Tailoring therapy in endometrial and cervical cancer

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CHAPTER 6

Nerve sparing radical abdominal trachelectomy versus nerve sparing radical hysterectomy in early stage (FIGO IA2 – IB) cervical cancer

A comparative study on feasibility and outcome

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6.1 ABSTRACT

Objectives

Standard treatment in early-stage cervical cancer is a radical hysterectomy (RH) with pelvic lymphadenectomy. In women who wish to preserve fertility radical vaginal trachelectomy has been proposed; however, this is not feasible in larger tumors, and nerve- sparing surgery is not possible. Nerve-sparing radical abdominal trachelectomy (NSRAT) overcomes these disadvantages.

Methods

Case-control study of women with early-stage cervical cancer (International Federation of Gynecology and Obstetrics IA2-IB) submitted to NSRAT from 2000 until 2011. Women submitted to nerve-sparing RH with early-stage cervical cancer were included as control subjects.

Results

Twenty-eight patients and 77 control subjects were included. Neoadjuvant chemotherapy was administered in 3 women before NSRAT because the linear extension was, or exceeded 40 mm. Local recurrence rate was 3.6% (95% confidence interval [CI], 0.00-10.6) in the NSRAT group compared with 7.8% (95% CI, 1.7-13.9) in the control group (P = 0.44). No significant difference was found between both groups regarding disease-free survival and survival. The overall pregnancy rate was 52.9% (95% CI, 28.7%-77.2%). The mean follow-up was 47.3 months (range, 6-122 months) for NSRAT and 51.8 months (11-129.6 months) for nerve-sparing RH.

Conclusions

Nerve-sparing radical abdominal trachelectomy seems safe and effective in women with early-stage cervical cancer who wish to preserve fertility. Respective women should be informed about this treatment option, especially if the tumor is too large for radical vaginal trachelectomy.

6.2 OBJECTIVES

At the time of our study, radical hysterectomy (RH) with pelvic lymphadenectomy was the treatment of choice in early-stage (International Federation of Gynecology and Obstetrics [FIGO] IA2-IB) cervical cancer. Radical hysterectomy is well known to have adverse effects such as bowel, bladder, and sexual functional impairment. [1-3] Damage to the autonomic nerves in the pelvis may be one of the leading causes of these complaints. [4] Therefore, nerve-sparing modifications have been developed. [5-8] Nerve-sparing RH (NSRH) has been proven feasible and is safe in the treatment of early- stage cervical cancer, with an equal prognosis compared with RH. [7, 9]

In patients who wish to preserve their fertility, radical vaginal trachelectomy (RVT), in combination with (laparoscopic) pelvic lymphadenectomy has been presented as a therapeutic option in early stage cervical cancer. [10, 11] However, the previously mentioned nerve-sparing techniques cannot be used in the vaginal approach. Moreover, the vaginal route is not suitable for larger tumors because the narrow operating field does not permit a really radical resection of the parametrium. Usually 20 mm is considered to be the maximum linear extension for women to be eligible for RVT. [7] To overcome these disadvantages of RVT, some advocate abdominal radical trachelectomy. [12, 13] Moreover, it has been shown that it is feasible indeed to selectively preserve the autonomic pelvic nerves during abdominal or laparoscopic trachelectomy. [14, 15] We have transferred our experience with NSRH to the radical trachelectomy and perform a nerve-sparing radical abdominal trachelectomy (NSRAT) in women with early-stage cervical cancer who wish to preserve their fertility.

In this article, we present the results of a case-control study on NSRAT. Apart from the technique, which is presented in detail, the clinical outcomes of NSRAT were compared with a cohort of women in whom NSRH was performed during the same period. In addition, obstetric outcomes of the women who underwent NSRAT are presented.

6.3 MATERIALS AND METHODS

Our department keeps a database in which patient characteristics, tumor characteristics, therapy, and follow-up of all women who are treated for cervical cancer in our referral center for gynecologic oncology are collected prospectively. From this database, all cases of women in whom NSRAT was performed were collected. We changed from vaginal radical trachelectomy to NSRAT on January 1, 2000. Nerve-sparing radical abdominal trachelectomy was offered to women with early-stage disease (FIGO IA2, IB) and a strong wish to preserve their fertility, regardless of histological subtype. Pelvic magnetic resonance imaging was performed routinely to prevent underestimation of tumor dimensions. Whenever gynecologic examination or pelvic magnetic resonance imaging

was suggestive for extra cervical spread or linear extension of or more than 40 mm, neoadjuvant chemotherapy (weekly paclitaxel 70 mg/m^2 and cisplatinum 70 mg/m^2, 6 cycles in total, no chemotherapy in week 4) was administered. [16-18] The control group consisted of women who underwent NSRH because of early-stage cervical cancer (FIGO stage IA2 and IB) shortly before or after each respective case and who did not have an indication for postoperative adjuvant (chemo)radiation therapy. Our protocol for adjuvant radiation therapy is according to the Gynecologic Oncology Group criteria. [19] For each case, we aimed to include 3 control subjects to increase the sample size and statistical power of our study. With this sample size, we would be able to detect a 10% difference in local recurrence (2-side significance 0.05, power 70%). Women in the control cohort were not matched apart from any need for radiation. The interval around each case to select control subjects was 9 months. Patient, tumor, and surgical characteristics and follow-up data of both control subjects and patients were obtained from the aforementioned database. Women who were included were treated between January 1, 2000, and February 1, 2011. Follow-up was obtained until August 1, 2011.

Our surgical procedure for NSRH has evolved over time: from 2000 until 2006, we used the "Leiden NSRH technique." [5] From 2006 onward, all nerve-sparing radical hysterectomies were performed according to Swift procedure. [20] The nerve-sparing procedure in abdominal radical trachelectomy has evolved accordingly. Tables 1a and 1b [21] describe both surgical procedures for NSRAT in detail. In case of lymph node metastasis, the procedure was abandoned, and women were excluded and scheduled for concomitant chemotherapy and radiation therapy. Two experienced gynecologic oncologists performed all surgeries. Antibiotic prophylaxis was administered during surgery (cefazolin 1000 mg/metronidazole 500 mg). After NSRAT, antibiotics (metronidazole 500 mg intravenously and cefuroxime 750 mg intravenously both tds) were continued for 7 days or as long as the uterine catheter was left in place. The uterine catheter was routinely removed 7 days after surgery. A suprapubic catheter was inserted in most women at the end of the procedure, and bladder training was started 5 days after surgery. The bladder catheter was removed whenever the postvoiding volume was less than 50 mL twice (consecutively). Patients were submitted to the same follow-up regimen except for the fact that after NSRAT cytological examination was performed of the neocervix at each follow-up visit. Women were encouraged to prevent pregnancy until at least 6 months after surgery.

Table 1a. The author's surgical procedure for NSRAT until 2006 (according to the Leiden NSRH technique)

	Crucial Surgical Steps in the NSRAT According to the Leiden NSRH (Until 2006) [5]
1	Midline or Maylard's incision
2	Complete pelvic lymphadenectomy (removal of the common and external iliac nodes and lymphatic tissue in the obturator loge above the obturator nerve (Level 2 pelvic lymph node dissection according to Querleu and Morrow[21]) Frozen section of representative portion from each section
3	Opening of the bladder peritoneum and dissection of the bladder from the cervix and vagina
4	Opening of the peritoneum of the pouch of Douglas and blunt and sharp development of the prerectal space
5	Dissection of the ureter from the medial leaf of the peritoneum
6	Separation of the uterosacral ligaments (bluntly) and clamping, cutting, and ligating the medial part. Because the hypogastric nerves run in the lateral part of the uterosacral ligament, the hypogastric nerves are spared
7	Identification of the uterine artery at its origin from the superior vesical artery, dissection of the uterine artery from the parametrium until its diversion in an ascending and descending branch close to the uterus at the level of the isthmus
8	Dissection of the ureter through its passage in the ureterchannel until its entrance in the bladder
9	Dissection of the parametrium from the internal iliac artery medially using the deep uterine vein as posterior border, flipping it over the ureter and saving the uterine artery and its ascending branch.
10	Cleavage of the uterus at the level of the isthmus just distally of the entry of the ascending branch of the uterine artery, a sample is taken from the uterine side of the dissection plane for frozen section
11	Dissection of the paracolpium until 2 cm vaginal margin can be obtained
12	Clamping of the vaginal vault and cutting the vagina below these clamps. The cervix with distal vagina, parametrium and medial parts of the utero-sacral ligaments can now be removed
13	Cerclage in the neo-cervix, placement of uterine catheter
14	Attachment of the neo-cervix to the vagina using interrupted absorbable stitches, usually the vagina needs to be closed partially before attaching the neo-cervix to the vaginal opening in order to match the diameter of the 2

Table 1b. The author's surgical procedure for NSRAT from 2006 onward (parallel to the Swift procedure for NSRH)

	Crucial Surgical Steps in the NSRAT According to the Swift Procedure (2006 onward)
1	Midline or Maylard's incision
2	Complete pelvic lymphadenectomy (removal of the common and external iliac nodes and lymphatic tissue in the obturator loge above the obturator nerve (Level 2 pelvic lymph node dissection according to Querleu and Morrow[21])
3	Opening of the bladder peritoneum and dissection of the bladder from the cervix and vagina
4	Opening of the peritoneum of the pouch of Douglas and blunt and sharp development of the prerectal space
5	Dissection of the hypogastric nerves from the medial leaf of the peritoneum posterior the ureter
6	Dissection of the ureter from the medial leaf of the peritoneum
7	Ligasure clamping and cutting the peritoneal flap medially attached to the rectum (posterior part of the cervical morphogenetic unit) at the level of halfway the circumference of the rectum. Ligasure clamping and cutting of the uterosacral ligaments lateralizing the ureter and the hypogastric plexus
8	Separation of the mesometrium (also called the parametrium: the fatty tissue around the uterine vessels) and the mesenterium of the bladder. The mesenterium of the bladder consists of the inferior vesical vessels, lymphatic vessels, fatty tissue and the distal branches of the inferior hypogastric plexus (branches to ureter, bladder, vagina and clitoris)
9	Identification of the uterine artery at its origin from the superior vesical artery, dissection of the uterine artery from the parametrium until its diversion in an ascending and descending branch close to the uterus at the level of the isthmus
10	Dissection of the ureter through its passage in the ureterchannel until its entrance in the bladder
11	Dissection and resection of the mesometrium from the internal iliac artery medially using the deep uterine vein as posterior border, saving the uterine artery and its ascending branch
12	Cleavage of the uterus at the level of the isthmus just distally of the entry of the ascending branch of the uterine artery, a sample is taken from the uterine side of the dissection plane for frozen section
13	Dissection of the paracolpium until 2-cm vaginal margin can be obtained
14	Clamping of the vaginal vault with Burkey clamps, cutting the vagina below these clamps. The cervix with vaginal margin, mesometrium wings and long-tailed sacro-uterine ligaments can now be removed
15	Cerclage in the neo-cervix, placement of uterine catheter
14	Attachment of the neo-cervix to the vagina using interrupted absorbable stitches; usually the vagina needs to be closed partially before attaching the neo-cervix to the vaginal opening in order to match the diameter of the 2

Data from our database were automatically converted into SPSS (Statistical Package for the Social Sciences 17.0; SPSS Inc, Chicago, IL). Data on pregnancies after NSRAT were added to this SPSS file. Patients and control subjects were compared concerning tumor characteristics, operative data, and postoperative data using either the χ^2 test or Fisher exact test, whichever was more appropriate (categorical data) or Student *t* test (continuous data). Apart from 2- and 5-year recurrence-free survival and overall survival, local recurrence-only rates were calculated. Local recurrence was defined as recurrence located at the ostium ("neocervix") of the uterus (NSRAT cohort) or vaginal vault (NSRH cohort). Kaplan-Meier curves were constructed, and the log-rank test used to compare survival curves. The recurrence-free survival was defined as the time in months from the date of surgery to diagnosis of recurrence or last follow-up, and overall survival was defined as the survival from the date of surgery until death or last follow-up. Patients were censored in the survival analysis whenever follow-up ended without the occurrence of death. Statistical significance was assumed whenever $P < 0.05$. Analyses were not performed on intention-to-treat- basis; women in whom fertility-preserving surgery could not be completed were not included in this study. According to local guidelines, it was not necessary to apply for approval by the local ethical committee.

6.4 RESULTS

A total of 28 women (cases) were treated by NSRAT between January 1, 2000, and February 1, 2011, and 77 control subjects were selected. Because of lack of eligible women, it was not possible to include 3 control subjects for each case. The mean follow-up was 47.3 months (range, 6-122 months) and 51.8 months (range, 11.0-129.6 months), respectively. The mean age was 31.2 years (range, 21-37 years) for the cases and 44.2 years (range, 32-73 years) for the control group. Patient and tumor characteristics are presented in Table 2. As expected, women treated with NSRAT were significantly younger ($P < 0.05$). With respect to the known prognostic factors (histological subtype, infiltration depth, presence of lymph-vascular space invasion, and linear extension) there was no significant difference between patients and control subjects (Table 2). The reported tumor characteristics are based on the surgical specimen. Three patients received neoadjuvant chemotherapy before the NSRAT because of tumor size of or greater than 40 mm. Surgical data are presented in Table 2. Apart from length of surgery (median duration, 255 vs210 minutes, $P < 0.01$), there were no significant differences between both groups. None of the women in both the NSRAT and the NSRH cohorts needed adjuvant treatment after surgery; hence, all women had negative node status, negative vaginal margins, and no parametrial invasion because each of this features would necessitate adjuvant treatment. Overall recurrence rates were 7.4% (95% confidence interval [CI], 0.00%-16.9%) and 14.3% (95% CI, 6.3%-22.3%) for NSRAT and NSRH, respectively ($P = 0.45$). Median follow-up

Table 2. Patient and tumor characteristics and surgical data

Patient and Tumor Characteristics	NSRAT (Patients), n = 28	NSRH (Control Subjects), n = 77	p
Age, mean (range), y	31.2(21-37)	44.2 (32-73)	< 0.01
Histological subtype, n (%)			
Squamous cell	14 (50.0)	55 (71.4)	0.06
Adeno	11 (39.3)	19 (24.7)	0.15
Adenosquamous	2 (7.1)	2 (2.6)	0.47
Other	1 (3.6)*	1 (1.3) †	0.46
Invasion depth, mean (range) [SE], mm	7.5 (0.0-35.0) [1.9]	6.8 (1-15) [0.41]	0.61
Invasion depth, median [SD], mm	4.0 [9.2]	6.0 [3.5]	
Maximum linear extension, mean [SE], mm	17.3 [2.43]	20.6 [1.5]	0.26
Maximum linear extension, median (range) [SD], mm	13.5 (0.1-38.0) [12.4]	18 (0.1-52.0) [13.0]	
Lymph space and vascular invasion, n(%)	10/28 (36)	19/77 (25)	0.41
No. removed nodes, mean (min-max)	20.6 (10-41)	23.5 (4-61)	0.17
High-risk patients (extension > 20 mm and/or infiltration > 10 mm), n (%)	10 (35.7)	39 (50.6)	0.18
High-risk patients (extension > 20 mm and lymph vascular space infiltration, n (%)	3 (10.7)	10 (13.0)	0.75
Stage, n (%)			0.89
1A	3 (10.7)	6 (7.8)	
1B1	22 (78.6)	63 (81.8)	
1B2	3 (10.7)	8 (10.4)	
Blood loss, median (range) [SD], mL	885 (250-3620) [708]	750 (75-3420) [549]	0.22
Length of surgery, median (range) [SD], min	255 (165-410) [59.2]	210 (120-360) [44]	< 0.01
Nerve sparing successful, n (%)			0.35
1-sided	0 (0)	1 (1.3)	
Both sides	25 (89.3)	73 (94.8)	
Unsuccesful	3 (10.7)	3 (3.9)	
Postoperative complications	0	2 ¥	0.40

* Neuroendocrine tumor † Poorly differentiated tumor ¥ Both ileus recovered with conservative management

for these patients with recurrence was as follows: 68.5 months (range, 15-122 months) for NSRAT and 77.5 months (range, 37.1-129.6 months) for NSRH. Local recurrence-only rates were 3.6% (95% CI, 0.00%-10.6%) and 7.8% (95% CI, 1.7%-13.9%) (P = 0.91). None of the women who received neoadjuvant chemotherapy before NSRAT had recurrent disease.

Survival data are presented in Table 3. Figure 1 displays the Kaplan-Meier curve of 2 years disease-free survival (P = 0.19, log rank). Among the 28 women in the NSRAT group, 2 women had recurrent disease. One of these is alive and in complete remission after chemoradiation (recurrence after 50 months); the other woman died of disease after 15 months (recurrence after 11 months). Both patients were compliant with our follow-up protocol and were submitted at least every 4 to 6 months to gynecologic physical examination. In the control group, 11 of 77 women had recurrent disease, of whom 2 women died of disease (after 13.7 and 28.2 months, respectively). Site of recurrence is detailed in Table 3. Details on the 2 patients treated with NSRAT with recurrent disease are listed in Table 4.

Nerve sparing was successful in the vast majority of women: at least 1-sided in 89.3% and 96.1% (in NSRAT and NSRH, respectively). All failures were due to the inability to identify the hypogastric nerve. There were a few postoperative complications (NSRAT, NSRH): voiding problems: 3.6% (urgency) and 18.2% (urgency, cystitis, stress-incontinence); defecation problems (10.7%): 11.7% (constipation in all women); and sexual dysfunction (3.6%; 1.3% dyspareunia in all women). Moreover, there were 2 cases of deep vein thrombosis in the control group (2.6%), whereas the incidence rates of lymph edema were 3.6% and 14.3% after NSRAT and NSRH, respectively. The maximum length of suprapubic catheterization was 7 days (n = 1 NSRAT and n = 4 NSRH); in all other women, the suprapubic catheter was removed on day 5. Of the 26 women in the NSRAT group without recurrent disease, only 17 (65.4%; 95% CI, 46.7%-84.0%) tried to conceive. Two of the 3 women who had neoadjuvant chemotherapy successfully conceived. Details on the patients treated with neoadjuvant chemotherapy are listed in Table 5. The overall pregnancy rate showed to be 52.9% (95% CI, 28.7%-77.2%) of those women aiming to get pregnant. There were 12 spontaneous pregnancies in 7 patients and 2 in vitro fertilization pregnancies in 2 patients. There were no fetal losses and no premature deliveries. All deliveries were after 37 weeks of pregnancy and by cesarean section. Four patients (24%; 95% CI, 3.0%-44.0%) are in the course of in vitro fertilization, one of these as a result of male infertility. The remaining 4 patients aiming to conceive are either awaiting spontaneous pregnancy or in the course of analyzing subfertility. Two women were pregnant at the time of NSRAT surgery, 7 and 12 2/7 weeks' gestation, both resulting in a spontaneous miscarriage at, respectively, 9 1/7 and 13 5/7 weeks' gestation.

Table 3. Recurrence and survival of NSRAT versus NSRH

	NSRAT (Patients), n= 28	NSRH (Control Subjects), n = 77	p
Follow-up, mean (range) [SE], mo	47.3 (6.2-122.1) [5.6]	51.8 (11.0-129.6) [2.9]	0.45
Total recurrence , n (%, 95% CI))	2 (7.4, 0.00–16.9)	11 (14.3, 6.3–22.3)	0.35
Local recurrence only, n (%)	1 (3.6, 0.00-10.6)	6 (7.8, 1.7-13.9)	0.44
Time to recurrence, (mean) [SE], mo	30.7 [19.5]	19.2 [17.6]	0.58
Site of recurrence (n)			0.29
Neocervix / vaginal vault	1	5	
Vaginal vault + bladder	0	1	
Pelvic side wall	1	0	
Para-aortic nodes	0	2	
Bowel / abdominal wall	0	3	
Survival, % [n/n] (95% CI)			
2 y	95% [19/20] (85-100%)	98% (63/64) (95-100%)	0.38
5 y	90% [9/10] (71-100%)	87 % (20/23) (73-100%)	0.81
Disease-free survival, % [n/n] (95% CI)			
2 y	95 % [19/20] (77-100%)	85 % [54/64] (75-93%)	0.22
5 y	80 % [8/10] (47-99%)	85% [17/20] (69-100%)	0.78

Table 4. Details on recurrences of the 2 out of 28 patients with recurrent disease after NSRAT

Case	A	B
Linear extension, mm	7	20
Infiltration depth, mm	4	12
Surgical margin isthmus, mm	14	25
Number of nodes removed at NSRAT	16	12
LVSI	Yes	Yes
Histology	Squamous	Squamous
Neo-adjuvant chemotherapy	No	No
Time to recurrence, mo	11	50
Location	Iliac lymphnodes (right side)	Neocervix
Therapy for recurrence	Chemoradiation	Abdominal hysterectomy with adjuvant radiation therapy
Status at end of follow-up (August 1st 2011)	Died of disease 4 months after diagnosis of recurrence	Alive with pulmonary, mediastinal, para-aortal and iliacal metastasis
Total follow-up (months)	15	122

Table 5. Details on patients who received Neo-adjuvant chemotherapy (NACT)

Case	A	B	C
Pre-NACT linear extension (mm)	40	40	42
Post- NACT histological linear extension (mm)	5	6	14
Post- NACT histological infiltration depth (mm)	3	4	5
Number of nodes removed at NSRAT	17	18	21
LVSI	No	Yes	Yes
Histology	Squamous	Squamous	Squamous
Follow up (months)	63.9	23.5	6.2
Recurrence	No	No	No
Pregnancy-outcome	2 Term deliveries	1 Term delivery	No attempt

NSRAT: nerve sparing radical abdominal trachelectomy

LVSI: lymph-vascular space invasion

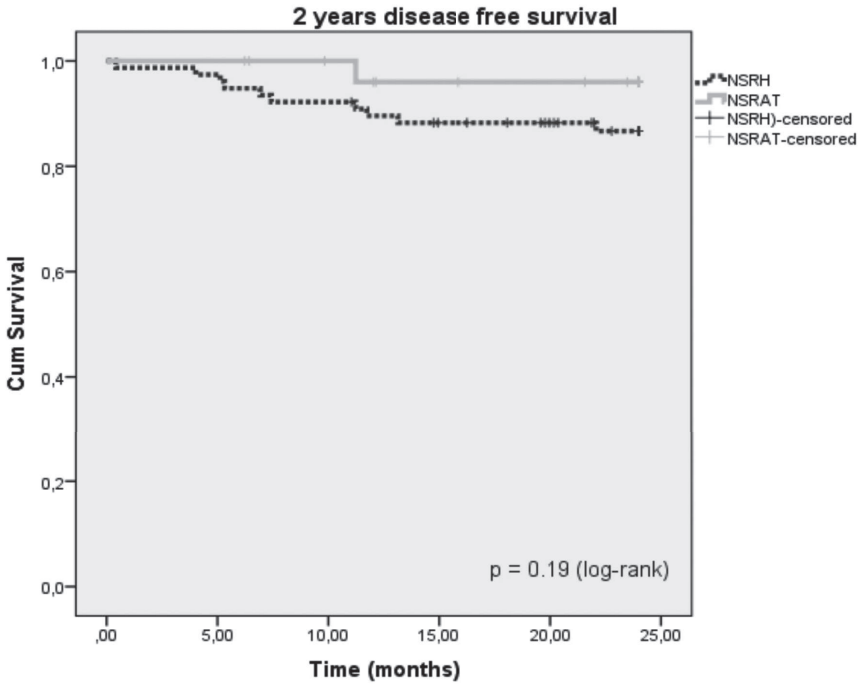

Figure 1. 2 years disease free survival curve

NSRAT: nerve sparing radical abdominal trachelectomy

NSRH: nerve sparing radical hysterectomy

6.5 DISCUSSION

Our case-control study shows that NSRAT appears safe and effective with regard to fertility preservation in women with early-stage cervical cancer. Local recurrence rate and overall survival and disease-free survival do not differ significantly after NSRAT and NSRH in our cohorts (Table 3). Moreover, site of recurrence does not differ between both groups. The non-statistically significant difference in overall recurrence rate (7.4% and 14.3% after NSRAT and NSRH, respectively) is, however, remarkable and may be due to selection, although the number of high-risk patients did not differ significantly between both cohorts. Our data implicate that, although numbers are small, NSRAT is safe in women with early-stage cervical cancer who wish to preserve fertility. Pregnancy rate is as high as 53% (95% CI, 28.7%-77.2%), indicating that NSRAT is effective in preserving fertility. Literature on abdominal trachelectomy is scarce, but our survival rates and pregnancy rates seem to be similar to those reported by others. [12, 13, 22, 23] A recent literature review by Pareja et al. [24] looking at surgical, oncological, and obstetrical outcomes shows that abdominal radical trachelectomy is a safe option for patients with early-stage cervical cancer.

Other recent studies have shown results of surgical treatment for early-stage cervical cancer by RVT in combination with pelvic lymphadenectomy with regard to fertility preservation. [10 25-27] These reports show that RVT is performed mostly in small cancers. For example, in the large series on VRT recently published by Speiser et al [27], the median tumor size is microscopic, whereas in our series the median tumor size at histological examination after surgery is 13.5 mm (mean, 17.3; range, 0.1-38 mm; Table 2). Because parametrial involvement is extremely rare in tumors less than 20 mm, especially in the absence of lymphovascular space infiltration (LVSI), one can argue whether these patients need a parametrectomy at all. [28, 29] In women with small tumors (i.e., <20 mm), an excisional cone or simple trachelectomy with pelvic lymphadenectomy has shown excellent survival and low recurrence rates, although the median follow-up was only 16 months. [28, 30, 31] These data indicate that we may end up performing excisional cones in the low-risk patients (small tumor < 20 mm in diameter without LVSI) and NSRAT in the higher-risk patients (larger tumors, with LVSI) with early- stage cervical cancer who wish to preserve fertility.

Because of small numbers, we could not differentiate the risk of recurrence for high- and low-risk women. As mentioned above, there is much debate about the need for parametrial resection and whether parametrial resection is in the detection of local spread or nodal spread. In this respect, it is important to compare the presence of nodes in the parametrium after (type 2) RVT and conventional RH: 8% versus greater than 90% of specimen. [26, 32] Hence, if nodal spread is considered an issue, RVT may leave a significant percentage of nodes undetected, especially if sentinel node detection is not performed.

Apart from tumor size, another important reason to prefer the abdominal approach above the vaginal route to perform a trachelectomy is the possibility of selectively sparing the autonomic nerves in the pelvis, as this is technically not possible in vaginal trachelectomy. Although there are, to our knowledge, no data on autonomic nerve damage after radical trachelectomy, there is abundant evidence that the pelvic autonomic nerves are damaged during RH. [33] This damage is thought to be the leading cause of the well-known long-term bladder, bowel, and sexual morbidity after conventional radical hysterectomy. [2] Because there is solid evidence that nerve-sparing surgery reduces these complications, [13, 33, 34] it seems more than logic to adopt nerve-sparing surgery in radical trachelectomy, especially because nerve- sparing surgery is considered safe and feasible in early-stage cervical cancer. [7, 35] Nerve-sparing was successful in the vast majority of both our patients and control subjects (89.3% and 96.1%, respectively). However, from the analysis of the dysfunctions, possibly due to nerve damage, it can be concluded that failed nerve-sparing surgery does not inevitably lead to dysfunction, nor will nerve-sparing surgery fully prevent dysfunctions. Clearly, autonomic function does not mimic autonomic nerve damage as suggested in our recent longitudinal in-depth analysis of bladder, bowel, and sexual function after conventional RH and NSRH. [2]

The main risk factors for recurrence of cervical cancer are tumor size more than 20 mm, stromal invasion of more than 10 mm, and presence of LVSI.[19] Our cases were treated with neoadjuvant chemotherapy if tumors were 40 mm or more in their largest diameter on histological examination. Others have proposed neoadjuvant chemotherapy for bulky cervical cancers in women who wish to preserve fertility as well: it is suggested to decrease the number of positive nodes, and it reduces tumor volume before surgery, permitting less radical and hence more successful fertility-preserving surgical techniques. [36, 37] Although not much has been published about the use of neoadjuvant chemotherapy in fertility preservation, the data on its use in cervical cancer are abundant, and this protocol is considered safe and effective. [38] Although small, our series adds data to support the use of neoadjuvant chemotherapy mainly because it does not hamper fertility preservation. As the aim of the radical trachelectomy is to preserve fertility, it is also important to consider the condition and functionality of the uterus after surgery with regard to possible pregnancies. Because of cervical incompetence (both mechanical and with regard to prevention of infection), second-trimester abortion and premature delivery are the main concerns after trachelectomy.[22] Because the uterine arteries are ligated in conventional trachelectomy, the blood supply to the uterine corpus may be reduced. Collateral circulation from the utero-ovarian ligaments is considered to keep the uterine tissue viable, but it is thought to provide reduced blood supply to the corpus leading to decreased fertility, less placental function, and consequently probably a higher risk of premature rupture of membranes and premature labour.[30] As described in detail, our technique allows specific sparing of the ascending branch of the

uterine artery, resulting in better blood supply to the uterine corpus during pregnancy. This uterine artery-sparing technique is used by others as well.[14] In our opinion, the fact that none of our cases had either second-trimester abortion or growth retardation may have been in relation to the sparing of the ascending branches of the uterine artery.

In this study, two experienced gynecologic oncologists have performed all surgeries. We have collected 28 cases for NSRAT in a period of a little more than 10 years. Incorporating our technique into one's clinic armamentarium needs consideration of the learning curve and experience, which are needed for achieving good results. Moreover, with the interpretation of our results, we have to take the small sample size and observational design of our study into account. Both may have led to bias. For example, women with non-favorable characteristics may have been counseled to non-fertility-preserving treatment. Moreover, we had to include a lower-than-intended number of control subjects. Although post hoc comparison of both groups does not show any differences with regard to the well-known risk factors for local recurrence, and data were collected prospectively, the previously mentioned methodological weaknesses need to be taken into account and incorporated into counseling respective women.

This study demonstrates that NSRAT results in recurrence and survival rates that do not differ from those after conventional treatment (NSRH) in women with early-stage cervical cancer. The overall pregnancy rate after NSRAT was 53%. There was no fetal loss or premature delivery in our series. In our opinion, NSRAT is feasible and safe and should be offered to women with early-stage cervical cancer who want to preserve their fertility. In women with larger tumors, neoadjuvant chemotherapy can be administered to downstage the tumor and allow for fertility-sparing surgery. In both situations, we have to bear in mind that the level of evidence of our study is moderate. That is why treating gynecologic-oncologists are obliged to give full and detailed information, and both counseling and treatment should be centralized to gain and maintain experience.

6.6 REFERENCES

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