 45 months after ART and the patient underwent hysterectomy with lymphadenectomy. In July 2018, the patient was alive without evidence of disease [8].

5. Fertility outcomes

Data about fertility were available for 12 patients (25%): 5 attempted to conceive (41.7%) [9,17,24], while 7 did not (58.3%) [17,19,23]. Most relevant data about those patients are summarized in **Table 3**. Of the 5 patients who attempted to conceive, 4 conceived (pregnancy rate: 80%) with a total of 6 pregnancies (patient #2 and #4 had 2 pregnancies including an ectopic pregnancy) and gave birth to five children in total (live birth rate: 83.3%). Four pregnancies were carried at term (80%) [17], whereas one ended with a preterm labor (premature delivery rate: 20%) [24]. In all five cases, a caesarean section (CS) was performed. Concerning the type of radical trachelectomy, 3 of these patients (3/4; 75%) had been treated with open ART [17,24], while 1 with VRT (1/4; 25%) [9]. All 4 patients underwent NACT before trachelectomy. Unfortunately, none of the studies reported data about the following surgical treatment after delivery, whether patients underwent standard treatment. Given the small number of patients who attempted to conceive, no statistical analysis was performed.

Table 3. Obstetrical outcomes and characteristics of pregnant patients after FSS

Patients	Patient 1	Patient 2	Patient 3	Patient 4
Study	Tsuji et al. [24]	van Gent et al. [17]	van Gent et al. [17]	Vercellino et al. [9] Gottschalk et al. [26]
Dimension of tumor (mm)	40	40	40	42
Histotype	SCC	SCC	SCC	ASC
NACT (yes/no)	Yes	Yes	Yes	Yes
Response to NACT	PR	PR	PR	PR
Type of surgery	ART	ART	ART	VRT
Pregnancies	1	2	1	2*
Pregnancies with birth	1	2	1	1
Time to first pregnancy with birth†	48 mo	NR	NR	16 mo
Type of conceive	Artificial	ND ND	ND	Spontaneous
Complication during pregnancy	Yes	ND ND	ND	Yes
Type of delivery	CS	CS CS	CS	CS
Term/preterm	Preterm	Term Term	Term	Term

ASC, adenosquamous carcinoma; ART, abdominal radical trachelectomy; CS, caesarean section; FSS, fertility-sparing surgery; NACT, neoadjuvant chemotherapy; ND, not deducible; NR, not reported; PR, partial response; SCC, squamous cell carcinoma; VRT, vaginal radical trachelectomy.
*One was an ectopic pregnancy; †Starting from FSS.

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Briefly, the first patient managed to conceive through in vitro fertilization-embryo transfer (IVF-ET) after five attempts with artificial inseminations [24]. The pregnancy was complicated by threatened abortion and a cervical cerclage was performed at 13 weeks of gestation. Absolute bed rest was prescribed from around 16 weeks. Rupture of the membrane occurred at 27 weeks and 8 days later an emergent CS was performed. After 5 years, the baby was growing healthily. The second patient, who had a 4-cm tumor and underwent ART after NACT, had 2 pregnancies, both ended with a term delivery through CS [17]. The third patient within the ART group underwent CS at term, but data regarding the type of conception and the course of pregnancy were missing [17]. Finally, the only patient in the VRT group conceived spontaneously after a first ectopic pregnancy managed with methotrexate [9,26]. There were no significant consequences related to the previous trachelectomy (i.e., no cervical shortening, vaginal bleeding, or threatened preterm labor); the patient developed gestational diabetes treated with insulin. An elective CS was performed at 38 weeks of gestation. The new-born was healthy and weighted 3,500 g and the infant development was normal.

DISCUSSION

According to current international guidelines, the presence of nodal metastasis is an absolute exclusion criteria for FSS in patients with cervical cancer [4,27]. The tumor size at diagnosis represents the key element in order to offer a tailored treatment not only aiming to the best oncological outcomes but also to the best quality of life. To date, only few studies have been reported on FSS for stage I cervical cancer ≥4 cm and they differ with respect to inclusion/exclusion criteria, thus providing heterogeneous cohort populations and making it challenging to draw definitive conclusions. Overall, in the literature, only 48 women with stage I cervical cancer ≥4 cm and a strong desire to preserve their fertility have completed the FSS.

There is no consensus amongst clinicians regarding the best treatment strategy for cervical tumors >2 cm between upfront FSS and NACT followed by FSS. The lack of clinical evidence prevents from drawing definitive conclusions. If on one hand, NACT, potentially allows to shrink the tumor volume, increase the resectability and reduce the radicality of surgical procedures, on the other hand, it may impair the ovarian reserve.

In a recent comprehensive review on FSS in cervical cancer patients with tumors of 2–4 cm, no differences in terms of oncological and fertility outcomes were reported in patients undergoing NACT before surgery and upfront abdominal radical trachelectomy [6]. The present analysis is the first one to exclusively evaluate tumors greater than 4 cm and, in line with previous literature [6], we failed to find any differences in terms of oncological and fertility outcomes between patients who received NACT before surgery and those who underwent upfront FSS. However, data are low powered for this sub-analysis.

In the present systematic review, the feasibility rate of FSS among these patients was 78.7% (48 out of 61 patients). However, since most of the studies were retrospective, this rate could be limited by selection bias. The 5-year OS rate for patients who completed the FSS was 97.6%. Therefore, it can be hypothesized that even patients with tumor ≥4 cm have a favorable long-term prognosis after FSS, as long as they are carefully selected. The recurrence rate was promising (5-year DFS: 92.4%), considering that these patients underwent conservative treatments even in the presence of a bulky disease. However, when the recurrence occurred, it was fatal in 33% (1 out of 3) of cases.

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Although not statistically significant, there was a trend towards a higher probability of recurrence in the presence of some risk factors, including grade 3 histology, non-squamous cell histotypes and tumor diameter ≥5 cm. Patients with at least one of the previous factors belong to the high-risk group for a poor prognosis. On the contrary, patients within the low-risk group had a good prognosis with no recurrences or deaths reported. These findings are pivotal, as they guide physicians to assess the pre-treatment risk and to offer the most safe and tailored treatment for each patient.

Data collection and classification of patient cohorts were challenging as many subtypes of procedures, various concepts of radicality, and variable anatomical definitions have been reported. The description of fertility-sparing procedures as regards the access route and the route for specimen extraction was not fully comprehensive and varied widely among selected studies, thus impairing a unanimous interpretation. Moreover, even if not clearly reported, ART is generally considered a potentially more radical procedure than VRT. However, ART, especially after NACT, may allow for tailored parametrectomy; thus, considering ART a surrogate of higher radicality could be erroneous. In the future, a universally homogenous report of techniques for communication, comparison, clinical research, and quality control is warranted.

Our suggestion is to explicitly indicate approach (abdominal or vaginal), route for specimen extraction (abdominal or vaginal), techniques used (laparotomic, vaginal, laparoscopic, or robotic surgery), and type of radicality of parametrectomy according to Querleu-Morrow classification [28].

Currently, a standard protocol of NACT for early-stage cervical cancer does not exist. However, considering the comparable efficacy and reduced toxicity, platinum-based dose-dense schedule has been suggested as a valid option compared to 3-weekly administration [29].

As regards the obstetrical outcomes, few data exist. The present analysis does not allow conclusions to be drawn on the type of techniques that offers greater chances to become pregnant and deliver a child at term. However, all pregnant patients have previously undergone NACT and probably a less radical surgery. Interestingly, only 1 patient had obstetrical complications related to FSS and the same patients was the only one delivering preterm. Surprisingly, to our knowledge, the vast majority of patients undergoing an experimental fertility-sparing procedure (tumor ≥4 cm) despite the acceptance of a higher risk of recurrence, did not attempt to conceive. Therefore, in our opinion, in order to safely manage patients requiring FSS affected by large tumor, it is absolutely recommended to carefully select patients at the time of diagnosis, not only on the basis of their strong desire to preserve fertility but also considering their real chances of attempting to conceive and achieving a pregnancy (favorable age, presence of a partner, anti-Müllerian hormone levels, co-morbidities that can interfere with pregnancy such as endometriosis [30], feasibility of providing assisted reproductive technologies). Patients with stage I cervical cancer of 4 cm or larger with strong desire to preserve fertility should be treated in the context of clinical trials in dedicated leading centers. Moreover, assisted reproductive technology should be offered to women who fail to achieve a pregnancy spontaneously after few attempts. Finally, the optimal treatment following childbirth still remains unclear and warrants further investigation.

Currently, there is no sufficient evidence to recommend FSS for patients with stage I cervical cancer greater than 4 cm in clinical practice and this strategy is still considered experimental. Oncologic outcomes are encouraging among low-risk patients (squamous histotype, G1–G2,

and diameter below 5 cm); nevertheless, the lack of high-quality studies makes it difficult to draw any firm conclusions. Women with high tumor grade, aggressive histology, and tumor size ≥5 cm have a higher risk of recurrence and FSS should be proposed only warning patients on the higher recurrence rate. Additionally, the low rate of attempt to conceive highlights the need of adequate counselling in patients with cervical cancer of 4 cm or larger who are willing to preserve their childbearing potential. Prospective clinical trials with a proper selection of inclusion/exclusion criteria should be conducted in women with low-risk factors, strong desire to preserve their fertility and high likelihood to conceive.

SUPPLEMENTARY MATERIALS

Table S1

Inclusion and exclusion criteria for FSS reported in selected studies

Click here to view

Table S2

Assessment at diagnosis and after NACT according to selected studies

Click here to view

Fig. S1

PRISMA flow chart.

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