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Review

The Conundrum of Prematurity and Pregnancy Outcomes after Fertility Sparing Treatment Modalities for Early Stage Cervical Cancer: A Systematic Review of the Literature

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Abstract

Advances in modern medicine have allowed patients with early stage cervical cancer (stages Ia - IIa1) to preserve their fertility with oncologic efficacy comparable to previous radical treatments. A variety of conservative-fertility sparing procedures, also known as Fertility Sparing Surgeries (FSS) have been proposed. The present review aimed to provide the current evidence on obstetric outcomes and the prematurity rates as well as to discuss the management modalities of these high-risk pregnancies. Our review of the literature included 3042 women with early cervical cancer, of whom 2838 underwent FSS (204 excluded for oncologic reasons). Almost half of these patients attempted to become pregnant and about two thirds of them achieved at least one pregnancy either spontaneously or with the help of Assisted Reproduction Technologies. Data revealed that 63.9% of these pregnancies resulted in live births, whereas 37.6% of them were preterm. The main cause of preterm births in this subpopulation is the postoperative cervical length restriction that consequently leads to cervical incompetence and ascending infections that eventually lead to (clinical or subclinical) chorioamnionitis. Radical operations such as ART, VRT and MIRT presented with higher prematurity rates. The lack of standardized protocols for the management of pregnancies after FSS precluded reaching to firm results with regards to the efficacy of them in achieving favourable obstetrical outcomes. Further large volume studies are warranted with the intent to acquire standardized guidelines for pregnancies achieved after FSS for early stage cervical cancer.

Keywords

abdominal trachelectomy, conization, cone resection cervix, early cervical cancer, fertility cervical cancer, fertility sparing surgery, lap* trachelectomy, neoadjuvant chemo* cervical, obstetrical management cervical cancer, pregnancy complications, trachelectomy, prematurity, robotic trachelectomy, radical trachelectomy, trachelectomy

Abbreviations:			
FSS:	fertility sparing surgeries;	PPROM:	preterm prelabour rupture of membranes;
LLETZ:	large loop excision of the transformation zone;	WG:	weeks of gestation;
Cone:	cone resection;	PROM:	prelabour rupture of membranes;
VT:	vaginal trachelectomy;	T1:	1st trimester;
VRT:	vaginal radical trachelectomy;	T2:	2nd trimester;
ART:	abdominal radical trachelectomy;	T3:	3rd trimester of pregnancy;
MIRT:	minimal invasive radical trachelectomy;	IVF:	in vitro fertilization;
		Ab:	abortions.

INTRODUCTION

Cervical cancer (CC) is the fourth most common cancer among women, constituting the fourth leading cause of cancer death.[1] According to the American Cancer Society, 13.240 new cases of CC were diagnosed in the USA in 2018, while the respective mortality was 4170 women. A diagnosis of CC reaches its peak between the ages of 35-44 whereas it rarely occurs in ages younger than 20 years. Accordingly, 15% of new cases involve women older than 65 years.[2,3]

Due to the fact that in recent years women tend to delay parenthood, women of reproductive age diagnosed with CC may wish to preserve their fertility.[3] Since the 1990s, when Dargent performed the first vaginal radical trachelectomy (VRT) combined with laparoscopic lymphadenectomy, various fertility sparing modalities have been proposed in patients with early-stage CC (IA-IIA1).[4] In that setting, cone Resection/Large Loop Excision of the Transformation Zone (LLETZ), Vaginal Trachelectomy (VT), Vaginal Radical Trachelectomy (VRT), Abdominal Radical Trachelectomy (ART) (open, laparoscopic or robot assisted), and Neo-Adjuvant Chemotherapy (NACT) followed by one of the aforementioned fertility sparing surgery (FSS).[5,6] The available literature presents favourable oncologic and obstetric outcomes after the aforementioned procedures with low reported recurrence rates and successful pregnancies and notable live birth rates. However, adverse pregnancy outcomes such as miscarriages, preterm prelabor rupture of membranes (pPROM), PROM or preterm labor have also been recorded. The exact pathogenesis and prevalence of the obstetrical complications after FSS still remain elusive.

AIM

The aim of this review is to update available evidence on obstetric outcomes and the prematurity rates as well as to discuss the management modalities of these high-risk pregnancies.

MATERIALS AND METHODS

Study design

All appropriate prospective and retrospective trials as well as case series and case reports reporting outcomes of women with early-stage CC who underwent various FSS for the management of their disease were considered eligible for inclusion in the present systematic review. Two authors (AP and IGP) independently and meticulously searched the literature, excluded overlaps and tabulated the selected indices in structured forms. Reviews and animal studies were excluded from analysis and tabulation. Only articles written in English language were considered eligible. Accordingly, articles reporting outcomes of in situ CC or stage IA1 without lymphovascular space invasion (LVSI) and articles on pediatric patients were excluded. In addition, for overlapping publication data by the same group of authors, only the most recent publication was enrolled. In cases where multiple (overlapping) publications stemming from the same study were identified, the larger size study was included, unless additional data were provided in multiple publications; in this case all articles were considered eligible.

Search strategy and data collection

We systematically searched the literature for articles published up to May 2019 MEDLINE database in articles relevant to the subject of our review. A manual cross-reference search of the bibliographies of relevant articles was conducted to identify studies not found through the computerized search. Keywords that were used include "fertility sparing surgery", "trachelectomy", "early cervical cancer", "lap* trachelectomy", "robotic trachelectomy", "radical trachelectomy", "abdominal trachelectomy", "neoadjuvant chemo* cervical", "conization", "cone resection cervix", "fertility cervical cancer", "prematurity", "pregnancy complications trachelectomy", "obstetrical management cervical cancer". A minimum number of search keywords were utilized in an attempt to assess an eligible number that could be easily

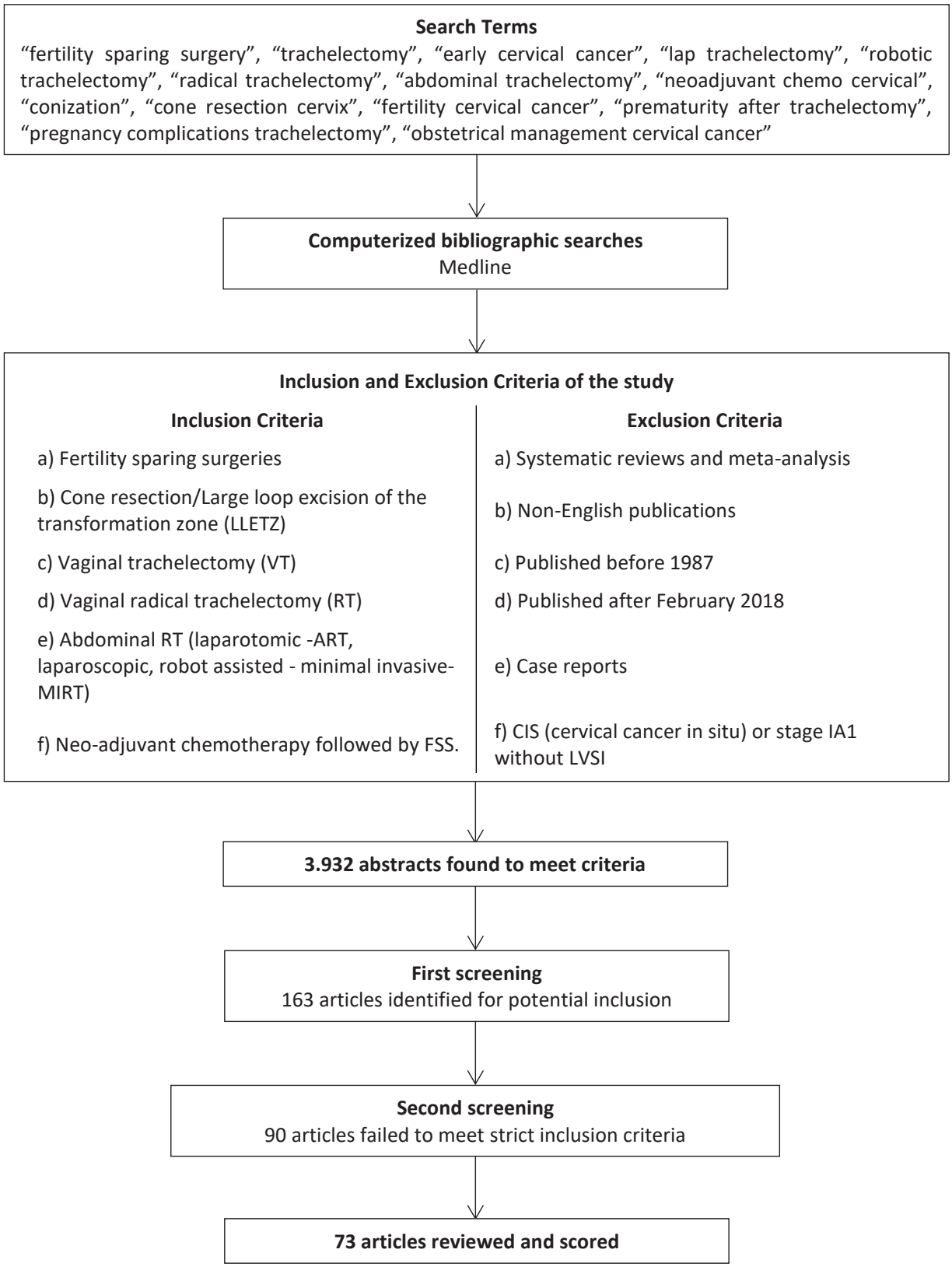

Figure 1. PRISMA flow diagram.

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searched while simultaneously minimizing the potential loss of articles.

The PRISMA flow diagram schematically presents the stages of article selection (**Fig. 1**). More specifically, our search yielded 3.932 articles published between 1987 and May 2019. A first screening was implemented retrieving 163 articles for potential inclusion which were reviewed in detail. A second screening was mandatory to exclude the ineligible studies. After the second screening, 90 articles were excluded, leaving 73 articles to form the basis of this systematic review.

Patients were divided into groups according to the radicality of the performed procedure which included ART, VRT, MIRT, Cone/LLETZ, and VT. Data on patients' characteristics included patient age, type of surgery, obstetric outcome, pregnancy complications and management of the latter.

RESULTS

A total of 88 studies which comprised 2895 women diagnosed with stage IA1-IIA CC and undergone FSS for the management of their disease were finally included in the present review. Among them, 785 (25.9%) underwent ART[7-30], 1256 (44.3%) had VRT, 257 (9.1%)[14,31-52] were treated with Cone Resection or LLETZ[53-63], and 302 (9.9%) underwent MIRT (Laparoscopic or Robot-assisted)[9,17,22,41,64-70] while 76 (3.6%) underwent vaginal trachelectomy (VT).[71-75] From the included studies, 204 women were excluded from analysis for oncologic reasons, change of operative strategy, positive margins on final pathology report, recurrences and sudden deaths. Cumulative data from patients included revealed total pregnancy rates of 37.4%. Pregnancy was achieved either spontaneously or with assisted reproduction technologies. However, 63.9% of them resulted in live births while at the same time prematurity rates were 37.6% **(Table 1)**.

Out of all women that underwent ART, 180 achieved pregnancies with a 21.6% (39/180) rate of pregnancy loss and 120 (66.6%) live births. Preterm birth rates in this group were 57.4%: 8.6% from 22nd to 28th gestational week, 21.2% from 29th to 33rd WG, and 27.5% from 34th to 36th WG. In the group of women that underwent VRT, 603 pregnancies were achieved. Pregnancy loss was 19.9% (120/603), and 351 (58.2%) live births were documented, with a prematurity rate of 31.6%: 5.5% from 22nd to 28th WG, 10.8% from 29th to 33rd WG, and 15.2% from 34th to 36th WG. In the group that underwent Cone/LLETZ procedures, 126 pregnancies were achieved while the pregnancy loss rate was 13.4% (17/126). Documented live births were 89 with a prematurity rate of 10%: 2% from 22nd to 28th WG, and 10.2% from 29th to 33rd WG. Women that underwent MIRT achieved 77 pregnancies, 61 (79.2%) of which resulted in live births, while the pregnancy loss rate was 31.1%. Prematurity rate was 47.3%: 10.5% from 22nd to 28th WG, 19.2% from 29th to 33rd WG, and 21% from 34th to 36th WG. In the VT group, 75 pregnancies were achieved. Of these, 14.6% ended in pregnancy loss and 58 (77.3%) were live births. The prematurity rate was 43.1%: 6.8% from 22nd to 28th WG, 3.4% from 29th to 33rd WG, and 32.7% from 34th to 36th WG. It is noteworthy that the vast majority of women gave birth via cesarean section because of the high risk of bleeding in a natural birth setting. Nevertheless, there were women who went into labor naturally, most of them had undergone Vaginal Trachelectomy or Cone Resection/LLETZ and had a significantly lower risk of bleeding.

DISCUSSION

Applications of FSS for the management of CC date back to 1956 when Aburel[76] first introduced the technique of Abdominal Radical Trachelectomy. Later on, Smith et al.[77] and Ungar et al.[78] resurfaced this technique in the late 1990s, while at the same time Dargent introduced the Vaginal Radical Trachelectomy technique after laparoscopic bilateral pelvic lymphadenectomy. Throughout the course of the history, the use of laparoscopy and robotics brought innovation and enhanced the aforementioned procedures[79] along with the addition of neoadjuvant chemotherapy setting as a final goal the improvement in oncological outcomes with acceptable morbidity and mortality rates.[36,80-82]

Table 1. Obstetric outcomes after FSS

Parameters	Cone resection/ LLETZ	VRT	ART	MIRT	VT	Total n=3042
FSS patients N (%)	278 (9.1)	1350 (44.3)	792 (25.9)	302 (9.9)	111 (3.6)	2838 (93.2)
Pregnancies N	126	603	180	77	75	1062
Fetal loss (T1/T2/Ab)	11/3/3	84/36/23	30/9/N/A	21/3/N/A	9/2/3	150/53/29
Preterm delivery (22-28 WG) N	1	19	11	6	4	41
Preterm delivery (29-33 WG) N	4	37	27	11	2	81
Preterm delivery (34-36 WG) N	0	52	35	12	19	118
Live births N	89	351	120	61	58	679
Prematurity rates N (%)	5/49 (10)	108/341 (31.66)	73/127 (57.4)	27/57 (47.3)	25/58 (43.1)	238/632 (37.6)

Additionally, several novel techniques such as the Extraperitoneal Radical Trachelectomy[6] and the Photodynamic Therapy combined with Cone Excision/ LEEP have been suggested but the oncologic and obstetric efficacy of them are still under estimation.

The aim of the present review was to focus on the obstetric outcomes and more specifically on the respective prematurity rates of the achieved pregnancies after FSS. Our results revealed that less radical procedures presented with lower prematurity rates. To that end, prematurity rates in women who underwent Radical Trachelectomy ranged from 36.6% to 56% depending on the type of the procedure. People who underwent ART and achieved pregnancy, presented with the highest prematurity rates whereas those who had VRT were less likely to deliver preterm neonates. In order to explain this variation, one could consider that ART was performed in patients with larger tumors (>2 cm)[14] thus leading to more radical and complex surgeries. Eventually, nowadays surgeons tend to opt for less invasive and less radical procedures such as Cone Resection/LLETZ and VT combined with Neo-Adjuvant Chemotherapy for early CC, that have been associated with similar to radical ones oncologic outcomes but additionally offer improved obstetrical outcomes and lower prematurity rates. Nonetheless, limited data is currently available with regards to the use of the recently introduced techniques such as MIRT[5] due to the small number of reported pregnancies, meanwhile the ongoing ones further prevent the interpretation of the analysis of their obstetric outcomes. The fact that almost all of the reported deliveries were made through caesarean section could be mainly attributed to the small length of the remaining cervix and the respective post-surgical alterations of the female genitalia. The main reasons that can lead to premature labor are cervical incompetence[83] and chorioamnionitis, probably caused by the absence of the natural mucus plug that the cervix produces during gestation.[47,48,84] With regards to cervical incompetence, cerclage[40,85,86] was performed in the majority of the cases. Placement of cervical cerclage[85] after FSS for CC still remains controversial, due to its significant association with severe complications such as stenosis, erosion, bacterial colonization, infection and abscess formation. Furthermore, the exact time of its application has also been extensively discussed. To that end, Kim et al. suggested that it should be placed before or during early pregnancy while others perform cerclage it during the FSS.[40] The technique of the procedure is also debatable, as the transabdominal method[87] is more effective than the transvaginal[88] one but has also been related to higher morbidity rates.[40] Bed rest and restriction of physical activity have been also recommended for cervical incompetence with the intention to prevent preterm labor. Takada et al.[89] even suggest early admission to the hospital during the second trimester, as it offers closer observation and better management of the ongoing pregnancies. Nonetheless, cervical cerclage alone or combined with the aforementioned modalities remains the most efficient method for the management of cervical incompetence and prevention of preterm birth.

Ascending infections are a leading cause of bacterial vaginosis, vaginitis, cervicitis and eventually chorioamnionitis (clinical or subclinical), pPROM, PROM, preterm labor, 1st and 2nd trimester (T1, T2) miscarriages or neonatal deaths from sepsis.[90] The prophylactic use of antibiotics[91,92] for the prevention of these infections is still debatable. On the contrary, their use is strongly recommended after positive vaginal/cervical cultures or under the suspicion of subclinical chorioamnionitis. Furthermore, other causes that can lead to preterm labor are those which are either related to the previous cervical surgical procedure such as colonization of the cerclage material, cerclage slackness[85] or not and referred to chronic diseases (hypertension, diabetes mellitus), other anatomic variations of the uterus, placental anomalies, history of preterm labor, IVF, multiple pregnancies, obesity, smoking, and stress.[93]

It is obvious that pregnancies after FSS, should be considered as high-risk and thereby should be managed in specialized centres. The early detection of the associated with trachelectomy procedures complications is of critical importance. In that setting, women that are diagnosed with cervical incompetence should be closely monitored with frequent ultrasound measurements of the cervical length.[89] Additionally, blood tests (white blood cells count, C-reactive protein, inflammation markers), vaginal cultures[85] and detailed clinical assessment of these patients are required for the early detection of chorioamnionitis. Moreover, tocolytic agents, steroid administration at 24 weeks of gestation[94], avoidance of stressful events and activities[95] as well as elective delivery by cesarean section after the 37th WG are also optional, but the exact efficacy of these has not yet been confirmed.[96] More specifically, in case of tocolysis, despite the fact that it allows corticosteroids to have an impact on fetal lung maturation when administered for 48 h, their administration must be dealt with caution as most of the cases of preterm labor are due to chorioamnionitis which constitutes an absolute contradiction to tocolysis.[97]

Before reaching firm results, there are some limitations of the present study that should be addressed. First of all, the significant heterogeneity among the included studies, along with the fact that some obstetric parameters are not sufficiently reported by some of them, is a critical limitation which precludes further analysis. Furthermore, the imbalance in the number of patients who had different FSS constitutes a further limitation of the study. To that end, some fertility sparing modalities are more innovative and still under investigation resulting in a small number of recruited patients and the respective obstetric outcomes, thus precluding us from getting satisfactory results.

CONCLUSION

Radical operations such as ART, VRT and MIRT presented with higher prematurity rates. A variety of measures during pregnancy can be taken in order to prevent or

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manage complications such as cervical incompetence and chorioamnionitis that can be associated with the previous surgical procedures for the management of CC. However, lack of standardized protocols for the management of these high-risk pregnancies precluded getting any good results with regards to the efficacy of FSS in achieving favourable obstetric outcomes. Large volume studies are further warranted to acquire standardized guidelines for pregnancies achieved after FSS for early stage CC.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Загадка преждевременных родов и исхода беременности после органосохраняющих методов лечения рака шейки матки на ранней стадии: систематический обзор литературы

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Резюме

Достижения современной медицины позволяют пациентам с ранней стадией рака шейки матки (стадия IA-IIAI) сохранять свою репродуктивную способность с онкологической эффективностью по сравнению с предыдущими радикальными методами лечения. Существует многообразие консервативных органосохраняющих процедур, также известных как органосохраняющие операции (ОСО). Цель этого обзора – предоставить новейшие данные о гинекологических исходах и частоте преждевременных родов, а также обсудить способы ведения этих беременностей с высоким риском. Наш обзор литературы включил 3042 женщины с ранней стадией рака шейки матки, из которых 2838 перенесли ОСО (204 были исключены на онкологических основаниях). Почти половина этих пациентов пыталась забеременеть, и около двух третей из них забеременели хотя бы один раз, либо спонтанно, либо с помощью вспомогательных репродуктивных технологий. Данные показывают, что 63.9% этих беременностей закончились живорождением, а 37.6% были преждевременными. Основной причиной преждевременных родов в этой группе населения является послеоперационное укорочение длины шейки матки, которое впоследствии приводит к недостаточности шейки матки и восходящим инфекциям, которые в конечном итоге приводят к (клиническому и субклиническому) хориоамниониту. Радикальные операции, такие как АРТ, ВРТ и МИРТ, имеют более высокую частоту преждевременных родов. Отсутствие стандартизированных протоколов ведения беременности после ОСО препятствует достижению конечных результатов с точки зрения их эффективности в достижении хороших акушерских результатов. Необходимы дополнительные широкомасштабные исследования для того, чтобы выработать стандартизированные руководящие принципы для зачатия после ОСО на ранней стадии рака шейки матки.

Ключевые слова

абдоминальная трахелэктомия, конизация, конизация шейки матки, ранний рак шейки матки, фертильность при раке шейки матки, органосохраняющая операция, лапароскопическая трахелэктомия, неоадъювантная химиотерапия рака шейки матки, акушерское лечение рака шейки матки, осложнения беременности, трахелэктомия, преждевременные роды, робот-ассистированная трахелэктомия, радикальная трахелэктомия, трахелэктомия