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# Long term oncologic and reproductive outcomes after robot-assisted radical trachelectomy for early-stage cervical cancer. An international multicenter study

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## HIGHLIGHTS

- 80% women with an attempt to conceive succeeded.
- The premature delivery rate before gestational week 32 was 14%.
- The intention to treat based recurrence rate was 7.2%.

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## ABSTRACT

*Objectives.* Long term outcomes following fertility sparing robot-assisted radical trachelectomy (RRT).

*Methods.* A retrospective study of consecutive women selected for RRT between 2007 and 2019 at five referral centres. Generally used selection criteria for fertility-sparing surgery were applied. Oncologic, reproductive and long-term clinical data were analysed.

*Results.* Of the 166 included women, 149 completed a RRT. Median tumor size was 9 mm (range 3-20 mm), 111 women (75%) had FIGO 2009 stage IB1 cancer and 4.8% were node positive. At a median follow up of 58 months, 12 of all women (7.2%) and 9 of 149 women (6%) who underwent completed RRT with fertility preservation had recurred and two had died. 70 of 88 women (80%) who attempted to conceive succeeded, resulting in 81 pregnancies that progressed beyond the first trimester and 76 live births of which 54 (70%) were delivered at term and 65 (86%) delivered after gestational week 32. A short postoperative cervical length was associated with impaired fertility. A late secondary hysterectomy was necessary in four women due to persistent bleeding ($n = 2$), hematometra due to a cervical stenosis ($n = 1$) and recurrent dysplasia ($n = 1$).

*Conclusion.* In this long-term follow-up of RRT the recurrence rate is comparable to larger individual studies of minimally invasive or vaginal radical trachelectomy with similar risk profile and follow up. The high pregnancy rate and low rate of premature delivery before 32 weeks GA may promote the use of robot-assisted approach.



## 1. Introduction

Cervical cancer is the fourth most common cancer among women globally and more than one third of cases are diagnosed in women under 45 years old [1,2]. The need for fertility-sparing treatment is increasing due to the trend in delayed childbearing [3]. The guidelines of European Society of Gynaecological Oncology (ESGO) and National Comprehensive Cancer Network (NCCN) recommend fertility-sparing

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surgery including conization and simple or radical trachelectomy as an option for early stage cervical cancer (tumors ≤2 cm) in women who request fertility preservation [4,5]. Reports show an increased implementation of trachelectomy over the last few decades [6,7]. In the early 1990s a radical vaginal trachelectomy (VRT) was first described by Dargent in combination with laparoscopic pelvic lymphadenectomy [8]. Alternative abdominal approaches are laparotomy (ART), traditional laparoscopic (LRT) or robot-assisted radical trachelectomy (RRT). A review from 2020 including 3000 women reports higher mean pregnancy rates (in women trying to conceive) after VRT (67.5%) than after ART (41.9%) and LRT (51.5%), while few RRTs were reported. The review reports a preterm delivery rate of 32% and a second trimester loss of 5.8% after radical trachelectomy with no difference between surgical approaches [9]. The few small, published studies on RRT report a pregnancy rate of up to 81% with 71% of pregnancies delivered later than 36 weeks gestational age (GA) [10,11].

The oncologic safety of radical trachelectomy is considered comparable to radical hysterectomy in tumors <2 cm of squamous or adenocarcinoma types [12]. High-risk histologies such as neuroendocrine or clear cell tumors are considered contraindications to RT due to their aggressive nature [13]. A review of RT from 2020 including 2566 women with median follow-up of 48 months (range 2–202 months) report a median recurrence rate of 3.3% (range 0–25%) across studies [14]. The recently published International Radical Trachelectomy Assessment Study (IRTA) found no difference in recurrence rate at 4.5 years between open surgery and minimal invasive surgery (4.8% vs 6.3% respectively) [15].

Robotic radical trachelectomy (RRT) was first described in 2008 [16]. Due to the rarity of the RRT procedure, larger cohorts with sufficient follow up and detailed reproductive outcome are missing. Second to oncologic safety, data on reproductive outcomes are crucial in order to adequately counsel women preoperatively.

The aim of this study was to provide a detailed evaluation of the reproductive outcomes, oncologic outcomes and long term complications after RRT of a large cohort of patients by combining data from five tertiary referral centers.

## 2. Material and methods

This is a retrospective, multicentre study of patients who underwent attempted robot-assisted radical trachelectomy (RRT) for primary treatment of International Federation of Gynecology and Obstetrics (FIGO) 2009 [17] clinical stage IA1, IA2 and IB1 cervical cancer. For stage IA1 patients, lympho- vascular space invasion, multifocal disease, adenosquamous histology, or a cone biopsy with positive margins were required. We included patients selected to undergo RRT between December 2007 and October 2019 for tumors ≤2 cm with squamous, adenocarcinoma or adenosqumaous histology at five referral centres (Skåne University Hospital, Sweden (SUH), Karolinska University Hospital, Sweden (KUH), University of North Carolina Hospitals, United States (UNC), Severance Hospital of the Yonsei University, South Korea (YUHS) and Royal Surrey County Hospital, the United Kingdom (RSCH)). Preoperative evaluation included vaginal ultrasonography, pelvic MRI and CT or PET/CT scan in order to measure tumor size and identify metastatic disease including potential nodal metastases.

One surgeon per site performed the majority of the procedures. For evaluation of surgical data, distinct parts of the procedure identified as possibly having a more explicit impact on the outcome were mutually agreed on to be evaluated. This included sparing of the uterine artery, placement of an inner cervical cerclage and a separate removal of the parauterine /parametrial lymphovascular tissue. Data was obtained from hospital records and local databases. The study was approved by the institutional ethical review boards at Lund University (DNR 2008–663, 2018–749) the Swedish national review board (DNR 2020–06968), Karolinska Institute (DNR 2015–2140), University of North Carolina (IRB 19–2154), Yonsei University Health System (4–2019-1274) and by the Clinical Audit Group at Royal Surrey NHS Foundation Trust.

The surgical procedure including preservation of the uterine arteries was performed as previously described [16,18]. The parauterine lymphovascular tissue was removed and sent as separate specimens [19]. A colpotomy was performed with the aid of a fornix presenter. No intracervical device was used. Vaginal closure prior to colpotomy was not performed. A cervical cerclage was placed medial to the ascending uterine artery at the level of the uterine isthmus using a permanent monofilament (0-Prolene®, Ethicon GmbH., Norderstedt, Germany or Ethilon®, Ethicon, Johnson & Johnson) or multifilament (Gore-Tex® CV-2 suture, W.L Gore & Associates LTD., Dundee, Scotland or Ethibond®, Ethicon, Johnson & Johnson) suture at surgeons' discretion.

Sentinel lymph node (SLN) detection using Indocyanine Green (or before 2011 using Tc 99) as tracers was performed in 54% of cases. In the majority of cases the pathologist divided each SLN in two and frozen section was performed on one half to obtain intraoperative information on nodal status whereas the remaining halflater was subjected to ultrastaging and immunohistochemistry. In women with negative SLNs, a full pelvic lymphadenectomy was performed. An intraoperative frozen section of the proximal margins (a section performed 4 mm from the proximal edge) of the trachelectomy specimen was performed in all cases in two of the institutions, and in selected cases in the remaining, i.e. was evaluated in 47% of cases. If lymph nodes were metastatic the fertility sparing attempt was aborted and, based on institutional preferences, ovarian transposition was performed prior to upfront chemoradiation (CRT). Incase of positive proximal margins a radical hysterecomy was performed.

Based on final histology a rescue hysterectomy was recommended in case of insufficient proximal cervical margins (<5 mm). In case of positive lymph nodes and/or any other insufficient margins or if indicated by Sedlis criteria [20], adjuvant radiotherapy (external beam radiation pelvic field (26 × 1.8 Gy) with concomitant weekly Cisplatin 4-6x40mg/m$^2$) was administered.

Postoperative complications were graded using the Clavien Dindo (CD) nomenclature [21]. Follow-up with a clinical examination including pap-smear, HPV-test and vaginal ultrasonography was performed according to national guidelines, at least once every six months. Imaging was performed when indicated. All recurrences were histologically verified. Date of biopsy and location of recurrence were recorded. Clinical data including attempts to conceive, reproductive outcome and long-term complications were recorded. Post trachelectomy non-pregnant cervical length was evaluated routinely at three of the institutions using vaginal ultrasonography ($n = 75$) or MRI ($n = 15$).

Women with an active attempt to conceive for at least 12 months were evaluated for reproductive outcomes. For analyses of factors associated with prematurity (cervical length, preservation of uterine artery, and parity prior RRT) all pregnancies were included. The rate of prematurity and second trimester miscarriage was evaluated among all pregnancies beyond first trimester. Cesareans performed as planned at 36 or above weeks GA were considered full term. The rate of women with at least one live birth was calculated among woman with an attempt to conceive (excluding ongoing pregnancies) as well as on an intention-to-treat basis among all women selected to undergo RRT.

Possible univariate associations were evaluated by Chi-square or Fisher's exact test or by Mann-Whitney test. Regression analyses were performed as appropriate. The Kaplan Meier estimator was used to estimate the survival rates. Deidentified data were entered into a database, pseudo-anonymized and analysed using SPSS version 12.0 statistical software (SPSS, Chicago, IL, USA). A $p$-value of less than 0.05 was considered significant in all statistical tests.

## 3. Results

Of 166 women, 17 women (10%) had the fertility sparing attempt aborted due to lymph node metastases ($n = 8$, 4.8%) or insufficient

margins ($n = 8$, 4.8%). One patient received adjuvant RT based on Sedlis criteria (0.5%) (Fig. 1). Characteristics of the study population are provided in Table 1 and Supplementary Tables 1 and 2.

At a median follow up of 58 months (range 2–151 months) 12 of all 166 women in the intention-to-treat population (7.2%) had recurred at a median of 16 months (range 4–43 months) after surgery. Lateral pelvic recurrence i.e. pelvic lymph nodes or peritoneal ($n = 6$) was most frequent. Two women died of disease at eight and 45 months after RRT respectively. Nine (6.0%) of 149 women who underwent completed RRT recurred. Ten of 12 recurrences in the whole cohort and eight of nine recurrences in women with completed RRT had FIGO stage IB1 disease. The three- and five-year disease-free survival rates (95% CI) of the 166 women were 92.9 (90.8–95.0) and 92.1 (89.9–94.3) respectively. The three- and five-year overall survival rates (95% CI) were 99.4 (98.8–1) and 98.5 (97.4–99.6) respectively. Data on all recurrences is available in Supplementary Table 1.

Of 149 women who underwent RRT with fertility preservation and had no evidence of disease recurrence, follow-up data for ≥12 months was available for 135 women of which 88 women (65%) actively tried to conceive, either naturally ($n = 71$) or by assisted reproduction ($n = 17$). Seventy (80%) of these women became pregnant using natural conception ($n = 59$, 84%) or assisted reproduction ($n = 11$, 16%)

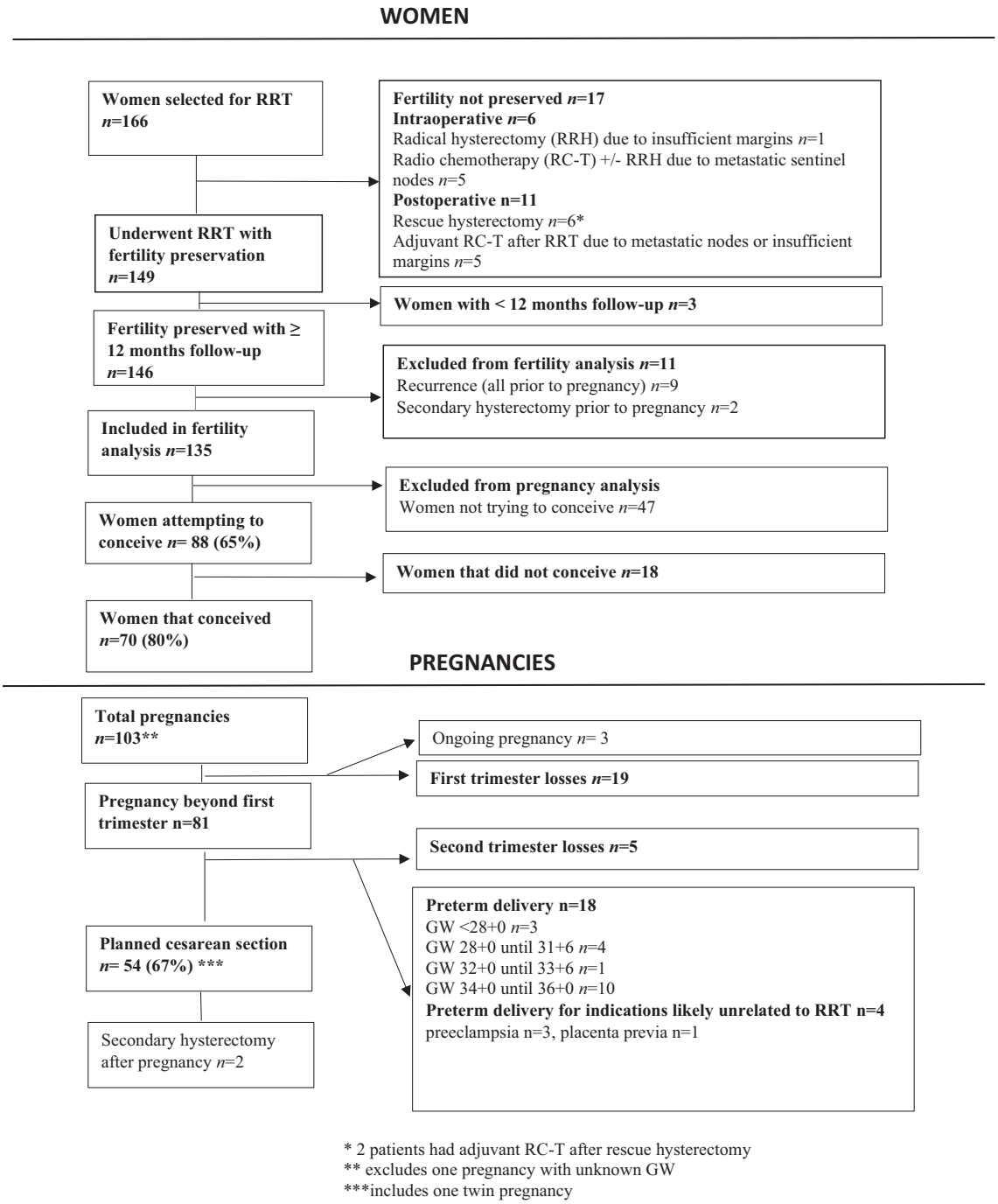


**Fig. 1.** Flow chart of women patients planned for robot-assisted radical trachelectomy (RRT) for early-stage cervical cancers and the pregnancies following RRT. Gestational week (GW).

**Table 1**
Characteristics of women selected for RRT ($n = 166$).

| n (%) or median (range) as appropriate | RRT completed n = 149 | Fertility not preserved n = 17 |
|---|---|---|
| Follow-up months | 64 (2–140) | 24 (4–60) |
| Age at surgery (years) | 31 (18–42) | 29 (23–38) |
| BMI (kg/m2) | 23.5 (17.0–47.0) | 23 (20–45) |
| Prior cone biopsy | 107 (72.8%) | 16 (94.1%) |
| Residual cancer after cone biopsy | 24/107 (22.4%) | 9/16 (56.2%) |
| FIGO 2009 Clinical stage | | |
| IA1 with LVSI | 8 (5.4%) | 2 (11.8%) |
| IA2 | 29 (19.5%) | 1 (5.9%) |
| IB1 | 111 (74.5%) | 14 (82.3%) |
| IIA | 1 (0.6%) | 0 |
| Histology | | |
| Squamous cell carcinoma | 88 (59%) | 10 (58.8%) |
| Adenocarcinoma[a] | 61 (41%) | 7 (41.2%) |
| LVSI positive[b] | 32 (21.5%) | 7 (41.2%) |
| Tumor size (mm)[c] | 9 (3−20) | 12 (8–20) |
| Tumor infiltration (mm)[d,e] | 4 (1–19) | 4 (2−12) |
| Lymph node metastases | 0 | 8 (47%) [e] |
| Lymph node count | 21 (1–53) | 18 (3–34) |
| Sentinel Node Performed in | 79 (53%) | 10 (58.8%) |
| Recurrences | 9 (6.0%) | 3 (17.6%) |

Node positivity was 4.8% in all 166 women.
[a] Includes 3 patients with adenosquamous histology.
[b] Data missing on lymphvascular space invasion (LVSI) in 38 patients.
[c] Data missing in 9 patients.
[d] Data missing in 14 patients.
[e] Tumor infiltration is equal to cervical stromal infiltration.

resulting in 103 pregnancies and 76 live births (including one twin pregnancy delivered at term and excluding one pregnancy with unknown GA at delivery) (Fig. 1).

Excluding three ongoing pregnancies, 27/81 (33%) pregnancies beyond the first trimester ended with either a second trimester loss ($n = 5$) or a preterm Cesarean section ($n = 22$) of which four were for indications likely unrelated to RRT (three preeclampsia/HELLP syndrome and one placenta previa). Babies born after the second trimester were all live infants. The rate of women with at least one live birth among women trying to conceive was 72%. 86% of live births were delivered after 32 + 0 GA. The rate of women with at least one live birth among the intention-to-treat population was 38%. Of the 135 women with preserved fertility, 47 (34%) did not try to conceive during the follow-up period (Fig. 1).

The attempt to preserve the uterine arteries bilaterally was successful in all but five women. The median postoperative non pregnant cervical length was 11 mm (range 5–24) mm (no data from two centres, $n = 59$ women, where this measurement is not routinely performed). In a linear regression analysis, a shorter cervical length, with no identifiable cut-off level, was associated with an inability to conceive ($p = 0.04$). No association was found linking premature birth with cervical length, preservation of uterine artery or type of cerclage. An internal cerclage was placed in 143 (96%) of the 149 women who underwent completed RRT.

Of the 149 women who underwent completed RRT, 36 (24%) experienced an early postoperative complication according to the Clavien Dindo classification (CD). More than 70% were mild to moderate (CD grade I-II) whereas CD grade IIIa-b complications occurred in 10 women (7%) (Table 2).

The prevalence of lymphedema was not consistently reported and therefore not analysed. Four women underwent secondary hysterectomy including two after having given birth (indications included abnormal uterine bleeding $n = 2$, cervical stenosis $n = 1$ and persistent dysplasia $n = 1$). Two intraoperative complications (bladder injury and compartment syndrome of the leg) occurred. Cerclage erosion to the vagina occurred in 5 of 25 women where a Gore-Tex® cerclage was placed compared with no erosions among 114 women with Prolene® or Ethibond® cerclages ($p < 0.01$).

**Table 2**
Intraoperative, moderate to severe postoperative complications categorized according to the Clavien Dindo nomenclature and late complications in 149 women that completed the robot-assisted radical trachelectomy.

| Type of complication | Number and explanation |
|---|---|
| *Intraoperative* | Bladder injury ($n = 1$) |
| | Compartment syndrome of the leg ($n = 1$) |
| *Early complications (<30 days)* | |
| CD IIIa-IIIb $n = 10$ (6.7%) | Vesico-vaginal fistula ($n = 1$) |
| | Pelvic lymph seroma ($n = 4$) |
| | Pelvic hematoma ($n = 2$) |
| | Bowel obstruction ($n = 1$) |
| | Vaginal bleeding ($n = 2$) |
| *Late complications[a] (>30 days)* | |
| $n = 11$ (7.4%) | Persistent vaginal bleeding ($n = 6$) |
| | Voiding problems ($n = 4$) |
| | Vesico-vaginal fistula ($n = 1$) |
| Cervical stenosis | $n = 18$[b] |
| External | $n = 15$ |
| Internal/Combined | $n = 3$ |
| Cerclage erosions | $n = 5$ |

[a] Not including lower limb lymphedema.
[b] One stenosis led to secondary hysterectomy.

Cervical stenoses were divided into “internal” (narrowing of the inner cervix with a risk for hematometra), “external” (narrowing of the external os due to epithelialization), or a combination of the two. Of the 125 women who underwent completed RRT with complete data on postoperative complications, 18 (14%) developed a cervical stenosis of which three (2%) were of internal or of combined type. Cervical stenosis was not associated with impaired fertility, however 2/3 women with internal stenosis and 4/15 with external stenosis did not attempt to conceive.

## 4. Discussion

In this retrospective study on 166 consecutive women selected to undergo fertility-sparing robot-assisted radical tracheletomy, the overall recurrence rate at a median follow-up time of 58 months was 7.2%. Seventy of 88 women (80%) trying to conceive became pregnant resulting in 103 pregnancies and 76 live births, 86% of whom delivered after 32 + 0 weeks GA.

The results of the LACC trial raised concerns about the safety of minimally-invasive surgery for cervical cancer [22]. Though there are no randomized data to compare the oncologic outcomes of abdominal and minimally invasive RT, the recent IRTA study where trachelectomy attempts aborted for RRH and FIGO stage IA1 were excluded, found no difference in the 4.5-year disease-free survival rate between open and minimally invasive radical trachelectomy. The five-year DFS (95% CI) of 92.1 (89.9–94.3) and OS of 98.5 (97.4–99.6) in the present study seems in accordance with the 4.5-year DFS (95% CI) of 91.5% (87.6%–95.6%) and OS of 99.0% (79.0%–99.8%) in the minimally invasive surgery cohort from the IRTA-study. The MIS cohort in the IRTA study had a rate of lymph node metastasis of 4.9%, median follow-up time of 3.1 years and a recurrence rate of 6.3% [15]. This can be compared to a median follow-up of 5.3 years, a lymph node metastasis of 5.2% and a recurrence rate of 7.1% (11/155), after excluding one woman converted to RRH and women with FIGO stage IA1 from the study population, in the present study. Comparison of oncologic outcome to data in published reviews [9,10,14,22] is difficult due to variable follow up times, different proportions of oncologic risk factors, and inconsistency or lack of information on whether recurrence rates were calculated on an intention-to-treat basis or among women with completed radical trachelectomy only. Given the lack of detailed information we believe the proportion of node positive patients and aborted trachelectomy attempts can serve as surrogate markers for the overall oncologic risk. In a cohort study by Zusterzeel et al. (2016) on 132 patients undergoing VRT using an intention-to-treat analysis with a similar follow up time and proportion

of node positivity (4.5% vs 4.8%) as in our study, the recurrence rate was 6.8% compared to 7.2% [23]. Similarly, Marchiole et al. (2007) reports a recurrence rate of 5.9% in a cohort of 118 patients undergoing VRT where 4.2% were node positive and 12.4% procedures were aborted compared to 10.2% aborted in our study [24]. Park et al. report a recurrence rate of 11.4% at a median follow up of 44 months from a cohort of 88 patients undergoing LRT (3.8% node positivity and 10.2% aborted trachelectomy attempts) [25]. In conclusion, the recurrence rates in our study is comparable to recurrence rates in cohorts of patients undergoing VRT and MIS-RT with a similar follow up time and tumor risk profile. A significant difference in the recurrence rate between the hospital with the lowest and the hospital with the highest recurrence rate was noted. Due to a low number of RRTs performed at the latter, the impact of a single recurrence was considerable. In addition, the same hospital had the highest percentage of stage 1B1 tumors, which was associated with a risk of recurrence. Given the selection of a low risk population for fertility sparing trachelectomy, the procedure regardless of surgical approach, is generally considered as safe as a radical hysterectomy. The recurrence rates in our and larger studies on alternative approaches with similar risk profiles may however indicate a somewhat higher risk of recurrence compared to the recurrence rates after a radical hysterectomy [26,27]. This information should be included when counselling patients. Whether it is necessary to perform a radical trachelectomy including the paracervical tissue or a simple trachelectomy will suffice is under debate. In our opinion, regardless of tumor size, removal of the parauterine (parametrial) lymphovascular tissue should be an integral part of the nodal staging [19,28,29]. A fertility rate of 80% among the 65.7% of women trying to conceive is higher than previously reported, alleviating any concerns that the more extensive intraabdominal surgery with a robotic procedure, compared with a vaginal trachelectomy, would compromise fertility. Plausible explanations for the comparatively high fertility rate in this study are supported by data that a shorter post trachelectomy cervix may impair fertility. In our study the median remaining non-pregnant cervical length was 11 mm (range 5-24 mm), and 34% of women had a cervical length of <10 mm compared to a study by Alvarez et al. where 19 of 29 (66%) women after VRT had a cervical length of <10 mm [30]. We believe the good visualisation in robotic surgery favours less variation in the transection level of the cervix. Furthermore, in a study by Egashira et al. on abdominal trachelectomy where the uterine arteries were ligated in the majority of women, 14 of 37 women unable to conceive were diagnosed with amenorrhea and Ashermans syndrome, never diagnosed in our cohort, possibly indicating a beneficial effect on endometrial blood supply by sparing the uterine arteries [31].

Direct comparison of term delivery rates are somewhat limited as prematurity is inconsistently defined across studies. In obstetrics literature, term delivery is defined as birth after 37 weeks GA. In patients with history of radical trachelectomy, a Cesarean is often planned between 36 and 37 weeks GA given the risk of labouring against an internal cerclage. For this reason, we defined premature deliveries as those occurring before 36 weeks. Given that neonatal morbidity decreases substantially after 32 weeks GA [32] we also present rates of delivery at 32 weeks GA and above. The term delivery rate of 71% and the 86% rate of delivery after 32 weeks GA in this study is comparable to the 81% (after 32 weeks GA) reported by Zusterzeel et al. after VRT [23] and within the upper range of term delivery rates reported in reviews [9,14,22,33].

The incidence of cervical stenosis after RT is difficult to compare between studies. In a review from 2015 a cervical stenosis was seen in 10.5% of women, consistent with the overall incidence in our study [34]. Most studies however do not differ between an external cervical stenosis, merely caused by a usually harmless narrowing of the external os, and an internal cervical stenosis, diagnosed in as few as three women (2%) in our study, carrying a risk for hematometra, secondary endometriosis, and infertility. Our data neither support nor contradict an association with the use of an internal cerclage and development of a cervical stenosis. Only 12/18 women with cervical stenosis tried to conceive, hence a possible association with fertility was not possible to investigate. Too few ($n = 6$) women had no cerclage for evaluation on an association between the use of an internal cerclage and a risk for developing a cervical stenosis. Our strong belief however is that no such association exist. Therefore, given the low incidence of internal stenosis and the potential preventive effect on premature deliveries we recommend the use of an internal cerclage in conjunction with the RRT.

No association was found linking premature delivery and preservation of uterine artery, possible due to the fact that they were bilaterally preserved in nearly all women.

The main strength of this study is the uniform surgical technique with regards to the use of cervical cerclage, sparing of the uterine arteries, removal of the upper parauterine/parametrial tissue, i.e. parts of the procedure with a possibility to more specifically effect the outcome. The other parts of the procedure might have changed over time and between institutions. Other strengths are the large number of consecutive women included, the detailed data collected, and the long median follow-up time. It is the largest cohort of RRT available that present both oncologic and detailed reproductive outcomes.

Weaknesses are the retrospective design and the lack of full data on presence of LVSI and tumor grade due to a non-centralized pathology review. Furthermore, measurement of post trachelectomy cervical length was not performed at all institutions. The multi-institutional international series over more than 10 years is both a weakness and a strength: a weakness as some inconsistencies inevitably occur, and a strength as it demonstrates the generalizability of the technique.

## 5. Conclusion

This study provides long-term follow-up data valuable for counselling and selection of women for robot-assisted radical trachelectomy. The intention to treat based recurrence rate of 7.2% appears in level with both the IRTA study and other larger individual studies of similar tumor risk profile and follow up times. Only 65% of women after completed RRT tried to conceive during the follow-up period. There is a high pregnancy rate and low rate of premature deliveries before 32 + 0 weeks GA in women trying to conceive after RRT.

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## Ethical approval

The study was approved by the institutional ethical review boards at Lund University (DNR 2008–663, 2018–749) the Swedish national review board (DNR 2020–06968), Karolinska Institute (DNR 2015–2140), University of North Carolina (IRB 19–2154), Yonsei University Health System (4–2019-1274), Clinical Audit Group approval at Royal Surrey NHS Foundation Trust.

## Disclosures

John F Boggess, Simon A. Butler-Samuel, Young Tae Kim, Kyung Jin Eoh, Henrik Falconer, and Jan Persson and have received honoraria

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2021.12.029.

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