Tailoring therapy in endometrial and cervical cancer

Gent, M.D.J.M. van

CHAPTER 5

Long term oncological outcome after conventional radical hysterectomy versus two nerve-sparing modalities for early stage cervical cancer

A study on oncological safety in the light of improving quality of life after surgery

Mignon van Gent
Mandy Rademaker
Yavanne van der Veer
Mariette van Poelgeest
Katja Gaarenstroom
Hein Putter
Baptist Trimbos
Cor de Kroon

2017, International Journal of Gynecologic Oncology, accepted

CHAPTER 5

Long term oncological outcome after conventional radical hysterectomy versus two nerve-sparing modalities for early stage cervical cancer

A study on oncological safety in the light of improving quality of life after surgery

5.1 ABSTRACT

Objectives

Nerve-sparing radical hysterectomy for early stage cervical cancer was introduced to improve quality of life after treatment. Sparing the pelvic autonomic nerves reduces bladder, bowel and sexual dysfunction. The Leiden nerve-sparing radical hysterectomy (LNSRH) was modified to the Swift procedure, the latter being more radical regarding the sacro-uterine and parametrial resection. We investigate whether nerve-sparing surgery has comparable oncological outcomes as the conventional radical hysterectomy (CRH). Concurrently, we investigate whether there is a difference regarding the oncological outcomes of the two nerve-sparing techniques.

Methods

Single centre, observational prospective cohort study analysing oncological outcomes in women undergoing CRH (1994 – 1999), LNSRH (2001 – 2005) or Swift procedure (2006 - 2010) for early stage cervical cancer (FIGO IA2-IIA).

Results

363 patients (124 CRH, 122 LNSRH, 117 Swift) were included. FIGO-stage ≥ IB2 ($p = 0.005$) was significantly more prevalent in the CRH cohort. The 5-year pelvic relapse free survival (PRFS) and overall survival (OS) were not significantly different between the 3 cohorts ($p = 0.116$). Regarding the nerve-sparing cohorts, the Swift cohort showed a significant better

5-year OS (87.2%), compared to the LNSRH cohort (78.8%) ($p = 0.04$). In the LNSRH cohort, resection planes < 5 mm free and need for adjuvant therapy were significantly higher than in the Swift cohort, $p = 0.026$ and 0.046 respectively.

Conclusions

The nerve-sparing radical hysterectomy shows a similar oncological outcome compared to the conventional radical hysterectomy. The more radical Swift version of nerve-sparing techniques is preferable to the former Leiden nerve-sparing radical hysterectomy procedure.

5.2 INTRODUCTION

Several nerve-sparing techniques on radical hysterectomy for early stage cervical cancer have been developed and modified over the last decades. The first nerve-sparing technique was introduced in Japan in the 1960s: a modification of the Okabayashi operation by gynaecologist Kobayashi [1] Nerve-sparing techniques are modifications of the conventional radical hysterectomy (CRH) aiming to preserve the pelvic autonomic nervous system. Damage to these nerves is thought to be responsible for the well-known long-term morbidity after radical surgery in the small pelvis: extensive bladder, bowel and sexual dysfunction. Sparing the autonomic nerves has been proven to be highly effective in maintaining the physiology of the pelvic organs. [2-6] From 2001 till 2005 at the LUMC an effective and feasible nerve-sparing technique was developed and performed: The Leiden Nerve-sparing Radical Hysterectomy (LNSRH). [7] The knowledge acquired by cadaver studies and the experience of Japanese colleagues was used to develop this technique. This technique is easy to adopt and can be used for any type of radical hysterectomy in Western patients who generally have a higher BMI and a different distribution of fat in the pelvis compared to Asian patients. [8] Earlier, we showed in a prospective observational cohort study that there was no difference in local recurrence rate and local recurrence free survival. [7] Höckel et al. [9] described new insights on tumour spread of cervical cancer cells showing that this is not a random process but follows a certain morphogenetic unit. This inspired us to develop an adaptation to this technique: the Swift operation, [10] which resembles the total mesometrial resection (TMMR) as developed and advocated by Höckel et al. [9] From 2006 onwards the Swift operation was used as the preferred procedure in all early stage cervical cancer patients at the LUMC. There are three main differences between the Swift operation and the LNSRH (figure 1). The first is that the hypogastric nerve is approached laterally and dissected free from the uterosacral ligaments and surrounding tissue, so the uterosacral ligaments and rectal pillars can be resected more radically. Secondly, the parametrial resection plane is performed more horizontally, dissecting the mesometrial tissue from the ventral side of the ureter. And third, the lateral leaf of the vesico-uterine ligament is only resected when it is necessary to obtain radically free surgical margins in this area.[10] By being more radical around the uterosacral ligaments and parametria and having better visibility at the hypogastric nerves, the Swift operation is thought to be an improvement of the LNSRH in sparing the autonomic nerve system.[10] In this cohort study we analysed whether the Swift procedure could be superior to the LNSRH in terms of oncological outcome. Concurrently, and most importantly, we compared the results of the two nerve-sparing techniques to the CRH to determine whether nerve-sparing surgery is equal to CRH regarding oncological outcome.

Figure 1. Graphical image of the dissection planes for the 3 different techniques

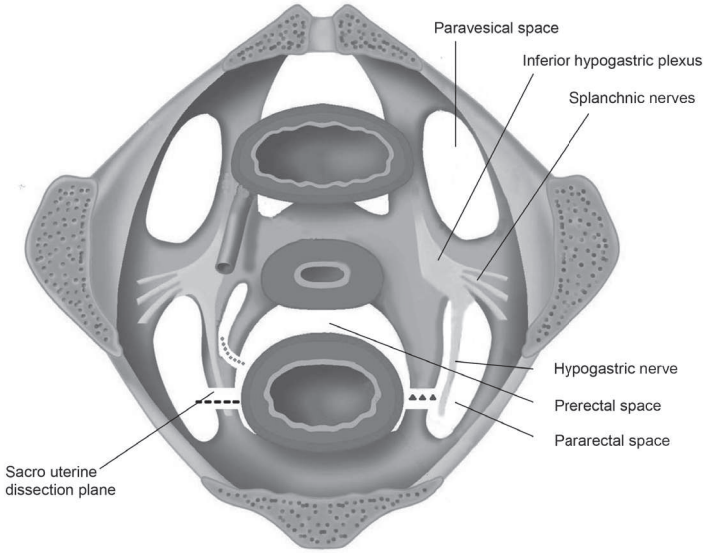


Diagram of the pelvic autonomic nerves in radical hysterectomy: transversal section through the pelvis showing the bladder, uterine cervix, and rectum within the pelvic connective tissues. Autonomic nerves are in yellow.

resection plane CRH resection plane NSRH resection plane Swift

5.3 MATERIALS AND METHODS

The study was performed on 3 LUMC cohorts: CRH was performed from 1-1-1994 to 1-1-1999, LNSRH from 1-1-2001 to 1-1-2005 and the Swift-procedure from 1-10-2006 to 31-05-2010. All patients had cervical cancer FIGO-stage IA-IIA and were scheduled to undergo a radical hysterectomy with curative intentions. The data required for this study were prospectively entered in a database especially developed for research purposes. Administrative censoring was performed for all cohorts at 5-year follow-up. This study was designed to evaluate 3 different surgical techniques. Patients in the CRH cohort received a non-nerve-sparing radical abdominal hysterectomy including a pelvic lymphadenectomy (Wertheim Meigs, Piver type III). [11] The techniques of the LNSRH and the Swift procedure have been described previously. [1 10, 12] During the periods January 1999 to January 2001 and January 2005 to October 2006, there was a transition from one technique to the next. Surgical procedures performed in these periods were not included in the analysis to exclude the possibility of mixing up different techniques and possi-

ble influence on results due to a learning curve. Pre-operative staging (FIGO) was done by general and gynaecological physical examination. We performed a chest X-ray and did an ultrasound of the kidneys to exclude hydronephrosis indicative of extra cervical spread. Post-operative histopathological review included histological typing, infiltration depth, maximum linear extension, lymph-vascular space-invasion (LVSI), parametrial involvement, number of lymph nodes removed and presence and number of lymph node metastases. Surgical margin with regard to vaginal cuff and parametria was defined as tumour free whenever the tumour free margin was more than 5 mm. Post-operative therapy, radiotherapy or concomitant chemotherapy and radiotherapy, was administered in case of lymph node metastases, parametrial involvement or in case of insufficient resection planes as explained above. From 1997 onwards, patients also received additional therapy if at least two out of three unfavourable prognostic factors were present: LVSI, tumour diameter > 4 cm or infiltration depth of > 15 mm. [13] Follow-up was performed 3-monthly in the first follow-up year, four-monthly in year two and half-yearly in year three, four and five. At follow-up the patient gets a general physical and gynaecological examination. Only on indication laboratory and/or radiological analysis are performed. We studied and compared the three cohorts with regard to: pelvic relapse (PR), extra pelvic relapse (EPR), 5-year pelvic relapse-free survival (PRFS) and overall survival (OS). Relapse is defined as recurrent disease diagnosed at follow-up and confirmed by CT and/or MRI and/or histology and/or cytology. The date of relapse was set upon the day on which the first diagnostic test was performed. A pelvic relapse is defined, according to the SHAPE trial criteria [14] as a relapse within the pelvis, below the brim and inferior to the L4-L5 vertebral level. Extra-pelvic relapse is defined as a relapse outside of the pelvis, including above the pelvic brim and/or superior to the L4-L5 vertebral level. Extra-pelvic relapse includes distant metastases. [14] Length of surgery (minutes) and the amount of blood loss (millimetres) were analysed. Follow-up is defined as the period between the date of surgery and the last check up or date of death. All statistics were done using SPSS (IBM SPSS statistics for Windows, Version 23.0. Armonk, NY). Different statistical tests were used to compare the characteristics of the three groups. The Chi-Square test was used to compare categorical data and One-Way ANOVA was used to compare means and numerical data. Non-normally distributed continuous outcomes were compared between the 3 cohorts using Kruskal-Wallis test. To analyse the survival data, a Kaplan Meier-curve was used where significance was assessed with the Log-Rank test. For PR, competing risks due to death were ignored because of the very small number of deaths before PR. A multivariate Cox proportional hazard regression model was used to assess the effect of FIGO-stage ≥ IB2, lymph node metastases present and LVSI infiltration depth > 15 mm on relapse. We produced a Cox-model based survival curve correcting for factors not resulting from the type of surgery, that significantly dif-

fered between the groups. The level of statistical significance was accepted at $p<0.05$. The study was approved by the Medical Ethics Committee of our institution.

5.4 RESULTS

Patient, tumour and perioperative characteristics

Table 1 describes the clinical characteristics of the 3 cohorts. There was no significant difference between the cohorts except for FIGO staging, with FIGO ≥ IB2 being most frequent in the CRH cohort ($p = 0.005$). The histopathological and tumour characteristics of the 3 cohorts are shown in table 2. The amount of blood loss was significantly higher in the CRH cohort whereas length of surgery was significantly longer for the Swift procedure compared to both other surgical techniques. There was a significant difference concerning the number of lymph nodes removed, with least number of nodes harvested in the CRH cohort ($p < 0.001$). No significant difference was found between the three groups regarding the presence of lymph node metastasis, parametrial involvement, tumour diameter (> 20 mm and > 40 mm), infiltration depth > 15 mm, resection planes nor need for adjuvant therapy.

Table 1. Clinical characteristics of 124 patients who had a conventional (non-nerve-sparing) hysterectomy, 122 patients who were scheduled for a nerve-sparing procedure and 117 patients who were scheduled for a modified nerve-sparing procedure called the Swift procedure

Group	**CRH**	**LNSRH**	**Swift**	**p**
(n)	**(124)**	**(122)**	**(117)**	
Period	1/1/1994 - 1/1/1999	1/1/2001 – 1/1/2005	1/10/2006 –1/05/2010	
Age, mean (median) [SD], y	46.5 (44) [14.2]	46.2 (43) [12.2]	46.9 (44) [12.1]	0.927
FIGO stage, n (%)				0.024
IA / IB1	87 (70.2)	98 (80.3)	102 (87.2)	
IB2	21 (16.9)	12 (9.8)	7 (6.0)	
IIA	16 (12.9)	12 (9.8)	8 (6.8)	
FIGO ≥ IB2	37 (29.8)	24 (19.7)	15 (12.8)	0.005
Histologic type, n (%)				0.124
Squamous	71 (57.3)	84 (68.9)	85 (72.6)	
Adeno	36 (29.0)	30 (24.6)	23 (19.7)	
Adenosquamous	9 (7.3)	5 (4.1)	7 (6.0)	
Other	8 (6.5)	3 (2.5)	2 (1.7)	

Legend: CRH: conventional radical hysterectomy; LNSRH: Leiden nerve sparing radical hysterectomy.

Table 2. Peri-operative, histopathological and tumour characteristics

Group (n)		**CRH (124)**		**LNSRH (122)**		**Swift (117)**		***p*** **all cohorts***	***p*** **LNSRH vs Swift****
Blood loss (ml),	median (range)	875	(175-11,000)	700	(125-4,500)	700	(75-6,500)	**<0.001**	
	(mean) [SD]	(1116)	[1116]	(838)	[594]	(855)	[761]		
Operating time (min.),	median (range)	180	(120-540)	180	(60-270)	217	145-390)	**<0.001**	
	(mean) [SD]	(200)	[66]	(176)	[35]	(226)	[47]		
No of nodes removed,	median (range)	17	(0-33)	22	(5-42)	23	(7-61)	**<0.001**	
	(mean) [SD]	(17)	[6.8]	(22)	[7.8]	(24)	[9.0]		
Lymph vascular space invasion, n(%)		38	(30.6)	48	(39.3)	54	(47.0)	0.085	0.312
Lymph node metastases, n(%)		21	(16.9)	32	(26.2)	22	(18.8)	0.165	0.170
Parametrial involvement, n(%)		9	(7.3)	9	(7.4)	9	(7.7)	0.991	0.926
Infiltration depth > 15 mm, n(%)		19	(15.3)	32	(26.2)	26	(22.2)	0.106	0.470
Tumour diameter > 20 mm, n(%)		65	(52.4)	73	(59.8)	65	(55.6)	0.501	
Tumour diameter > 40 mm, n(%)		23	(18.5)	26	(21.3)	25	(21.4)	0.822	
No residual disease in surgery sample, n(%)		24	(19.4)	25	(20.5)	22	(18.8)	0.945	
Resection margins < 5 mm free, n(%)		15	(12.1)	21	(17.2)	9	(7.7)	0.082	**0.026**
Adjuvant therapy, n(%)		41	(33.1)	55	(45.1)	38	(32.5)	0.072	**0.046**
	radiotherapy	40	(32.3)	48	(39.3)	30	(25.6)		
	chemoradiation	1	(0.8)	7	(5.7)	8	(6.8)		

Legend: n: number of patients (with); CRH: conventional radical hysterectomy; LNSRH: Leiden nerve sparing radical hysterectomy; * comparing CRH versus LNSRH versus Swift; ** comparing the two nerve-sparing modalities

Follow-up

Five-year follow-up was completed in 100% of the patients in the CRH- and LNSRH-cohort. There were two patients lost to follow-up in the Swift cohort (1.7%) with follow-up lengths of 46.7 months and 32.2 months, both disease-free at the time. These 2 women were censored at last follow-up. Median time to pelvic relapse was 23.8, 14.3 and 9.6 months (p = 0.192) for CRH, LNSRH and Swift cohort respectively.

LNSRH versus Swift

We compared the two nerve-sparing modalities regarding oncological outcomes to investigate the effect of changing the surgical technique. In the LNSRH cohort significantly more often resection planes were < 5 mm free (p = 0.026) and with subsequently more often a need for adjuvant therapy (p = 0.046). However, using the Log-rank analysis, 5-year PRFS did not significantly differ between the two nerve-sparing modalities (p = 0.202). (Figure 2A) In contrast, there was a significant difference in overall survival at 5 years with 78.7% for LNSRH versus 87.2% for the Swift cohort (p = 0.040) again using the Log-rank analysis. (Figure 2B)

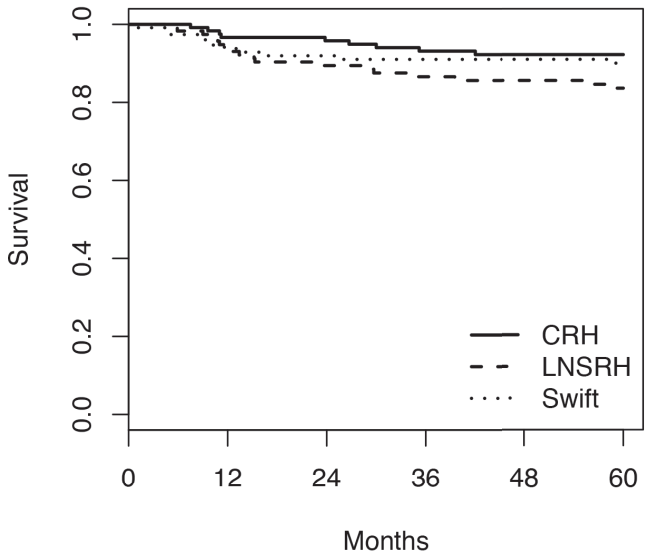
CRH versus LNSRH versus Swift

When comparing the 3 cohorts to investigate whether nerve-sparing surgery compromises the oncological outcome of the patient, no significant difference could be demonstrated between the three cohorts regarding 5-year PRFS and OS. (table 3). Figure 2C and 2D show the Cox-model based survival curves for the 5-year PRFS and OS. The nerve-sparing surgical modalities do not significantly influence the adjusted hazard (corrected for FIGO > IB2, lymph node metastasis and infiltration depth > 15 mm) on developing a pelvic relapse. (table 4) There was no significant difference in survival outcomes between CRH and the Swift cohort. (p = 0.505 and p = 0.134 respectively, table 3)

Table 3. Oncological outcomes after 5 years following treatment by radical hysterectomy

Group (n)	CRH (124)	LNSRH (122)	Swift (117)	*p* all cohorts*	*p* LNSRH vs Swift**	*p* CRH vs Swift***
5yr PR, n (%)	9 (7.3%)	18 (14.8%)	11 (9.4%)			
5yr EPR, n (%)	14 (11.3%)	17 (13.9%)	11 (9.4%)			
5yr PRFS	80.6%	71.3%	79.5%	0.116	0.202	0.505
5yr OS	81.5%	78.7%	87.2%	0.116	0.040	0.134

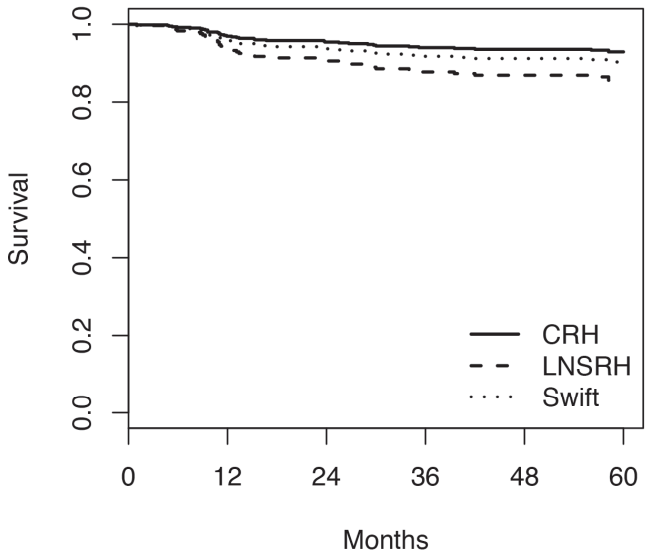
Legend: CRH: conventional radical hysterectomy; LNSRH: Leiden nerve sparing radical hysterectomy; PR: pelvic relapse; EPR: extra pelvic relapse; PRFS: pelvic relapse free survival; OS: overall survival. * comparing CRH, LNSRH and Swift; *** comparing CRH to Swift.** comparing LNSRH to Swift;



2A. Kaplan-Meier curve of PRFS

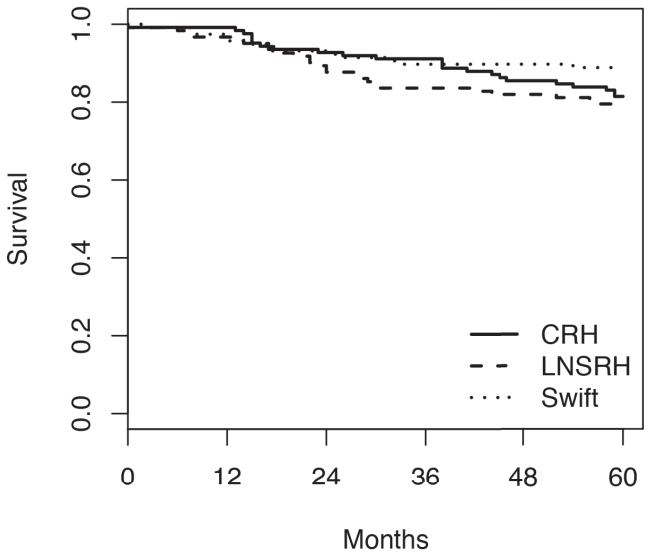
Log-Rank comparing all 3 cohorts: p = 0.116

Log-Rank when comparing LNSRH to Swift: **p = 0.202**



2C. Cox-model based survival curve of PRFS

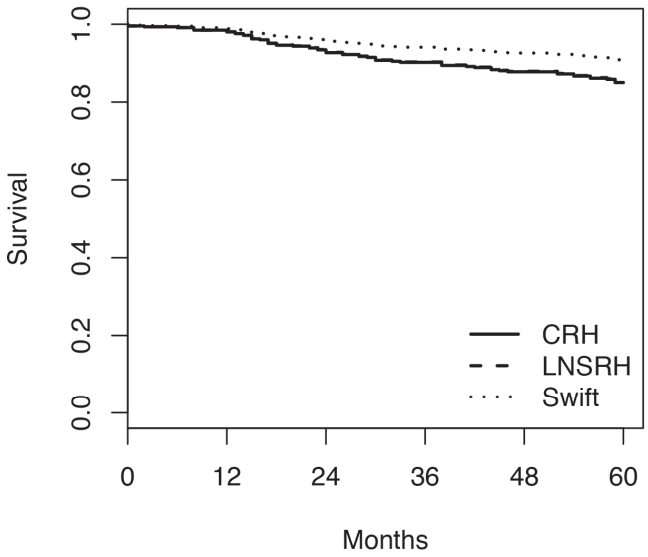
Figure 2. Survival curves of the radical hysterectomy cohorts with respect to 5 year pelvic relapse free survival (PRFS) and 5 year overall survival (OS).



2B. Kaplan-Meier curve of OS

Log-Rank comparing all 3 cohorts: p = 0.116

Log-Rank when comparing LNSRH to Swift: **p = 0.040**



2D. Cox-model based survival curve of OS

Table 4. Effect of NS-modalities on pelvic relapse free survival and overall survival after correcting for unfavourable prognostic factors in a Cox proportional hazards regression model

	With regard to PRFS:			With regard to OS:		
	HR	**95% CI**	**p**	**HR**	**95% CI**	**p**
Conventional RH						
+ LNSRH	2.112	(0.937 - 4.763)	0.071	0.989	(0.551 - 1.774)	0.970
+ Swift	1.387	(0.562 - 3.422)	0.478	0.590	(0.293 - 1.189)	0.140
+ FIGO ≥ 1B2	1.873	(0.922 - 3.807)	0.083	2.308	(1.356 - 3.927)	0.002
+ LVSI	1.936	(0.895 - 4.186)	0.093	1.629	(0.867 - 3.059)	0.129
+ lymph node status	1.579	(0.709 - 3.515)	0.263	2.247	(1.220 - 4.138)	0.009
+ infiltration depth >15mm	0.879	(0.391 - 1.976)	0.756	1.878	(1.036 - 3.403)	0.038

Legend: PRFS: pelvic relapse free survival, OS: overall survival; HR: hazard ratio; CI: confidence interval; CRH: conventional radical hysterectomy; LNSRH: Leiden nerve sparing radical hysterectomy; LVSI: lymph vascular space invasion

Subgroup analysis tumour size

Subgroup analysis of tumours smaller than 20 mm or tumours smaller than 40 mm showed no significant difference regarding PRFS and OS between the 3 surgical cohorts. Subgroup analysis of tumours larger than 40 mm, showed an improved but not statistically significant, 5-year OS probabilities of 79.2% in the Swift cohort versus 52.2% in the CRH cohort and 57.7% in the LNSRH cohort (p = 0.125). (Supplemental figure 1)

5.5 DISCUSSION

We compared the oncological outcome of three different surgical techniques (the conventional radical hysterectomy (CRH), the Leiden nerve-sparing radical hysterectomy (LNSRH) and the nerve-sparing Swift procedure) for the treatment of early stage cervical cancer (FIGO-stage IA-IIA). We found no significant differences concerning pelvic and extra-pelvic relapse rates nor survival rates between the conventional non-nerve-sparing cohort (CRH) and the two nerve-sparing cohorts when correcting for unfavourable prognostic factors using a Cox model base survival analysis. There was no significant difference in survival outcomes between the Swift procedure and the CRH. However, in the nerve-sparing Swift cohort, overall survival was significantly higher compared to the LNSRH-cohort. From these findings, we conclude that nerve-sparing radical hysterectomy shows similar oncological outcomes compared to non-nerve sparing radical hysterectomy in early stage cervical cancer. Furthermore, the Swift technique is preferable to the former LNSRH.

Our data are concordant with the results of our systematic review and meta-analysis analysing the oncological outcomes of conventional radical hysterectomy versus nerve-sparing radical hysterectomy. In this meta-analysis we showed that there was no significant difference in 2-,3- and 5 year disease-free and overall survival rates between nerve-sparing and non-nerve-sparing techniques in early stage cervical cancer. [15] Long et al. and Basaran et al. have recently performed reviews and concluded that NSRH is not inferior to CRH regarding surgical margins and survival outcomes as well. [16, 17]

We changed the former LNSRH procedure in 2006 to the Swift procedure. [7] This was done in view of the work of Höckel and co-workers, who postulated that local tumour spread is not a random process but is orchestrated on the basis of embryological pathways. [18] Höckel defined the so called morphogenetic unit by investigating the migration of paramesonephric ducts during the embryologic development. [8] Complete resection of the morphogenetic unit (the TMMR procedure) showed very promising relapse-free and overall survival after 5 years in early stage cervical cancer. [18] In this light, the Swift operation was introduced since it was more radical than the LNSRH regarding the removal of the uterosacral ligaments without compromising the preservation of the hypogastric nerve fibres in that area. [7] Although somewhat speculative the improved survival outcome after the Swift procedure may be seen as supportive to the concept of the theory of tumour spread following the morphogenetic unit.

The occurrence of non-radical surgical margins in the present study may seem high. In the literature these rates vary, depending on definitions of radicality and, even more, on the comprehensiveness of pathology assessment. In the present study, the entire vaginal cuff was systematically examined microscopically for the presence of small isolated tumour entities anywhere in the removed vaginal tissue and this presence was not seldom the reason for non-radical margins. Furthermore, tumour extension to the anterior or posterior cervical border, beyond which no surrounding tissue can be resected, was also included in the definition of non-radical surgical margins while from literature it is unclear whether this was defined as such. Moreover, it was demonstrated some time ago that adjuvant treatment on the indication of affected margins abolished the unfavourable prognostic consequences of these non-radical margins. [19] It remains questionable whether the difference in overall survival between the LNSRH and the Swift cohort can be explained by the difference in non-radical surgical margins.

We found 11.3 %, 13.9 % and 9.4 % extra pelvic relapses within 5 years with a median of 20.7, 14.7 and 10.1 months for the CRH, LNSRH and Swift, respectively. Although these differences are not statistically significant, especially the decrease in median time to the diagnosis of an extra-pelvic relapse is remarkable. Assuming that at least some of this extra-pelvic disease may have been present during surgery, more adequate pre-operative staging in the Swift cohort may have led to the decrease number of extra pelvic recurrences and thus the better overall survival.

The whole concept behind the introduction of nerve-sparing techniques for radical hysterectomy in early stage cervical cancer, is to decrease the well-known and long-term negative impact on quality of life after CRH. Especially since survival is good and women are relatively young, improvement in quality of life after treatment is of utmost importance. In this study, we did not choose to add quality of life as an outcome measurement since these data have been published previously. [3, 4, 20, 21]. Recently, Derks et al performed a quality of life study evaluating the quality of life after non nerve-sparing Wertheim Okabayashi versus nerve-sparing Wertheim Meigs, confirming urinary functions differing significantly where feeling of urine retention, less/no urge to void and the need of timed voiding were more frequent in the Wertheim Okabayashi cohort. [22] They showed no significant difference with regard to bowel symptoms nor overall quality of life, but sexual functioning was not comprehensively investigated. In our systematic review and meta-analysis on radical hysterectomy versus nerve-sparing radical hysterectomy for early stage cervical cancer, we found bladder functioning to be significantly less impaired in the nerve-sparing modality with shorter time to spontaneous micturition post operatively. [15] Previously, Pieterse et al. found in an objective laboratory study that a non-nerve-sparing radical hysterectomy induces more lubrication problems, more narrowing and shortening of the vagina, more senseless areas around the labia, more dyspareunia and more sexual dissatisfaction compared to an age-matched control group. [4]

One of the major limitations of our study is that we have to consider the big time-span in which patients were treated. Between the first patient of the CRH-cohort and the last patient of the Swift-cohort 16 years have elapsed. Changes in anaesthesia techniques, blood transfusions, the administration of antibiotics and surgical aids like vessel sealing devices have occurred in this time span as well as indications for adjuvant treatment have changed. Especially since pelvic-recurrence free survival did not differ between the cohorts, the favourable overall survival of the Swift procedure may be due to this phenomenon.

In order to prevent confounding, we did not include patients treated during the learning curves of both the LNSRH and the Swift procedure. In addition, the study is a single-centre study, with a fixed and restricted group of gynaecologic oncologists performing the procedure. Moreover, data were registered prospectively and the number of patients lost to follow-up was extremely low.

In summary, we found no significant difference regarding oncological outcome between the CRH and both nerve-sparing surgical techniques. However, overall survival was significantly better in nerve-sparing cohort operated by the Swift procedure, compared to the former LNSRH procedure. Nerve-sparing techniques did not influence the hazard on getting pelvic relapses nor on overall survival.

We conclude that nerve-sparing surgery is safe in early stage cervical cancer if this is done without concessions whatsoever with regard to the extent of radical resection of

the parametrium and sacro-uterine ligaments. Since sparing the autonomic nerves in radical hysterectomy results in significantly better functional outcome with regard to sexual- and bladder function, nerve-sparing radical hysterectomy should be considered standard practise in women with early stage cervical cancer.

5.6 REFERENCES

1. Maas CP, Trimbos JB, Deruiter MC, van de Velde CJ, Kenter GG. Nerve sparing radical hysterectomy: latest developments and historical perspective. Crit Rev Oncol Hematol. 2003;48(3):271-9.
2. Bergmark K, Avall-Lundqvist E, Dickman PW, Henningsohn L, Steineck G. Lymphedema and bladder-emptying difficulties after radical hysterectomy for early cervical cancer and among population controls. Int J Gynecol Cancer. 2006;16(3):1130-9.
3. Pieterse QD, Kenter GG, Maas CP, de Kroon CD, Creutzberg CL, Trimbos JB, et al. Self-reported sexual, bowel and bladder function in cervical cancer patients following different treatment modalities: longitudinal prospective cohort study. Int J Gynecol Cancer. 2013;23(9):1717-25.
4. Pieterse QD, Maas CP, Ter Kuile MM, Lowik M, van Eijkeren MA, Trimbos JB, et al. An observational longitudinal study to evaluate miction, defecation, and sexual function after radical hysterectomy with pelvic lymphadenectomy for early-stage cervical cancer. IntJGynecolCancer. 2006;16(3):1119-29.
5. Axelsen SM, Petersen LK. Urogynaecological dysfunction after radical hysterectomy. Eur J Surg Oncol. 2006;32(4):445-9.
6. Maas CP, Ter Kuile MM, Laan E, Tuijnman CC, Weijenborg PT, Trimbos JB, et al. Objective assessment of sexual arousal in women with a history of hysterectomy. BJOG. 2004;111(5):456-62.
7. van den Tillaart SA, Kenter GG, Peters AA, Dekker FW, Gaarenstroom KN, Fleuren GJ, et al. Nerve-sparing radical hysterectomy: local recurrence rate, feasibility, and safety in cervical cancer patients stage IA to IIA. Int J Gynecol Cancer. 2009;19(1):39-45.
8. Trimbos JB, Maas CP, Deruiter MC, Peters AA, Kenter GG. A nerve-sparing radical hysterectomy: guidelines and feasibility in Western patients. Int J Gynecol Cancer. 2001;11(3):180-6.
9. Hockel M, Horn LC, Hentschel B, Hockel S, Naumann G. Total mesometrial resection: high resolution nerve-sparing radical hysterectomy based on developmentally defined surgical anatomy. Int J Gynecol Cancer. 2003;13(6):791-803.
10. Trimbos JB, Van Den Tillaart SAHM, Maas CP, Peters AAW, Gaarenstroom KN, Deruiter MC, et al. The Swift operation: A modification of the Leiden nerve-sparing radical hysterectomy. Gynecological Surgery. 2008;5(3):193-8.
11. Piver MS, Rutledge F, Smith JP. Five classes of extended hysterectomy for women with cervical cancer. Obstet Gynecol. 1974;44(2):265-72.
12. van Gent MD, van den Haak LW, Gaarenstroom KN, Peters AA, van Poelgeest MI, Trimbos JB, et al. 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. Int J Gynecol Cancer. 2014;24(4):735-43.

13. Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, Zaino RJ. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: A Gynecologic Oncology Group Study. Gynecol Oncol. 1999;73(2):177-83.

14. Plante M. NCT01658930 Shape trial [Available from: https://clinicaltrials.gov/.

15. van Gent MDJM, Romijn LM, van Santen KE, Trimbos JBMZ, De Kroon CD. Nerve-sparing radical hysterectomy versus conventional radical hysterectomy in early stage cervical cancer. A systematic review and meta analysis of survival and quality of life. Maturitas. 2016;94.

16. Long Y, Yao DS, Pan XW, Ou TY. Clinical efficacy and safety of nerve-sparing radical hysterectomy for cervical cancer: a systematic review and meta-analysis. PLoS One. 2014;9(4):e94116.

17. Basaran D, Dusek L, Majek O, Cibula D. Oncological outcomes of nerve-sparing radical hysterectomy for cervical cancer: a systematic review. Ann Surg Oncol. 2015;22(9):3033-40.

18. Hockel M, Horn LC, Manthey N, Braumann UD, Wolf U, Teichmann G, et al. Resection of the embryologically defined uterovaginal (Mullerian) compartment and pelvic control in patients with cervical cancer: a prospective analysis. Lancet Oncology. 2009;10(7):683-92.

19. Snijders-Keilholz A, Hellebrekers BW, Zwinderman AH, van de Vijver MJ, Trimbos JB. Adjuvant radiotherapy following radical hysterectomy for patients with early-stage cervical carcinoma (1984-1996). Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 1999;51(2):161-7.

20. Pieterse QD, Ter Kuile MM, Maas CP, Kenter GG. The Gynaecologic Leiden Questionnaire: psychometric properties of a self-report questionnaire of sexual function and vaginal changes for gynaecological cancer patients. Psychooncology. 2008;17(7):681-9.

21. Pieterse QD, Ter Kuile MM, Deruiter MC, Trimbos JB, Kenter GG, Maas CP. Vaginal blood flow after radical hysterectomy with and without nerve sparing. A preliminary report. Int J Gynecol Cancer. 2008;18(3):576-83.

22. Derks M, van der Velden J, Frijstein MM, Vermeer WM, Stiggelbout AM, Roovers JP, et al. Long-term Pelvic Floor Function and Quality of Life After Radical Surgery for Cervical Cancer: A Multicenter Comparison Between Different Techniques for Radical Hysterectomy With Pelvic Lymphadenectomy. Int J Gynecol Cancer. 2016.

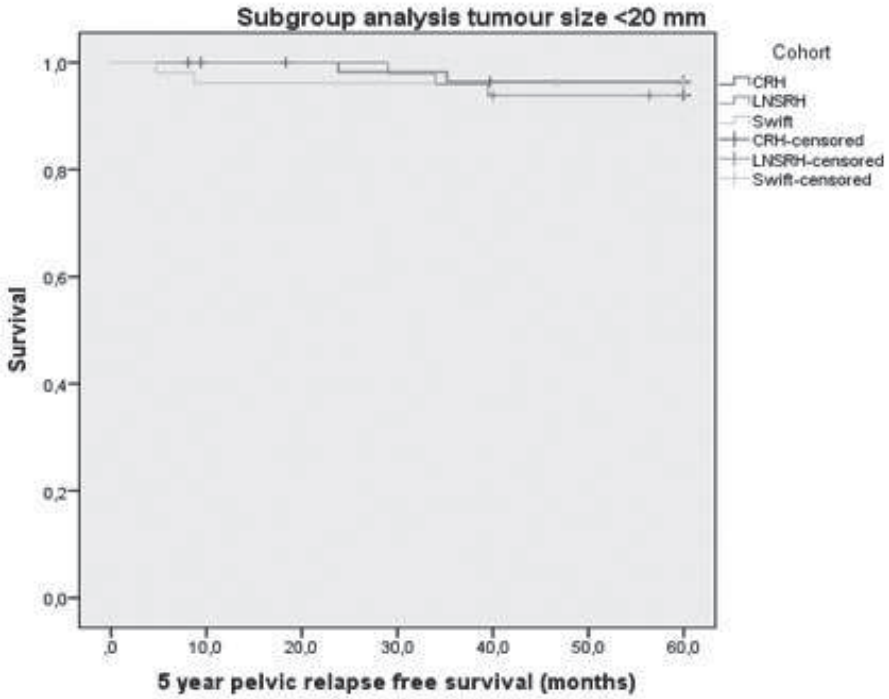
23. Bakker RM, Pieterse QD, van Lonkhuijzen LRCW, Trimbos JBMZ, Creutzberg CL, Kenter GG, et al., editors. An observational controlled study on vaginal blood flow and sexual functioning after early stage cervical cancer treatment. 18th International Psycho Oncology Society Congress; 2016; Dublin.

S1.a. Subgroup analysis by size: < 20mm

Group	**CRH**	**LNSRH**	**Swift**	***p***
n	**59**	**49**	**52**	
Lymph node metastases	4 (6.8%)	4 (8.2%)	2 (3.8%)	0.767
LVSI	10 (16.9%)	3 (6.1%)	10 (19.2%)	0.134
Infiltration depth >15mm	0	0	0	NA
PR	2 (3.4%)	3 (6.1%)	2 (3.8%)	0.767
5 yr PRFS	54 (91.5%)	44 (89.8%)	49 (96.1%)	0.798
5 yr OS	55 (93.2%)	46 (93.9%)	49 (96.1%)	0.798

Legend: CRH: conventional radical hysterectomy; LNSRH: Leiden nerve sparing radical hysterectomy; LVSI: lymph vascular space invasion; PR: pelvic relapse; PRFS: pelvic relapse free survival; OS: overall survival

Kaplan-Meier survival curve regarding PRFS

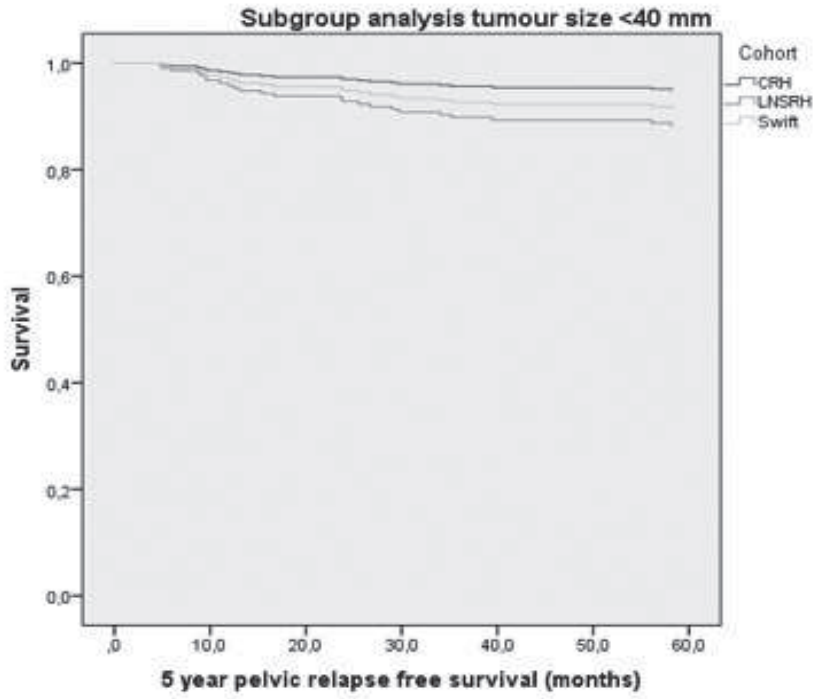


S1.b. Subgroup analysis by size: < 40mm

Group	CRH	LNSRH	Swift	*p*
n	**101**	**96**	**92**	
Lymph node metastases	14 (13.9%)	22 (22.9%)	10 (10.9%)	0.061
LVSI	27 (26.7%)	32 (33.3%)	36 (39.1%)	0.186
Infiltration depth >15mm	7 (6.9%)	16 (16.7%)	13 (14.1%)	0.099
PR	5 (5.0%)	12 (12.5%)	7 (7.6%)	
5 yr PRFS	88 (87.1%)	73 (76.0%)	78 (85.7%)	0.137
5 yr OS	89 (88.1%)	81 (84.4%)	83 (91.2%)	0.366

Legend: CRH: conventional radical hysterectomy; LNSRH: Leiden nerve sparing radical hysterectomy; LVSI: lymph vascular space invasion; PR: pelvic relapse; PRFS: pelvic relapse free survival; OS: overall survival

Cox-model based survival curve regarding PRFS when corrected for lymph node metastases

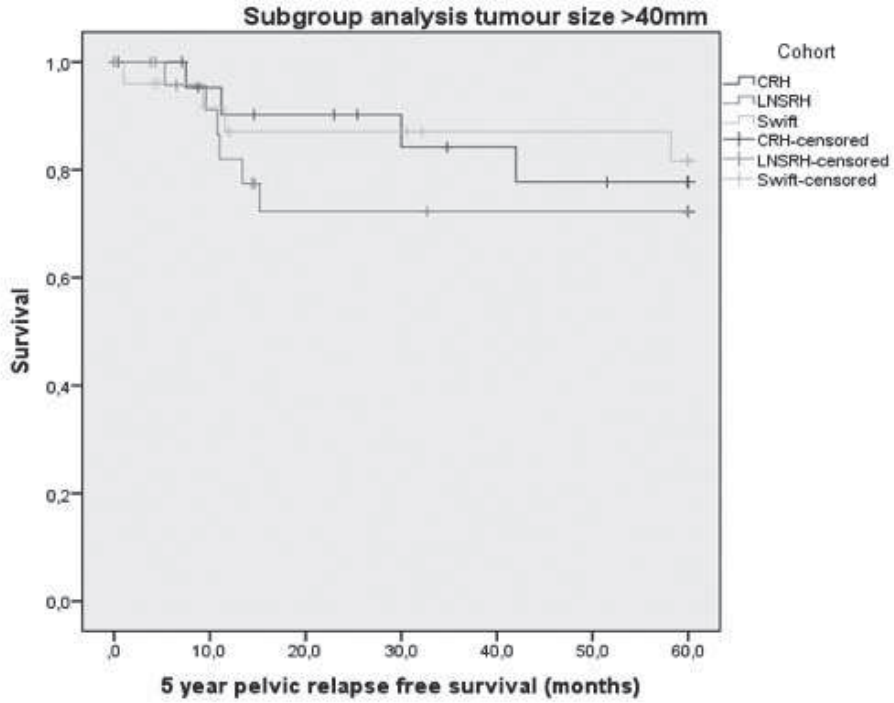


S1.c. Subgroup analysis by size: > 40mm

Group	CRH	LNSRH	Swift	*p*
n	**23**	**26**	**25**	
Lymph node metastases	7 (30.4%)	10 (38.5%)	12 (48.0%)	0.458
LVSI	11 (47.8%)	16 (64.0%)	18 (72.0%)	0.218
Infiltration depth >15mm	12 (52.2%)	16 (61.5%)	13 (52.0%)	0.737
PR	4 (17.4%)	6 (23.1%)	4 (16.0%)	
5yr PRFS	12 (52.2%)	14 (53.8%)	15 (62.5%)	0.713
5yr OS	12 (52.2%)	15 (57.7%)	19 (79.2%)	0.161

Legend: CRH: conventional radical hysterectomy; LNSRH: Leiden nerve sparing radical hysterectomy; LVSI: lymph vascular space invasion; PR: pelvic relapse; PRFS: pelvic relapse free survival; OS: overall survival;

Kaplan-Meier survival curve regarding PRFS



5