



## Review

# Immediate radical trachelectomy versus neoadjuvant chemotherapy followed by conservative surgery for patients with stage IB1 cervical cancer with tumors 2 cm or larger: A literature review and analysis of oncological and obstetrical outcomes



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## HIGHLIGHTS

- Fertility preservation is feasible after neoadjuvant chemotherapy and conservative surgery
- Overall pregnancy rates are higher after neoadjuvant chemotherapy and surgery in patients with stage IB1 (2–4 cms) tumors
- The recurrence rate was 7.6% after neoadjuvant chemotherapy followed by conservative surgery in tumors >2cms

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## ABSTRACT

Radical trachelectomy is the treatment of choice in women with early-stage cervical cancer wishing to preserve fertility. Radical trachelectomy can be performed with a vaginal, abdominal, or laparoscopic/robotic approach. Vaginal radical trachelectomy (VRT) is generally not offered to patients with tumors 2 cm or larger because of a high recurrence rate. There are no conclusive recommendations regarding the safety of abdominal radical trachelectomy (ART) or laparoscopic radical trachelectomy (LRT) in such patients. Several investigators have used neoadjuvant chemotherapy in patients with tumors 2 to 4 cm to reduce tumor size so that fertility preservation may be offered. However, to our knowledge, no published study has compared outcomes between patients with cervical tumors 2 cm or larger who underwent immediate radical trachelectomy and those who underwent neoadjuvant chemotherapy followed by radical trachelectomy. We conducted a literature review to compare outcomes with these 2 approaches. Our main endpoints for evaluation were oncological and obstetrical outcomes. The fertility preservation rate was 82.7%, 85.1%, 89%, and 91.1% for ART (tumors larger than >2 cm), ART (all sizes), NACT followed by surgery and VRT (all sizes); respectively. The global pregnancy rate was 16.2%, 24% and 30.7% for ART, VRT, and NACT followed by surgery; respectively. The recurrence rate was 3.8%, 4.2%, 6%, 7.6% and 17% for ART (all sizes), VRT (all sizes), ART (tumors >2 cm), NACT followed by surgery, and VRT (tumors >2 cm). These outcomes must be considered when offering a fertility sparing technique to patients with a tumor larger than 2 cm.

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## 1. Introduction

The American Cancer Society estimates that in 2014, there were 12,360 new cases of cervical cancer and 4020 cervical cancer-related deaths [1]. In women with early-stage cervical cancer wishing to preserve fertility, radical trachelectomy produces acceptable oncological and obstetrical outcomes. Radical trachelectomy can be performed with a vaginal, abdominal, laparoscopic, or robotics approach. According to the 2014 National Comprehensive Cancer Network (NCCN) cervix cancer guidelines, radical trachelectomy is acceptable for patients with early-stage cervical cancer (stages IA1 with lymph-vascular space invasion, IA2, and IB1) interested in future fertility; however, the guidelines also note that “fertility-sparing surgery for stage IB1 has been most validated for tumors < 2 cm” [2]. It is almost universally accepted that vaginal radical trachelectomy (VRT) should not be offered to patients with tumors 2 cm or larger because of a high relapse rate (22%) [3]. Currently, there are no conclusive recommendations regarding the safety of upfront abdominal radical trachelectomy (ART), laparoscopic radical trachelectomy (LRT), or robotic radical trachelectomy (RRT) in patients with tumors 2 cm or larger. Given the higher relapse rate after radical trachelectomy among patients with cervical tumors 2 cm or larger, administration of neoadjuvant chemotherapy before radical trachelectomy has been explored in such patients who desire future fertility [4]. However, to our knowledge, no published study has compared outcomes between patients with cervical tumors 2 cm or larger who underwent immediate radical trachelectomy and those who underwent neoadjuvant chemotherapy followed by radical trachelectomy.

We sought to compare outcomes with these 2 approaches. We reviewed the published literature on conservative management of cervical cancer in patients with tumors 2 cm or larger and analyzed the intraoperative and postoperative surgical outcomes as well as oncological and obstetrical outcomes.

## 2. Materials and methods

We performed a review of the English-language literature on fertility-sparing surgery in patients with cervical cancer with tumors 2 cm or larger. The MEDLINE, EMBASE, and CINAHL databases were searched for articles published from 1994 through 2014. The terms used in the search were *uterine cervix neoplasms, early cervical cancer, tumor size, abdominal radical trachelectomy, vaginal radical trachelectomy, laparoscopic radical trachelectomy, robotic radical trachelectomy, fertility-sparing surgery, neoadjuvant chemotherapy* and *fertility preservation*. Reference lists of all articles identified by our searches were reviewed to identify additional articles. We excluded articles with duplicate patient information, and for articles updating prior published series, we included only the more recently published article.

We reviewed each relevant article for information about patient and tumor characteristics (age, tumor size), details of neoadjuvant chemotherapy (if delivered), type of surgery, lymph node status, intraoperative and postoperative surgical outcomes, recurrences, deaths, fertility preservation (means the uterus was preserved, regardless of the technique used), and pregnancies. The data of interest were summarized using measures of central tendency and dispersion for continuous

variables and proportions for categorical or ordinal variables. The results of the frequencies of the different variables were assessed using descriptive statistics. The data were analyzed using STATA software, version 12.1.

## 3. Results

In our review of the literature, we found reports on a total of 394 women with cervical tumors 2 cm or larger who attempted to preserve fertility. A total of 329 patients had immediate radical trachelectomy: ART in 191 patients, VRT in 99 patients, and LRT in 39 patients. The other 65 patients underwent neoadjuvant chemotherapy followed by radical trachelectomy. The order in which we discuss articles in the text does not directly match the chronological order in which articles are presented in the tables because some articles specifically reported on comparison of patients with tumors 2 cm or larger while others reported on such patients as part of the overall study cohorts.

### 3.1. Immediate radical trachelectomy

#### 3.1.1. Abdominal radical trachelectomy

We identified 10 published series of immediate ART in patients with tumors 2 cm or larger (Table 1). The largest of these series were those published by Wethington et al. [5], Lintner et al. [6], and Li et al. [7], which together included 127 patients; the other 7 series included 64 patients, for a total of 191 patients. Overall, 12 patients (6%) had relapse, 2 patients (1%) died, and 158 patients (82.7%) had fertility preserved.

Wethington et al. [5] reported on 29 patients with tumor size of 2 to 4 cm. The median patient age was 31 years (range, 22–40 years). Twenty-two patients underwent ART, 6 patients underwent VRT, and 1 patient underwent RRT. One trachelectomy was aborted because of macroscopic pelvic nodal involvement, and the patient was treated with chemoradiotherapy. Six additional patients underwent chemoradiotherapy after trachelectomy because they had high-risk disease features. After trachelectomy, 4 patients were converted to radical hysterectomy, and also nine additional patients were converted to radical hysterectomy and received adjuvant chemoradiotherapy. Thirteen of

**Table 1**

Reported outcomes of immediate abdominal radical trachelectomy in patients with cervical tumors larger than 2 cm.

First author (year)	No. of patients with			
	Planned surgery	Relapse	Death	Fertility preserved
Nishio (2009) [8]	13	5	NR	13 (100%)
Cibula (2009) [10]	6	0	0	5 (83%)
Karateke (2010) [11]	5	0	0	5 (100%)
Du (2011) [9]	12	2	NR	12 (100%)
Saso (2012) [12]	5	1	NR	5 (100%)
Testa (2013) [13]	4	0	0	4 (100%)
Cao (2013) [14]	19	0	0	19 (100%)
Li (2013) [7]	62	0	0	55 (89%)
Lintner (2013) [6]	45	4	2	31 (69%)
Wethington (2013) [5]	22	0	0	9 (41%)
Total	191	12 (6.2%)	2 (1%)	158 (82.7%)

Abbreviation: NR: not reported.

the 29 patients (45%) had positive pelvic nodes. At a median follow-up time of 44 months (range, 1–90 months), the authors reported 1 patient with relapse, 9 months after a RRT. The recurrent disease involved the right adnexa, iliac nodes, and peritoneum. The patient was alive 18 months after the relapse. There were no deaths reported. Fertility was preserved in 9 of 29 patients (31%). Of these 9 patients, 2 attempted to get pregnant, and neither was successful. There was 1 unintended pregnancy, and this ended in an elective pregnancy termination.

Lintner et al. [6] reported on 45 patients with tumors larger than 2 cm. Thirty-one patients (69%) underwent definitive ART. Of these, 17 patients had tumors 2–4 cm, and 14 patients had stage IB2 disease. The other 14 patients required a conversion to radical hysterectomy. The reasons for conversion were lymph node metastasis (in 9 patients), positive endocervical surgical margin (3 patients), injury of the ovarian artery (1 patient), and parametrial tumor spread (1 patient). Of the 31 patients who underwent definitive ART, 4 patients had positive lymph nodes and these were treated with adjuvant chemotherapy (3) or neoadjuvant chemotherapy (1). At a median follow-up time of 90 months (range, 60–148 months), 4 patients who had undergone definitive ART had a relapse, and 2 had died of disease. Four pregnancies occurred in 3 patients. There was 1 miscarriage during the first trimester, and there were 3 deliveries, 1 preterm and 2 at term.

Li et al. [7] reported on 62 patients with tumors 2 to 4 cm that underwent ART. The median patient age was 30.4 years (range, 20–44 years). Six patients (10%) had conversion to radical hysterectomy (4 because of positive pelvic nodes and 2 because of an involved endocervical margin), and all 6 received adjuvant chemotherapy and radiation therapy. Of the 56 patients who underwent definitive ART, three (4.8%) patients were found to have positive lymph nodes on final pathology. This totaled seven (11.6%) patients who had positive nodes. A total of 21 (38%) patients received adjuvant therapy (chemoradiotherapy in 1 patient and chemotherapy alone in 20 patients). The reasons for chemotherapy administration were positive pelvic nodes (in 2 patients), deep stromal invasion (7 patients), lymph-vascular space invasion (5 patients), and both deep invasion and lymph-vascular space invasion (6 patients). Fertility was preserved in 55 patients (89%). At a median follow-up time of 30.2 months (range, 2–108 months), there had been no relapses. Three pregnancies occurred; at the time of the report, there had been 1 term delivery, and 2 pregnancies were ongoing.

In the 7 additional series [8–14] of patients who underwent ART for tumors measuring 2 to 4 cm (Table 1), calculations on obstetrical outcome were not possible because obstetrical outcomes were reported for the entire cohort and not for patients with specific tumor sizes.

### 3.1.2. Vaginal radical trachelectomy

We identified 8 published series of immediate VRT in patients with tumors 2 cm or larger (Table 2) [5,14,16–21]. The series included a total of 99 patients. Obstetrical calculations were not possible, given the authors did not differentiate the obstetrical outcome with tumor sizes in any of the reviewed papers. Overall, 17 patients (17%) had recurrence, and 4 patients (4%) died.

**Table 2**

Reported outcomes of immediate vaginal radical trachelectomy in patients with cervical tumors larger than 2 cm.

First author (year)	Planned surgeries	Relapse	Death
Beiner (2007) [20]	8	1	0
Marchiole (2007) [21]	27	6	0
Pahisa (2008) [17]	3	1	1
Chen (2008) [19]	7	0	0
Lanowska (2011) [18]	6	1	0
Plante (2011) [16]	19	3	1
Wethington (2013) [5]	6	0	0
Cao (2013) [14]	23	5	2
Total	99	17 (17%)	4 (4%)

The relapse rate after VRT is approximately 3% for tumors smaller than 2 cm [15] but may be as high as 22% for tumors 2 cm or larger [3]. Thus, it is widely agreed that VRT should be restricted to women wishing to preserve fertility, without high-risk histology, with tumors smaller than 2 cm [3]. Plante et al. [16] reported 6 recurrences among 125 patients who underwent VRT, and 3 of the 6 recurrences occurred in patients with lesions larger than 2 cm ( $p = 0.002$ ). Cao et al. [14] compared 77 patients who underwent VRT and 73 patients who underwent ART. In the VRT group, 24 of 77 patients (31%) had tumors measuring 2 to 4 cm, whereas in the ART group, 24 of 73 patients (33%) had tumors measuring 2 to 4 cm. The investigators found that the relapse rate was 22% (5/23) for patients who underwent VRT, compared to zero for patients who underwent ART.

### 3.1.3. Laparoscopic radical trachelectomy

The largest series on immediate LRT was published by Park et al. [34] in 2014 and included 88 patients. Fertility preservation was achieved in 79 patients, and 29 of these (37%) patients had a tumor size of 2 to 4 cm. The authors found a 5-year median disease-free survival of 76 months for patients with tumors larger than 2 cm and 89 months for patients with tumors 2 cm or smaller ( $p = 0.039$ ). The recurrence rate after a median follow up of 44 months (range, 3–105) was 6% (1/40) for tumors smaller than 2 cm, compared with 20% (6/30) for tumors 2 cm or larger ( $p = 0.016$ ). The denominator for recurrence rate adds to 70, because the authors excluded patients that received adjuvant chemotherapy. The authors concluded that tumor size of 2 cm or larger is a risk factor for recurrence after LRT.

To date, 225 cases of immediate LRT have been reported in the literature [22–34]. Overall, 13 patients (5.7%) had relapses, and 4 patients (1.7%) died. Among the 39 patients with tumors measuring 2 to 4 cm, there were 8 relapses, for a relapse rate of 21%. These figures are very similar to the reported relapse rates for tumors 2 cm or larger after VRT.

### 3.2. Neoadjuvant chemotherapy prior to surgery

We identified a total of 14 reports [35–48] addressing the use of neoadjuvant chemotherapy in patients with early-stage cervical cancer interested in future fertility. These reports included 73 patients with tumor size of 2 to 4 cm (Table 3). (Table 3 summarizes 12 rather than 14 reports because 2 of the reports we found, by Vercellino et al. [44] and Lanowska et al. [48], had overlapping patients, and we have described those patients only once in the table. In addition the patient reported by Gottschalk et al. [37], is included in the Lanowska's case series).

Overall, a total of 8 patients did not preserve fertility and among the remaining 65 patients who preserved fertility after neoadjuvant chemotherapy, 20 pregnancies were reported, with 16 deliveries (6 preterm and 10 at term), 2 ongoing pregnancies, 1 ectopic pregnancy, and 3 miscarriages (some women delivered more than one baby). The overall pregnancy rate was 30.7% (20/65). The fertility preservation rate after neoadjuvant chemotherapy was 89% (65/73). The relapse rate was 7.6% (5/65), and the death rate was 3% (2/65).

Six reports [35–40] included only 1 patient each with tumors > 2 cm. None of these 6 patients had a recurrence or died of disease. Among these 6 patients, 3 pregnancies were reported in 3 patients, resulting in 1 preterm delivery and 2 term deliveries. The follow-up times ranged from 14 to 48 months. The types of surgeries performed after chemotherapy were conization without lymphadenectomy [35], simple trachelectomy and laparoscopic pelvic lymphadenectomy [36], VRT and laparoscopic pelvic/paraortic lymphadenectomy [37], ART and pelvic lymphadenectomy [38], VRT and pelvic lymphadenectomy [39], and RRT with pelvic/paraortic lymphadenectomy and bilateral tubal reanastomosis [40]. A total of 10 patients underwent neoadjuvant chemotherapy followed by conization [43,46]. There were no relapses reported in those patients.

The remaining reports described 2 or more patients and will be discussed individually in the following paragraphs.

**Table 3**  
Studies on neoadjuvant chemotherapy in tumors larger than 2 cm.

First author (year)	Attempted	Preserved	Stage	Neoadjuvant chemotherapy	Surgery	Disease-free survival, median (range), mo	Deaths	Pregnancies	Miscarriages	Births
Plante (2006) [42]	3	3	IB1	Paclitaxel 175 mg/m <sup>2</sup> day 1 Cisplatin 75 mg/m <sup>2</sup> day 2 Ifosfamide 5 g/m <sup>2</sup>	Laparoscopic PND and VRT	(48–57)	0	0	0	0
Kobayashi (2006) [35]	1	1	IB1	Cisplatin 10 mg/m <sup>2</sup> Bleomycin 5 mg/m <sup>2</sup> Vincristine 0.7 mg/m <sup>2</sup> Mitomycin C 7 mg/m <sup>2</sup>	Cold-knife conization	48	0	1	0	1
Landoni (2007) [43]	2 <sup>a</sup>	2	IB1	Cisplatin 75 mg/m <sup>2</sup>	Laparoscopic PND and laser conization	ND	0	0	0	0
Maneo (2008) [46]	8 <sup>b</sup>	8	IB1	Paclitaxel 175 mg/m <sup>2</sup> Ifosfamide 5 g/m <sup>2</sup>	Cold-knife conization and PND	69 (10–124)	0	NR	NR	NR
Liu (2008) [38]	1	1	IB1	(Epirubicin 80 mg/mq for adenocarcinomas) Bleomycin 15 mg/m <sup>2</sup> days 1 and 2 Cisplatin 70 mg/m <sup>2</sup> day 1	Transabdominal PND and ART	ND	0	1	0	1
Palaia (2011) [36]	1	1	IB2	Paclitaxel 175 mg/m <sup>2</sup> Ifosfamide 5 g/m <sup>2</sup>	Laparoscopic PND and vaginal simple trachelectomy	18	0	0	0	0
Marchiole (2011) [45]	7	7	IB-IIA1	Cisplatin 75 mg/m <sup>2</sup> Paclitaxel 175 mg/mq Ifosfamide 5 g/m <sup>2</sup>	Laparoscopic PND and VRT	22 (5–49)	0	1	0	0
Singh (2011) [39]	1	1	IB1	Paclitaxel 175 mg/m <sup>2</sup> (Epirubicin 80 mg/mq for adenocarcinomas)	Laparoscopic PND and VRT	14	0	0	0	0
Hamed (2012) [40]	1	1	IB1	Paclitaxel 135 mg/m <sup>2</sup> Cisplatin 50 mg/m <sup>2</sup>	RRT, PND, periaortic lymph node dissection, and tubal anastomosis	16	0	0	0	0
Wang (2013) [41]	2	2	IB1	Cisplatin 100 mg/m <sup>2</sup> day 1 5-fluorouracil 1000 mg/m <sup>2</sup> days 1–4 Bleomycin 15 mg/m <sup>2</sup> day 1	Laparoscopic PND and VRT	84	0	0	0	0
Lanowska (2014) [47]	18	18	IB1, IB2, IIA	Cisplatin 25 mg/m <sup>2</sup> days 1–3 Cisplatin 100 mg/m <sup>2</sup> Paclitaxel 200 mg/m <sup>2</sup> Ifosfamide 5 g/m <sup>2</sup>	PND, para-aortic node dissection, and VRT	23.1 (1–88)	1	7	2 <sup>d</sup>	4
Robova (2014) [48]	28	20	IB1	Cisplatin 75 mg/m <sup>2</sup> Ifosfamide 2 g/m <sup>2</sup> (Doxorubicin 35 mg/m <sup>2</sup> for adenocarcinoma)	SLN identification, PND, simple trachelectomy	NR	4	10	2	10
Total	73	65/73 (89%)					5/65 (7.6%)	20/65 (30.7%)	4/65 (6.1%)	16/65 (24.61%)

Abbreviations: ART: abdominal radical trachelectomy; NR: not reported; PND: pelvic node dissection; RRT: robotic radical trachelectomy; SLN: sentinel lymph node; VRT: vaginal radical trachelectomy.

<sup>a</sup>One pregnancy ongoing at time of report.

<sup>b</sup>Landoni, from 11 patients, just 2 received NACT, no data on pregnancy result related with tumor size. No data on PFS and OS, related with tumor size.

<sup>c</sup>Original study included 16 patients, but only 8 had tumors larger than 2 cm.

<sup>d</sup>One was an ectopic pregnancy.

Wang et al. [41] reported on 2 patients (tumor size of 2.5 cm and 3.5 cm, respectively) who received neoadjuvant chemotherapy followed by VRT and laparoscopic pelvic lymphadenectomy. No relapses or pregnancies had occurred at follow-up times of 69 months for one patient and 99 months for the other patient.

Plante et al. [42] reported on 3 patients (tumor size, 2–4 cm) who underwent neoadjuvant chemotherapy followed by VRT and laparoscopic pelvic lymphadenectomy. At follow-up times ranging from 48 to 57 months, there had been no recurrences or deaths, and no pregnancies had been reported. Landoni et al. [43] reported on 2 patients who underwent neoadjuvant chemotherapy followed by laser conization and laparoscopic pelvic lymphadenectomy. At a median follow-up time of 20 months, no relapses or deaths and no pregnancies had occurred. Vercellino et al. [44] published a study highlighting the need for pelvic nodal assessment before neoadjuvant chemotherapy in women with stage I cervical cancer larger than 2 cm seeking fertility preservation. In that study, the patients underwent laparoscopic pelvic and para-aortic lymphadenectomy, and when no nodal metastasis was detected, neoadjuvant chemotherapy followed by VRT was offered. If nodal metastasis was present, patients received primary chemotherapy and radiation therapy. Of the 18 women in the study, 12 (66%) were diagnosed with metastasis in 1 or more pelvic and/or para-aortic lymph nodes and thus received primary chemoradiation; 6 patients (33%) received neoadjuvant chemotherapy and VRT and were included in the report by Lanowska et al., described below [47]. The authors concluded that patients with stage I cervical cancer, primary tumors measuring 2 to 4 cm, and desiring to preserve fertility should undergo histopathologic evaluation of lymph nodes before consideration of fertility-sparing surgery.

Marchiole et al. [45] reported the outcomes of 7 patients (4 with squamous carcinoma and 3 with adenocarcinoma) with disease stages ranging from IB1 to IIA1. Four patients had tumors measuring 2 to 4 cm, and 3 patients had tumors larger than 4 cm. All were treated with neoadjuvant chemotherapy followed by VRT and laparoscopic pelvic lymphadenectomy. At a median follow-up time of 22 months (range, 5–49 months), no relapses or deaths had occurred, and there was 1 ongoing pregnancy.

Maneo et al. [46] published a study on 21 patients with cervical tumors ranging in size from 1 to 3 cm who received neoadjuvant chemotherapy. Only 8 patients had tumors 2 cm or larger. After chemotherapy, all patients underwent simple conization plus pelvic lymphadenectomy. At a median follow-up time of 69 months (range, 10–124 months), no relapses had occurred (follow up period for the entire cohort, since the authors did not specify follow up time based on tumor size). Analysis of obstetrical outcome was not possible because the authors did not stratify patients according to tumor size.

Recently, Lanowska et al. [47] published on neoadjuvant chemotherapy before VRT. The study included 20 patients, all with tumors larger than 2 cm. At the time of the report, 18 patients had undergone surgery, and 2 had completed chemotherapy and were waiting for surgery. The strategy used in that study was to perform a laparoscopic pelvic lymphadenectomy first to rule out lymph node metastases, and if none were found, to then deliver neoadjuvant chemotherapy (2 or 3 cycles of cisplatin, paclitaxel, and ifosfamide) followed by VRT. The mean patient

age was 32 years (range, 26–41 years), and the mean tumor size was 3 cm (range, 2.1–5.0 cm). No intraoperative complications were reported. In the 18 patients who had undergone VRT at the time of the report, there were 2 intraoperative complications (ureteral and vascular injury). Two of the 18 patients received adjuvant chemoradiotherapy. At the mean follow-up time of 23 months (range, 1–88 months), only 1 patient had had a relapse. Five women attempted to get pregnant, and 7 pregnancies occurred. Two pregnancies resulted in either a miscarriage or an ectopic pregnancy, 2 pregnancies ended in premature delivery, 2 infants were delivered at term, and 1 pregnancy was ongoing at the time of the report.

Robova et al. [48] published an update of their previous series, in a study including 28 patients with early-stage cervical and tumors larger than 2 cm. The authors were able to preserve fertility in 20 patients (two women showed positive nodes on frozen section, and another six had positive or close margins in the trachelectomy specimen). These twenty patients underwent neoadjuvant chemotherapy followed by simple trachelectomy and laparoscopic pelvic lymphadenectomy. After a median follow-up time of 42 months (5–103), there were 4 recurrences and 2 deaths. A total of 10 patients became pregnant.

In summary, a total of 73 patients underwent neoadjuvant chemotherapy followed by surgery and all of them had at least a partial response. This finding was noted regardless of tumor histology. In the entire group, there were five patients who recurred and three of these recurrences were in patients who underwent simple conization.

#### 4. Discussion

In our study, we found that the fertility preservation rate was 82.7%, 85%, 89% and 91% for ART (tumors larger than >2 cm), ART (all sizes), NACT followed by surgery and VRT (all sizes); respectively. The pregnancy rate was 16%, 24%, and 30.6% for ART, VRT and NACT followed by surgery; respectively. When considering oncologic outcomes, the recurrence rates were 3.8%, 4.2%, 6%, 7.1% and 17% for ART (all sizes), VRT (all sizes), ART (tumors > 2 cm), NACT followed by surgery, and VRT (tumors > 2 cm) [see Table 4].

It is well established that the risk of positive lymph nodes, deep infiltration, and lymph-vascular space invasion increases with increasing tumor size. Park et al. [49] published a study of 1415 patients with early cervical cancer divided into 4 groups based on tumor size: smaller than 2 cm, 2 to less than 4 cm, 4 to 6 cm, and larger than 6 cm. Comparing the groups with tumors smaller than 2 cm and tumors 2 to less than 4 cm, the authors found that patients with smaller tumors had significantly lower rates of lymph-vascular space invasion (11.4% vs. 25.7%;  $p < 0.001$ ), deep stromal infiltration (15.7% vs. 40.2%;  $p < 0.001$ ), vaginal involvement (5.2% vs. 11.2%;  $p < 0.001$ ), parametrial involvement (2.8% vs. 12.2%;  $p < 0.001$ ), resection margin involvement (0.9% vs. 3.4%;  $p = 0.019$ ), lymph node metastases (6.0% vs. 18.4%;  $p < 0.001$ ), and need for adjuvant therapy (13.6% vs. 34.0%;  $p < 0.001$ ). The authors concluded that the incidence of intermediate and high-risk factors gradually increased with increasing tumor size. Most studies in the literature have published a rate of 10–20% of nodal involvement in patients with tumors 2–4 cm. However, a number of groups have suggested that the rate of nodal disease is actually higher. In the study by Whethington

**Table 4**  
Results of radical trachelectomy for cervical cancer according to treatment modality.

Treatment	Fertility preservation rate, %	Pregnancy rate (overall), %	Recurrence rate, %	Death rate, %
ART (all sizes)	85.1 <sup>a</sup>	16.2 <sup>a</sup>	3.8 <sup>a</sup>	0.4 <sup>a</sup>
VRT (all sizes)	91.1 <sup>b</sup>	24 <sup>a</sup>	4.2 <sup>a,b</sup>	2.9 <sup>a,b</sup>
NACT	89.6	30.6	7.6	1.7
ART, tumor $\geq 2$ cm	82.7	NC	6	1
VRT, tumor $\geq 2$ cm	NC	NC	17.1	4

NC, not calculable, because reference article values are composite of the entire cohort.

<sup>a</sup> [50].

<sup>b</sup> [51].

et al. [5], the authors found that the rate of nodal disease in patients with tumors 2–4 cm was 45%. Similarly, in the study by Vercellino et al. [44], the rate of nodal involvement in patients with tumors larger than 2 cm who underwent lymphadenectomy before neoadjuvant chemotherapy was 66%.

We found that fertility preservation was achieved in 82.7% of patients with tumors 2 cm or larger who underwent primary ART and in 89% of patients with tumors 2 cm or larger who underwent neoadjuvant chemotherapy followed by surgery (Table 4). These rates of fertility preservation are not very different from those previously reported for patients with tumors of any size undergoing primary ART (85.1%) or primary VRT (91.1%) [50]. The observed overall pregnancy rate after neoadjuvant chemotherapy followed by radical trachelectomy was 30.7%. This pregnancy rate is greater than that previously reported for VRT (24%) or for ART (16.2%) [50] (Table 4). We found that the rates of fertility preservation in individual series on immediate radical trachelectomy ranged from 30% [5] to 88.7% [7]. However, in the report of the study that showed an 88.7% fertility preservation rate, the authors indicated that 35.7% of patients underwent chemotherapy after radical trachelectomy. One needs to interpret this data with caution as in the article that demonstrated a fertility preservation rate of 88.7%, the authors elected to treat patients that otherwise would have required radiotherapy under standard circumstances with chemotherapy alone, thus increasing the pool of patients who would be potential candidates for fertility preservation.

One should note that there is a paucity of conclusive data regarding the ideal chemotherapy regimen or the surgical approach after neoadjuvant chemotherapy. In addition, the oncologic safety of simple trachelectomy neoadjuvant chemotherapy is yet to be determined given that in five recurrences after neoadjuvant chemotherapy, three were in patients who had undergone a simple trachelectomy. As a result, there is a need for prospective trials that will control for the chemotherapy regimen and the surgical approach after neoadjuvant chemotherapy.

The oncologic safety of any treatment should be considered of paramount importance. Our finding that the recurrence rate after immediate VRT and LRT in patients with tumors larger than 2 cm was 17% and 21%; respectively, indicates that immediate VRT or LRT in these patients should be avoided. The recurrence rates in patients undergoing ART (all sizes), VRT (all sizes), NACT and ART (tumors > 2 cm) are low and very similar, ranging from 3.8–7.6%. Interestingly, the death rate for all approaches regardless of tumor size was low, ranging from 0.4–2.9% (Table 4).

The limitations of our review include the fact that criteria for selection and care of patients may vary between institutions. The patterns of practice may be influenced by surgeon expertise, institutional resources, and patient choice. In addition, criteria for adjuvant therapy, methods of follow-up, and frequency of follow up examinations may vary between institutions. Another limitation is that because raw data were not available, we could not perform overall calculations for all parameters of interest. The obstetrical outcome must be carefully analyzed as it depends on a number of factors, including the surgical technique, number of patients attempting to get pregnant, and type of surgery performed after neoadjuvant chemotherapy. Our study is also limited by the fact that the number of patients with tumors 2 cm or larger is small and thus making it difficult to draw conclusions that are generalizable to the overall population.

From an oncological point of view, our study provides strong evidence that VRT should not be offered as a primary treatment to patients with tumors larger than 2 cm wishing to preserve fertility, given the high associated recurrence rate. Also, we noted that LRT for tumors 2 to 4 cm, is associated with a relapse rate of 20% and should be avoided in patients with these tumor sizes. Tumors larger than 2 cm are associated with a higher risk of nodal involvement and therefore caution is recommended in decision-making regarding immediate radical trachelectomy for patients with such tumors [44].

In summary, our review demonstrates that in patients with tumors > 2 cm the oncologic outcomes are similar when performing

either immediate ART, provided that lymph node evaluation has been performed and confirmed to be negative for disease, or neoadjuvant chemotherapy followed by surgery. However, we did find that pregnancy rate for patients with tumors 2 cm or larger who underwent neoadjuvant chemotherapy followed by conservative surgery (30.6%) appeared to be higher than pregnancy rates previously reported for patients with tumors of any size who underwent immediate VRT (24%) or ART (16.5%) [50]. The fertility rates are highest in those patients treated with neoadjuvant chemotherapy followed by conservative surgery and thus this approach should be offered as the ideal approach to patients with tumors > 2 cm.

#### Conflict of interest

The authors report no conflict of interest.

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