Tailoring therapy in endometrial and cervical cancer

Gent, M.D.J.M. van

CHAPTER 4

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

Mignon van Gent
Loes Romijn
Karin van Santen
Baptist Trimbos
Cor de Kroon

Maturitas 94 (2016) 30-38

CHAPTER 4

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

4.1 ABSTRACT

Background and aims

Survival after radical hysterectomy (RH) for early stage cervical cancer is good. Hence quality of life (QOL) after treatment is an important issue. Nerve sparing radical hysterectomy (NSRH) improves QOL by selectively sparing innervation of bladder, bowel and vagina, reducing therapy-induced morbidity. However, the oncological outcome and the functional outcome after NSRH are subjects of debate. We aim to present the best possible evidence available regarding both QOL and survival after NSRH in early-stage cervical cancer.

Methods

Systematic review and meta-analysis on studies comparing NSRH and RH.

Results

Forty-one studies were included and 27 were used for the meta-analysis. There was no difference in 2-, 3- and 5-year overall survival: the risk ratios (RRs) were respectively 1.02 (95% CI 0.99-1.05, n = 879), 1.01 (95% CI 0.95-1.08, n = 1324) and 1.03 (95% CI 0.99-1.08, n = 638). No difference was found in 2-, 3- and 5-year disease-free survival: RR 1.01 (95% CI 0.95-1.05, n = 1175), 0.99 (95% CI 0.94-1.03, n = 1130) and 1.00 (95% CI 0.95-1.06, n = 933) respectively. Post-operative time to micturition was significantly shorter in the NSRH group: standardized mean difference (SMD) -0.84 (CI 95% -1.07 to -0.60).

Conclusions

NSRH can be considered safe and effective for early-stage cervical cancer since short- and long-term survival do not differ from those of conventional RH, while bladder function after NSRH is significantly less impaired.

4.2 INTRODUCTION

Cervical cancer is the third most common type of cancer in women worldwide. Furthermore, it is the fourth most lethal type of cancer in women after breast-, lung- and colon carcinoma. [1] In 2010 453,970 new patients were diagnosed with cervical cancer worldwide and 44 % of these women were under the age of 50. Only 24% of the cases concerned women from developed countries. Treatment of cervical cancer depends on the stage of the disease. Microscopic disease (FIGO IA1) is usually treated with a cone biopsy or simple hysterectomy. So called 'early-stage cervical cancer' (FIGO IA2, IB, IIA and IIB) is usually treated with a radical hysterectomy: depending on the radicality (classified according to Piver I-IV) both the sacro-uterine ligaments and the parametria are resected more extensively but usually the parametrium is resected up to the internal iliac artery and down to the deep uterine vein. [2] In order to rule out lymph node metastasis, a pelvic lymphadenectomy is performed. Adjuvant (chemo-) radiation is administered in case of lymph node metastasis, extra cervical spread and unfavourable tumour characteristics. Prognosis after RH depends on the aforementioned prognostic factors. Five-year survival rates of between 88% and 97% have been reported. [3, 4] Given such survival rates, quality of life after treatment is an important issue. One way to improve quality of life is by reducing therapy-induced morbidity. Up to 25% of women treated with radical hysterectomy suffer from bladder, bowel and sexual complaints. [5, 6] Maas et al showed that conventional radical hysterectomy (Piver III) inevitably results in damage to the autonomic nerves in both the hypogastric plexus (resection of the sacro-uterine ligaments) and the splanchnic nerves (resection of the parametrium below the deep uterine vein). [7] The autonomic nerves innervate the bowel and are important for optimal sexual function: the autonomic nerves regulate lubrication-swelling response of the female genitals during sexual arousal. [8] It is well known that accidental damage to these nerves in the pelvis can lead to urine incontinence, diarrhoea or constipation and sexual problems. [9] In the 1960s the Japanese gynaecologist Kobayasi described the first technique to conserve the autonomic nerves during pelvic surgery. In 1988 Sakamoto published the first article on nerve-sparing radical hysterectomy (NSRH) in English. [7, 10] From that time many different techniques to spare the autonomic nerves in radical hysterectomy have been published and more recently reviews on nerve sparing radical hysterectomy summarised the evidence on the oncological safety of nerve sparing radical hysterectomy. [3, 4, 11] However, nerve-sparing surgery is still subject to a fierce debate in the world of gynaecologic oncology. Proponents state the technique is safe and beneficial for the quality of life of patients. Opponents are reluctant to use the technique arguing that literature is too heterogeneous to be certain about both oncological safety and anatomical and physiological advantage. In this meta-analysis, of the data obtained after systematically reviewing all available literature, we aim to provide the

best possible evidence available regarding both quality of life and survival after NSRH in early stage cervical cancer. Since none of the aforementioned reviews performed a proper meta-analysis to the extent as we did, our paper will hopefully close the debate in favour of the effect and safe use of NSRH. This will allow women to undergo the most optimal surgical treatment for early stage cervical cancer.

4.3 MATERIALS AND METHODS

Definitions

Early stage cervical cancer includes stage IA2, IB, IIA and IIB cervical cancer according to the Féderation Internationale de Gynécologie et d'Obstétrique (FIGO) staging.[12] The intervention under review is nerve sparing radical hysterectomy (NSRH), which is compared to conventional radical hysterectomy (RH). The PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-analyses) were used during the development and execution of this systematic review and meta-analyses.

Sources

We searched PubMed, EMBASE, Web of Science, the Cochrane Library, CINAHL, Academic Search Premier, ScienceDirect, Springer, WileyBlackwell, LWW, HighWire and Taylor & Francis/Informaworld (final search November 21st 2015). The following terms with synonyms were used: (radical) hysterectomy, nerve-sparing, cervical cancer and autonomic nerves.) A single librarian of the Waleaus library of the Leiden University Medical Center (JS) performed the literature searches.

Study selection

We included case-control studies, randomised controlled trials and comparative cohort studies. To avoid publication bias, no limitations on language or publication date were made. The meta-analyses were performed on the comparative studies. We excluded studies without the definition of cervical cancer or nerve sparing surgery. Four independent reviewers (M.v.G, L.R., K.v.S and C.d.K) screened the titles and abstracts. If the title was not specific enough for decision, we reviewed the abstract. If a reference was eligible, the full-text article was scored using a pre-tested scoring list conducted by the reviewers (M.v.G, L.R., K.v.S and C.d.K). Inconsistency between the reviewers was resolved by discussion and consensus. Data were extracted using a pre-designed data extraction form. Hence both methodology and results of all eligible papers were reviewed in a systematic manner. If the full text paper was not available (e.g. in case of a conference abstract) the scoring list was used to score the abstract. We determined whether the study properties were homogeneous by looking at the period of inclusion, number of patients, whether the study was prospective or retrospective and whether

the study was multi or single centre. To determine clinical homogeneity, when given, the FIGO stage, histology type, age, BMI, percentage of patients receiving neoadjuvant chemotherapy, tumour size, relative and absolute depth of the tumour, the percentage of positive lymph nodes and the vascular invasion were examined. After scoring was completed, to avoid multiple publication bias, we contacted authors and their affiliations to clarify any uncertainties or incomplete data.

Outcomes of interest

The following outcome measures were considered in the meta-analyses: 2/3/5-years (disease-free) survival, operation time, intraoperative blood loss, time to micturition and duration of hospital stay. Quality of life was analysed by determining urinary-, bowel- and sexual dysfunction and general quality of life.

Data synthesis

To determine the risk of bias, the questionnaire for methodological quality of the Dutch Cochrane Library was answered for every article. [13] The data extracted from the data forms were put in to a pre-designed database (Access version 2007-2013, Microsoft Corp, Redmond, WA, USA). The meta-analyses were conducted using software designed for composing Cochrane reviews. (Review Manager v.5.3.4, 2015, Cochrane Community, London, UK). Statistical heterogeneity was determined using the Chi-square test. [14] Whenever 5 or more articles were used in the meta-analysis random effects models were used. If less than 5 articles were used in the respective meta-analysis fixed effects models were used. For dichotomous variables, results were given as risk ratios (RR with 95% CI). For continuous outcomes, the results were expressed as standardized mean differences (SMD). Because of the skewed distribution of variables, we applied a log-normal distribution. If only median and range were given, data were transformed into mean and standard deviation, according to the definitions described by Hozo. [15] A p-value of less than 0.05 was considered significant for all variables. [14] When not presented, survival data were extracted from the Kaplan-Meier estimator.

4.4 RESULTS

Literature identification and study selection

After removing duplicate references, a total of 1288 unique titles remained. 731 Publications were considered not eligible after screening the titles leaving 557 abstracts for further evaluation. 221 Titles were retrieved for detailed evaluation of the full text or abstract in case of conference abstract. After evaluation of the abstract 180 studies were considered not eligible because of various reasons. Detailed information on selection of articles included in the review can be found in figure 1.

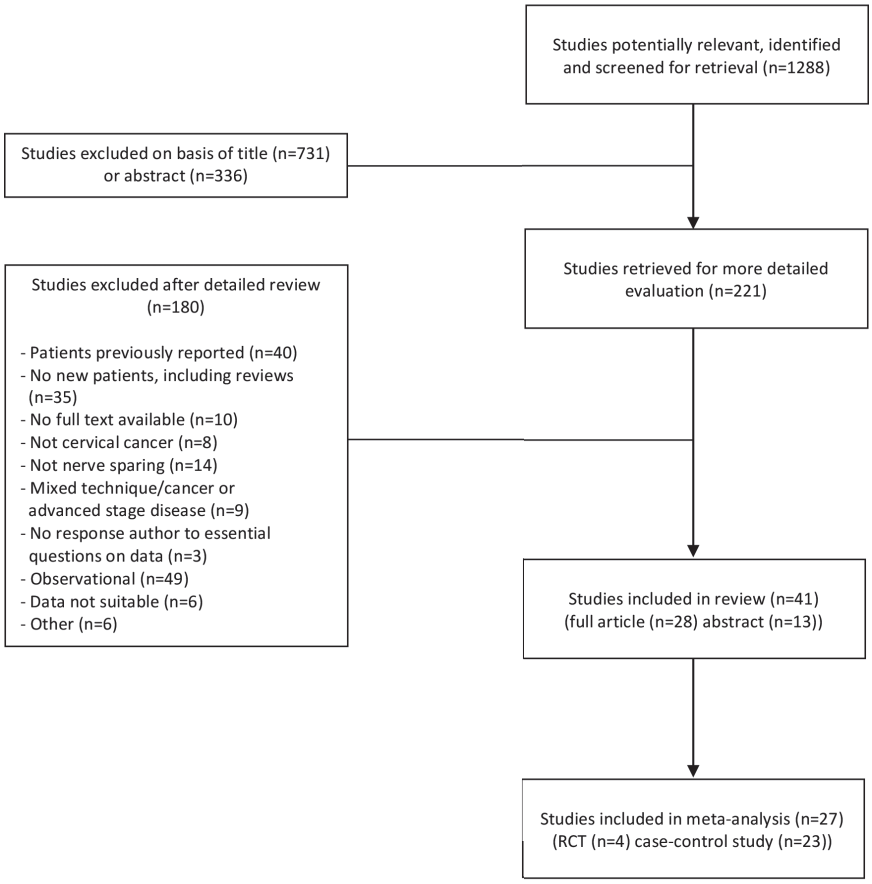


Figure 1. Flowchart review.

Study characteristics

41 Studies were selected for inclusion in the review: 28 full text articles and 13 conference abstracts. The studies were published between 2000 and 2015. 18 Papers concerned prospective studies (2 had a retrospective control group), 9 studies were retrospective and of the other 14 articles it was not clearly described whether data were collected retro- or prospectively. From the 27 studies that could be used for meta-analysis, 4 were RCTs and 23 case-control studies. The 14 publications not included for meta-analysis contained valuable data but they were not suitable for statistical analysis. Study characteristics of the 41 studies included in our systematic review are presented in Table 1. The risk of bias was assessed for all studies (Table 1 and S2). [5, 16-55]

Table 1. Study characteristics.

Author	Year	Publication type	Study design	Evaluation	Number of patients (NSRH)	Number of patients (RH)	Used for Meta-analysis	Used for QOL tables (supplemental data)	Study quality
Wu [16]	2010	article	RCT	prospective	14	15	x	x	high
Chen [17]	2012	article	RCT	prospective	12	13	x	x	high
Chen [18]	2014	article	RCT	prospective	30	35	x	x	intermediate
Roh [19]	2015	article	RCT	prospective	46	40	x	x	high
Asmussen [20]	1987	article	case-control	prospective	13	5	-	x	low
Hockel [21]	2000	article	case-control	prospective*	41	139	x	-	low
Kuwabara [22]	2000	article	case-control	prospective	19	18	x	-	intermediate
Possover [23]	2000	article	case-control	prospective	38	28	x	-	low
Sakuragi [24]	2005	article	case-control	prospective	22	5	x	x	low
Rodolakis [25]	2008	abstract	case-control	prospective	15	30	-	x	low
Chen [26]	2009	abstract	case-control	-	37	25	x	x	intermediate
Ju [27]	2009	article	case-control	retrospective	24	69	-	x	intermediate
Sun [28]	2009	article	case-control	prospective	21	21	x	-	intermediate
van den Tillaart [29]	2009	article	case-control	prospective	122	124	x	-	intermediate
Espino-Strebel [30]	2010	article	case-control	retrospective	27	52	x	-	low
Liang [31]	2010	article	case-control	prospective	82	81	x	x	intermediate
Runnebaum [32]	2010	abstract	case-control	-	53	11	x	-	low
Skret-Magierlo [33]	2010	article	case-control	prospective	10	10	x	x	intermediate
Ditto [34]	2011	article	case-control	-	185	311	x	x	low
Dowaji 2 [35]	2011	abstract	case-control	-	60	40	-	x	low
Merlot [36]	2011	abstract	case-control	-	19	28	x	-	low

Mukhtarulina [37]	2011	abstract	case-control	-	23	17	-	x	low
Radlovic [38]	2011	abstract	case-control	-	41	46	-	x	low
Ceccaroni [39]	2012	article	case-control	retrospective	25	31	x	x	low
Tseng [40]	2012	article	case-control	prospective	18	12	x	x	low
Chang [41]	2013	abstract	case-control	retrospective	32	36	-	x	low
Pieterse [5]	2013	article	case-control	prospective	123	106	-	x	intermediate
Prajwala [42]	2013	abstract	case-control	retrospective	5	18	x	x	low
Bogani 1 [43]	2014	article	case-control	prospective	33	63	x	x	intermediate
Bogani 2 [44]	2014	article	case-control	-	20	20	x	-	intermediate
Dermenzhy 1 [45]	2014	abstract	case-control	-	23	23	-	x	low
Dermenzhy 2 [46]	2014	abstract	case-control	-	25	25	-	x	intermediate
Kanao [47]	2014	article	case-control	-	40	13	x	-	intermediate
Makowski [48]	2014	article	case-control	-	20	53	x	-	low
Rademaker [49]	2014	abstract	case-control	prospective	121	124	x	-	low
Sowa [50]	2014	article	case-control	retrospective	74	36	-	x	intermediate
Wenwen 1 [51]	2014	article	case-control	retrospective	78	160	-	x	intermediate
Wenwen 2 [52]	2014	abstract	case-control	-	102	204	x	x	low
Wirawan [53]	2014	abstract	case-control	-	15	19	-	x	low
Shi [54]	2015	article	case-control	retrospective	64	42	x	x	intermediate
Xie [55]	2015	article	case-control	retrospective	52	54	-	x	intermediate

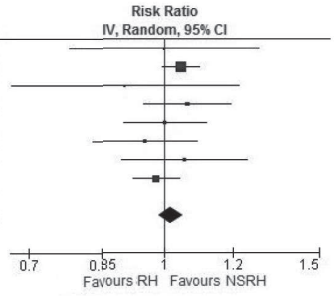
NSRH: nerve sparing radical hysterectomy; RH: conventional radical hysterectomy; * controle group retrospective.

Overall Survival

2 year

Study or Subgroup	NSRH Events	NSRH Total	RH Events	RH Total	Weight	Risk Ratio IV, Random, 95% CI
Sakuragi (2005)	22	22	5	5	1.7%	1.00 [0.78, 1.28]
Ditto (2011)	176	185	283	311	44.8%	1.05 [1.00, 1.10]
Chen (2012)	10	12	12	13	1.2%	0.90 [0.67, 1.22]
Ceccaroni (2012)	25	25	29	31	7.8%	1.06 [0.95, 1.19]
Bogani 1 (2014)	31	33	59	63	8.8%	1.00 [0.90, 1.12]
Bogani 2 (2014)	19	20	20	20	5.5%	0.95 [0.83, 1.09]
Kanao (2014)	39	40	12	13	3.8%	1.06 [0.90, 1.25]
Roh (2015)	45	46	40	40	26.5%	0.98 [0.92, 1.04]
Total (95% CI)		**383**		**496**	**100.0%**	**1.02 [0.99, 1.05]**
Total events	367		460			

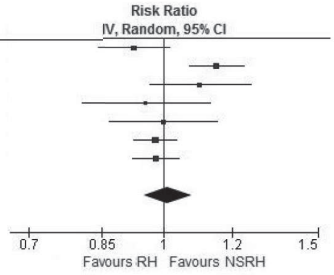
Heterogeneity: Tau² = 0.00; Chi² = 5.07, df = 7 (P = 0.65); I² = 0%
Test for overall effect: Z = 1.09 (P = 0.28)



3 year

Study or Subgroup	NSRH Events	NSRH Total	RH Events	RH Total	Weight	Risk Ratio IV, Random, 95% CI
Tillaart (2009)	102	121	112	123	14.9%	0.93 [0.84, 1.02]
Ditto (2011)	169	185	247	311	17.4%	1.15 [1.07, 1.24]
Ceccaroni (2012)	25	25	28	31	11.2%	1.10 [0.96, 1.26]
Bogani 1 (2014)	28	33	56	63	8.5%	0.95 [0.81, 1.13]
Bogani 2 (2014)	19	20	19	20	10.4%	1.00 [0.87, 1.15]
Wenwen 2 (2014)	96	102	196	204	19.1%	0.98 [0.93, 1.04]
Roh (2015)	45	46	40	40	18.5%	0.98 [0.92, 1.04]
Total (95% CI)		**532**		**792**	**100.0%**	**1.01 [0.95, 1.08]**
Total events	484		698			

Heterogeneity: Tau² = 0.00; Chi² = 19.94, df = 6 (P = 0.003); I² = 70%
Test for overall effect: Z = 0.38 (P = 0.71)



5 year

Study or Subgroup	NSRH Events	NSRH Total	RH Events	RH Total	Weight	Risk Ratio IV, Fixed, 95% CI
Ditto (2011)	168	185	262	311	41.7%	1.08 [1.01, 1.15]
Ceccaroni (2012)	25	25	28	31	10.4%	1.10 [0.96, 1.26]
Roh (2015)	45	46	40	40	47.8%	0.98 [0.92, 1.04]
Total (95% CI)		**256**		**382**	**100.0%**	**1.03 [0.99, 1.08]**
Total events	238		330			

Heterogeneity: Chi² = 5.23, df = 2 (P = 0.07); I² = 62%
Test for overall effect: Z = 1.45 (P = 0.15)

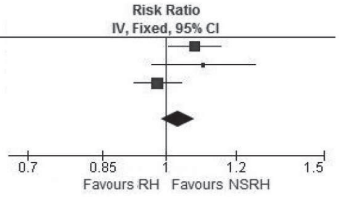
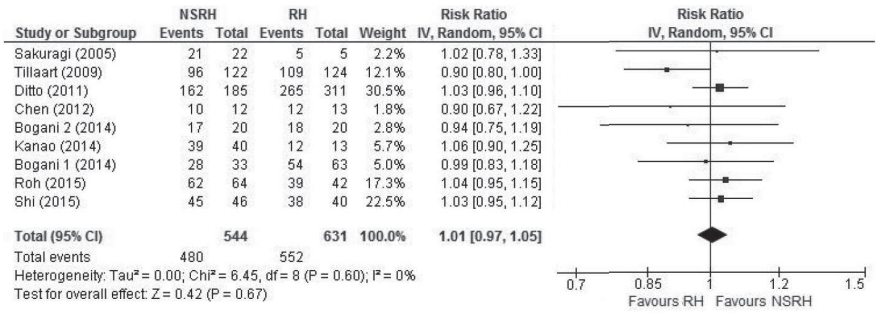


Figure 2. Meta-analysis: Survival.

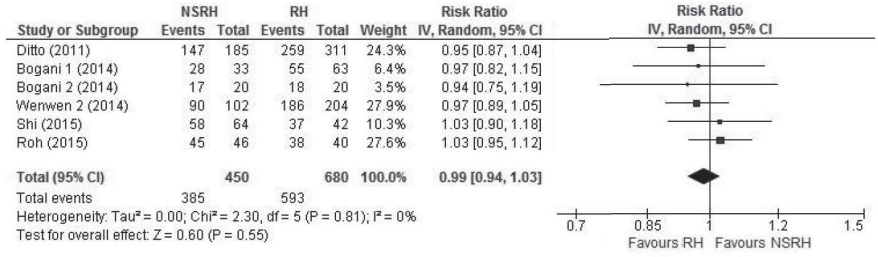
NSRH = nerve sparing radical hysterectomy; RH = conventional radical hysterectomy; Events = number of surviving patients; Total = number of patients in group; IV = inverse variance; CI = confidence interval.

Disease-free Survival

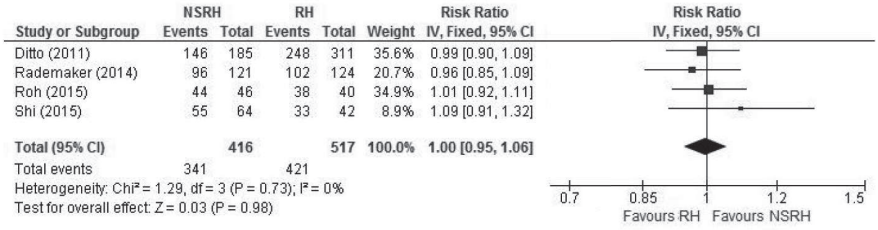
2 year



3 year



5 year



Meta-analyses

Meta-analyses have been performed on the following outcomes: 2/3/5 years (disease-free) survival, time to micturition, blood loss, hospital stay and operating time.

1. Survival (figure 2)

According to our meta-analyses 2, 3 and 5 year overall survival did not differ in either group: Risk ratios (RRs) were respectively 1.02 (95% CI 0.99-1.05, I^2 0%, n = 879 in 8 studies), 1.01 (95% CI 0.95-1.08, I^2 12%, n = 1324 in 7 studies) and 1.03 (95% CI 0.99-1.08, I^2 62%, n = 638 in 3 studies). With regard to 2-, 3- and 5-year disease-free survival there is no difference between both groups: RRs were respectively 1.01 (95% CI 0.95-1.05, I^2 0%, n = 1175 in 9 studies), 0.99 (95% CI 0.94-1.03, I^2 0%, n = 1130 in 6 studies) and 1.00 (95% CI 0.95-1.06, I^2 0%, n = 933 in 4 studies).

2. Quality of life – Time to micturition (figure 3)

For the meta-analysis on time to micturition 18 studies were included. In total 1470 patients were included in these studies. 647 underwent NSRH and 823 underwent RH. The time to micturition after surgery was significantly shorter in the NSRH group (SMD -0.84, 95% CI -1.07 to -0.60, I^2 72%).

3. Feasibility/safety (figure 4)

Blood loss

Fourteen articles were included in the meta-analysis regarding the amount of intraoperative blood loss (figure 4). The NSRH group consists of 701 patients and the RH group of 845 patients. There was no significant difference (SMD -0.30, 95% CI 0.64-1.04, I^2 89%).

Operation time

The meta-analysis on the operation time consists of 9 studies with a total of 1992 patients. 852 patients underwent NSRH and 1140 RH. The operation time is significantly longer for the patients who underwent NSRH (SMD 0.48, 95% CI 0.16 - 0.79) which corresponds with an average of 20 minutes, in favour of RH. It must be taken into consideration that the chance of heterogeneity is big with an I^2 of 90%.

Hospital stay

The hospital stay after surgery was reported in 9 studies with a total of 1253 patients. 487 patients underwent NSRH and 775 RH. The result favours NSRH (SMD -0.82, 95% CI -1.50 to -1.05) and is significant. Yet there is a high chance of heterogeneity: the I^2 is 96%. This corresponds with a prolonged hospital stay of 2.4 days in the RH group.

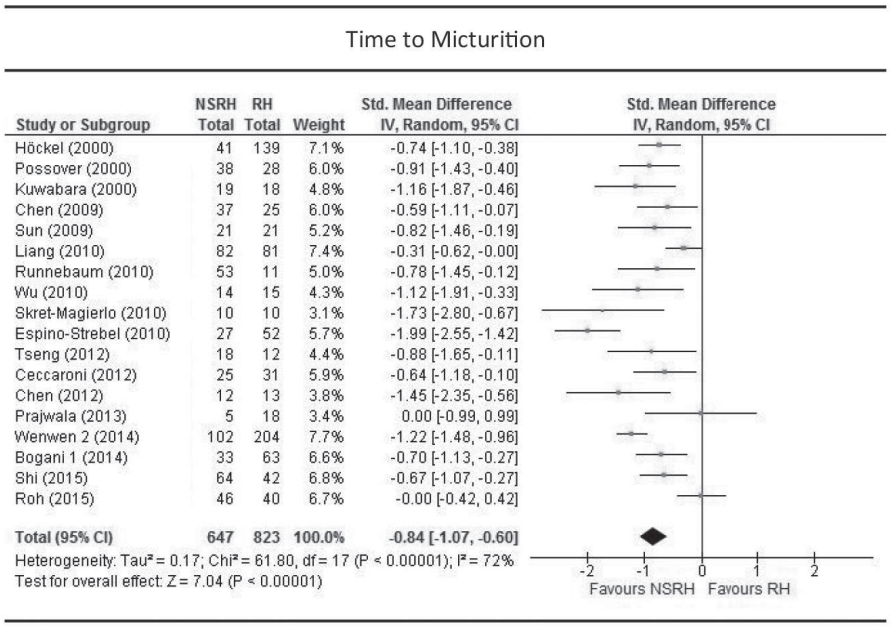


Figure. 3. Meta-analysis: Quality of life.

NSRH = nerve sparing radical hysterectomy; RH = conventional radical hysterectomy; Total = number of patients in group; Std = standardized; IV = inverse variance; CI = confidence interval.

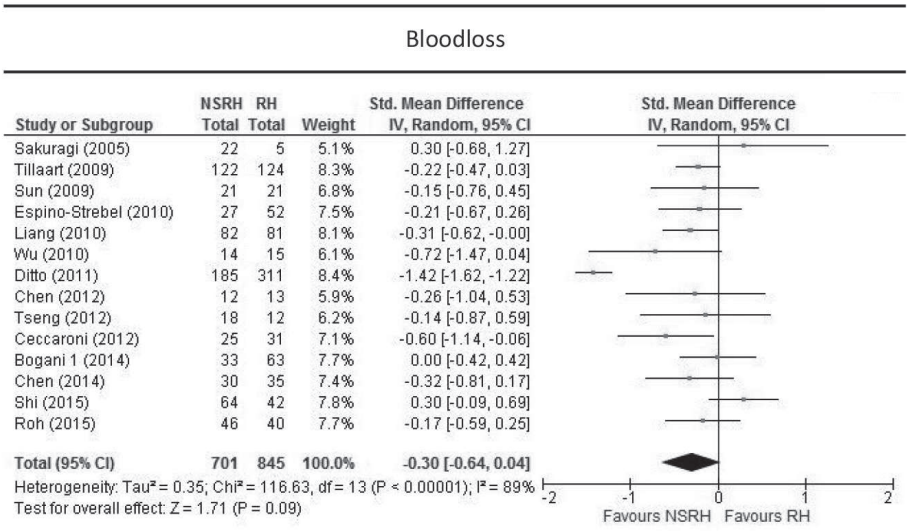


Figure. 4. Meta-analysis: Feasibility/Safety.

NSRH = nerve sparing radical hysterectomy; RH = conventional radical hysterectomy; Total = number of patients in group; Std = standardized; IV = inverse variance; CI = confidence interval.

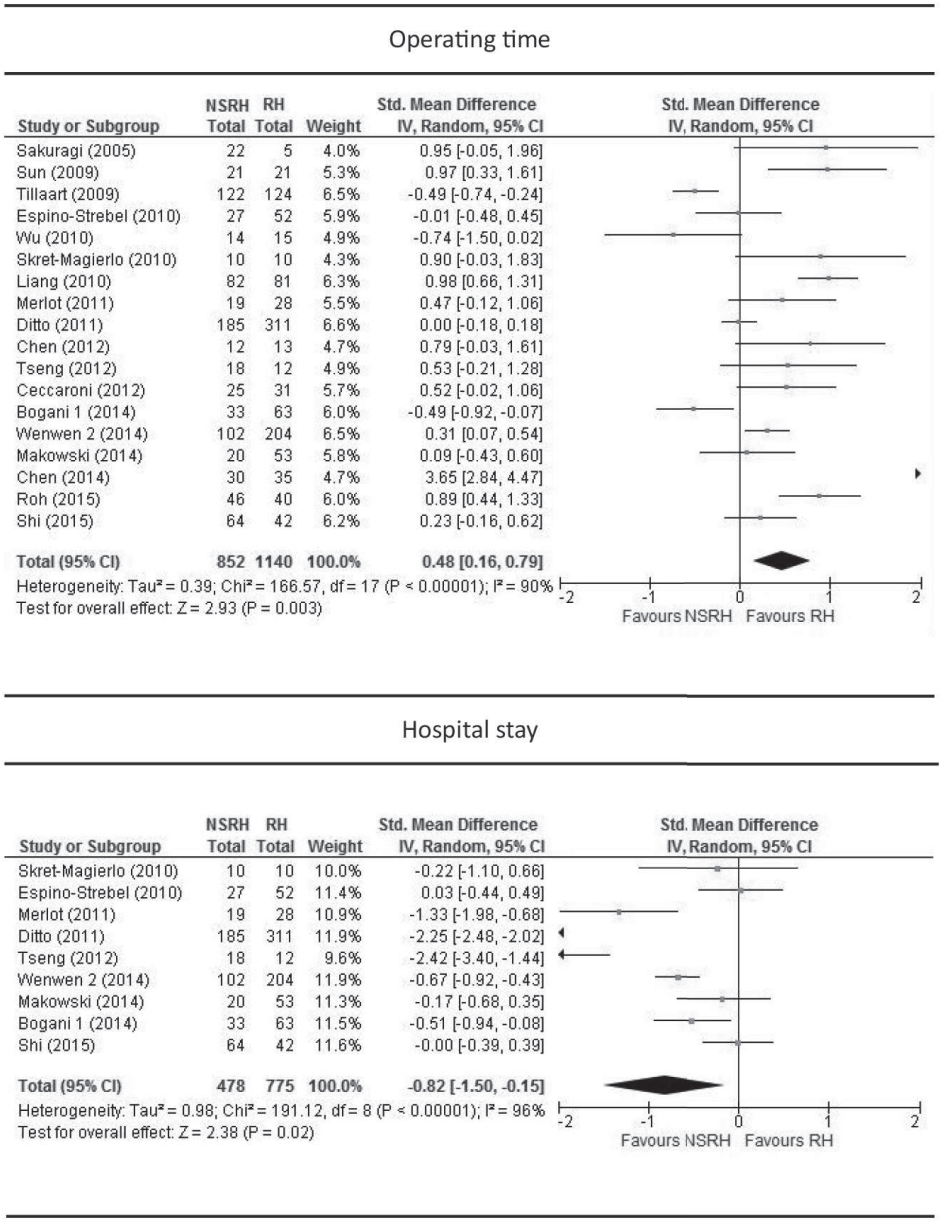


Figure. 4. Continued

NSRH = nerve sparing radical hysterectomy; RH = conventional radical hysterectomy; Total = number of patients in group; Std = standardized; IV = inverse variance; CI = confidence interval.

Quality of life

Due to the high variance in quality of life outcomes reported and lack of adequate data for statistical analyses in the reviewed papers, many of the reviewed articles turned out to be unsuitable for meta-analysis on quality of life after NSRH. In order to have a complete review of the available data on urinary function, bowel function, sexual function and general quality of life, we have presented these data in four different tables available as supplementary data (S2, S3, S4 and S5 respectively). In these tables we have summarized 25 studies evaluating urinary function, 13 bowel function, 10 sexual function and 4 studies describing quality of life in general. Post voidal residual volume, urinary retention, recovery of bladder function, satisfaction of micturition, abnormal bladder sensation, bladder dysfunction and need for intermittent self-catheterization, dysuria, good sensation, urgency, frequency and stress incontinence, are analyzed. We described time to defecation, constipation and diarrhea. Sexual functioning data concern (dis-) satisfaction, frequency, activity, dysfunction, dyspareunia, vaginal dryness, numbness of labia and psychological distress. The general quality of life issues that have not been processed in the meta-analyses are given in supplemental table 5. The EORTC QLQ was used in two of the four studies. [50, 55] Ceccaroni [39] and Wu [16] use a modified questionnaire adapted from the Bergmark series [6, 56] and the Functional Assessment of Cancer Therapy (FACT)[57] for cervical cancer respectively.

4.5 DISCUSSION

The aim was to perform a systematic review and meta-analysis comparing conventional radical hysterectomy (RH) with nerve sparing radical hysterectomy (NSRH) in early stage cervical cancer. As presented in figure 2, taking considerable heterogeneity into account, there is no evidence of inferior disease-free and overall survival after NSRH in early stage cervical cancer. One can argue that some (single-centre) cohorts of RH do claim higher survival rates. [58, 59] However, such studies are prone to numerous kinds of bias. In our opinion the results of the systematic review and meta-analyses presented in this paper is the best available evidence on survival of RH compared to NSRH. Many, both comparative and non-comparative studies have shown improved physiological outcomes after nerve sparing therapy. [5, 60] Unfortunately, data on quality of life was grossly heterogeneous and reported outcomes differed extensively between studies. Hence we could only perform a meta-analysis with data on time to micturition, which significantly favoured NSRH. Reviewing the 4 randomized papers on NSRH versus RH all 4 favoured NSRH with regard to urinary function but could, due to the aforementioned reasons, not be included in the meta-analysis. [16-18, 61] Apart from physical functioning, questionnaires can be used to assess psychological distress due to morbidity. Pieterse et al published longitudinally evaluated quality of life using validated questionnaires. [17] Despite the

earlier mentioned favourable results on preserving the autonomic nerves with regard to bladder and sexual function, there was no significant difference in self-reported outcomes 2 years after neither NSRH nor RH. This might be explained by the fact that in both cohorts a large proportion of patients received adjuvant radiation therapy, which may have diminished the advantageous effect of preserving the autonomic nerves. So, physiological function is well preserved after NSRH but self-assessed function seems to depend on more factors than functional autonomic nerves alone. Current medicine prioritizes patient related outcome measurements in the treatment and follow-up of the patient. [62] Corresponding with this development, the next goal in research on quality of life after radical hysterectomy should be to find and overcome all factors that influence self-assessed function. Others also tried to summarize the data on NSRH. Rob was the first with a review in Lancet Oncology. [3] His paper is of main interest because it summarizes the anatomy and the different techniques of nerve sparing surgery. Moreover this paper holds a plea for performing a less radical parametrectomy; hence nerve sparing, in selected cases. The latter is under investigation in the international SHAPE trial, led by Plante. [63] Next, Basaran et al calculated that the number of patients needed to prove non-inferiority of NSRH to RH with regard to recurrence would be between 4300 and 1000 depending on the expected risk of recurrence (5 and 20% respectively) and thus of the population under investigation. [11] Most recently Long et al published an interesting systematic review trying to differentiate between laparoscopic and open procedures. Although operating time was significantly longer when performing NSRH, NSRH favoured RH with regard to bladder function. [4] Compared to both Basaran and Long we were able to include many more trials (41 compared to 21 and 17 respectively). Moreover we performed meta-analyses on oncological outcome showing equal long- and short-term (disease-) free survival of NSRH compared to RH. Summarizing the available reviews we can conclude that with regard to bladder function NSRH significantly favours RH and there are no data showing a negative effect on survival of recurrence after NSRH. The most important drawback of our meta-analyses is the considerable heterogeneity among studies. [8] The risk of bias of the included studies was assessed in a systematic way (table 1 and supplemental figure 1). [14] Although the largest proportion of the included studies has a prospective design (18/41) some use a retrospective control group. Finally, the mean number of patients included in the papers reviewed was only 50 per group which is relatively small. All these unfavourable methodological features may weaken the conclusion of our systematic review and meta-analyses. However, we included 4 RCTs in our meta-analyses [16-18, 61] all favouring NSRH with regard to quality of life and not showing a difference in survival rates. (figure 2, 3 and 4) This strongly supports and strengthens our conclusions and indicates that the results of our review are valid. There are many authors who have published just as many different surgical procedures to selectively spare the autonomic nerves in the small pelvis. [3, 8, 64-66] Especially the extent

to which the autonomic nerves should be selectively dissected from the vesico-cervical ligament is under debate. [64] We decided not to take the surgical procedure into account since the different techniques all identify and selectively lateralise the hypogastric plexus when dissecting the sacro-uterine ligament and stay above the deep uterine vein to spare the splanchnic nerves. [2, 3, 65] When the deep uterine vein is considered as the ventral margin of the dissection of the parametrium one may argue that the parametrectomy is less radical and consequently not adequate. However the proportion of patients with microscopic metastasis in the dorsal parametrium as the only extra-cervical spread of the disease is considered extremely low and additional (microscopic) metastasis in the dorsal parametrium will be effectively treated since patients with metastasis will receive adjuvant radiation therapy. [67] The aforementioned argument with regard to the dorsal parametrium may as well be valid for the lateral parametrium. It may well be that the indication for a true radical hysterectomy, in which the pelvic nerves are damaged if not selectively spared, may be limited. Moreover other studies have shown favourable results of neo-adjuvant chemotherapy in combination with less radical surgery. [68] Although these studies included women seeking a possibility to preserve fertility, their conclusions are equally valuable, and probably equally valid, in women in whom fertility preservation is not an issue. [68-70] Having said that, there will always be women in whom radical surgery is first choice of treatment. In these women the nerve sparing techniques should be considered since our systematic review showed a significant advantage with regard to bladder function and recovery after NSRH. Moreover, our research shows that both disease-free and overall survival after NSRH and RH are equal.

ACKNOWLEDGEMENTS

We would like to thank Jan Schoones, librarian at the Walaeus Library at the Leiden University Medical Center (LUMC) for his thourough work on the literature searches. Professor Dr. T. Stijnen, Medical statistics (LUMC), for his help and advice in our statistical analyses and Dr. O.M. Dekkers, M.D, M.A., MSc, Clinical Epidemiology (LUMC), for transforming data into clinical relevance.

4.6 REFERENCES

1. Arbyn M, Castellsague X, de SS, Bruni L, Saraiya M, Bray F, et al. Worldwide burden of cervical cancer in 2008. AnnOncol. 2011;22(12):2675-86.
2. Cibula D, Abu-Rustum NR, Benedetti-Panici P, Kohler C, Raspagliesi F, Querleu D, et al. New classification system of radical hysterectomy: emphasis on a three-dimensional anatomic template for parametrial resection. Gynecol Oncol. 2011;122(2):264-8.
3. Rob L, Halaska M, Robova H. Nerve-sparing and individually tailored surgery for cervical cancer. Lancet Oncol. 2010;11(3):292-301.
4. 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.
5. 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.
6. Bergmark K, Avall-Lundqvist E, Dickman PW, Henningsohn L, Steineck G. Vaginal changes and sexuality in women with a history of cervical cancer. N Engl J Med. 1999;340(18):1383-9.
7. 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.
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. 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.
10. Sakamoto S, Takizawa K. An improved radical hysterectomy with fewer urological complications and with no loss of therapeutic results for invasive cervical cancer. Baillieres Clin Obstet Gynaecol. 1988;2(4):953-62.
11. 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.
12. Sobin L. TNM Classification of malignant tumours. Geneva2002 [updated 2002. UICC Internation Union against Cancer:[155-7].
13. Scholten RJPM OM, Assendelft WJJ. Inleiding in Evidence-Based Medicine. Klinisch handelen gebaseerd op bewijsmateriaal. Houten: Bohn, Stafleu, Van Loghum; 2013. 285 p.
14. Collaboration TC. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 2008 [updated September 2008. Available from: www.cochrane-handbook.org.

15. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMCMedResMethodol. 2005;5:13.

16. Wu J, Liu X, Hua K, Hu C, Chen X, Lu X. Effect of nerve-sparing radical hysterectomy on bladder function recovery and quality of life in patients with cervical carcinoma. Int J Gynecol Cancer. 2010;20(5):905-9.

17. Chen C, Li W, Li F, Liu P, Zhou J, Lu L, et al. Classical and nerve-sparing radical hysterectomy: an evaluation of the nerve trauma in cardinal ligament. Gynecol Oncol. 2012;125(1):245-51.

18. Chen L, Zhang WN, Zhang SM, Yang ZH, Zhang P. Effect of laparoscopic nerve-sparing radical hysterectomy on bladder function, intestinal function recovery and quality of sexual life in patients with cervical carcinoma. Asian Pac J Cancer Prev. 2014;15(24):10971-5.

19. Roh JW, Lee DO, Suh DH, Lim MC, Seo SS, Chung J, et al. Efficacy and oncologic safety of nerve-sparing radical hysterectomy for cervical cancer: a randomized controlled trial. J Gynecol Oncol. 2015;26(2):90-9.

20. Asmussen M, Andresen A. [Immediate disorders of urination following radical hysterectomy in cervix cancer]. ZentralblGynakol. 1987;109(4):222-7.

21. Hockel M, Naumann G, Alexander H, Horn LC, Fischer U, Schmidt F, et al. Nerve-sparing radical hysterectomy: II. Results after three years. [German]. Geburtshilfe und Frauenheilkunde. 2000;60(6):320-5.

22. Kuwabara Y, Suzuki M, Hashimoto M, Furugen Y, Yoshida K, Mitsuhashi N. New method to prevent bladder dysfunction after radical hysterectomy for uterine cervical cancer. J Obstet GynaecolRes. 2000;26(1):1-8.

23. Possover M, Stober S, Plaul K, Schneider A. Identification and preservation of the motoric innervation of the bladder in radical hysterectomy type III. Gynecol Oncol. 2000;79(2):154-7.

24. Sakuragi N, Todo Y, Kudo M, Yamamoto R, Sato T. A systematic nerve-sparing radical hysterectomy technique in invasive cervical cancer for preserving postsurgical bladder function. Int J Gynecol Cancer. 2005;15(2):389-97.

25. Rodolakis A, Mantzaris G, Thomakos N, Vlachos G, Bakos D, Antsaklis A. Rectal dysfunction in loupes assisted nerve-sparing and radical hysterectomies types II and III: A manometric evaluation. Gynecologic Oncology. 2008;108(3):339.

26. Chen Y, Li Y, Xu HC, Li JN, Li YY, Liang ZQ. Laparoscopic anatomical nerve sparing radical hysterectomy for cervical cancer: a clinical analysis of 37 cases. Zhonghua Fu Chan KeZa Zhi. 2009;44(5):359-63.

27. Ju XZ, Li ZT, Yang HJ, Wu XH. Nerve-sparing radical hysterectomy and radical hysterectomy: a retrospective study. Zhonghua Fu Chan KeZa Zhi. 2009;44(8):605-9.

28. Sun L, Wu LY, Zhang WH, Li XG, Song Y, Zhang X. Preliminary study of nerve sparing radical hysterectomy in patients with cervical cancer. Zhonghua Zhong Liu Za Zhi. 2009;31(8):607-11.

29. 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.

30. Espino-Strebel EE, Luna JT, Domingo EJ. A comparison of the feasibility and safety of nerve-sparing radical hysterectomy with the conventional radical hysterectomy. Int J Gynecol Cancer. 2010;20(7):1274-83.

31. Liang Z, Chen Y, Xu H, Li Y, Wang D. Laparoscopic nerve-sparing radical hysterectomy with fascia space dissection technique for cervical cancer: description of technique and outcomes. Gynecol Oncol. 2010;119(2):202-7.

32. Runnebaum IB, Camara O, Diebolder H. Nerve-sparing Vaginal Assisted Laparoscopic Radical Hysterectomy (VALRH): Evaluation of type C1 radicality for low and high-risk early cervical cancer. Archives of Gynecology and Obstetrics. 2010;Conference(Deutsche Gesellschaft fur Gynakologie und Geburtshilfe: :(var.pagings):S170.

33. Skret-Magierlo J, Narog M, Kruczek A, Kluza R, Kluz T, Magon T, et al. Radical hysterectomy during the transition period from traditional to nerve-sparing technique. Gynecol Oncol. 2010;116(3):502-5.

34. Ditto A, Martinelli F, Mattana F, Reato C, Solima E, Carcangiu M, et al. Class III Nerve-sparing Radical Hysterectomy Versus Standard Class III Radical Hysterectomy: An Observational Study. Ann Surg Oncol. 2011.

35. Dowaji J, Jaenicke F. The outcome of nerve sparing radical hysterectomy in patients with cervical cancer (IB2-IIIA). International Journal of Gynecological Cancer. 2011;Conference(var. pagings):S141.

36. Merlot B, Narducci F, Lambaudie E, Phalippou J, Taieb S, Houvenaeghel G, et al. Robotic nerve-sparing versus laparoscopic without nerve-sparing radical hysterectomy in early cervical cancer: Urinary diseases. International Journal of Gynecological Cancer. 2011;Conference(var. pagings):S105.

37. Mukhtarulina S, Ushakov I, Poliakova S. Systematic Nerve-Sparing Radical Hysterectomy (NSRG) in cervical cancer: Urodynamic study on postsurgical bladder function. International Journal of Gynecological Cancer. 2011;Conference(var.pagings):S140.

38. Radlovic P, Cetkovic A, Djakovic M, Rulic B. Comparative study of postoperative morbidity after nerve-sparing radical hysterectomy and traditional radical hysterectomy. International Journal of Gynecological Cancer. 2011;Conference(var.pagings):S177.

39. Ceccaroni M, Roviglione G, Spagnolo E, Casadio P, Clarizia R, Peiretti M, et al. Pelvic dysfunctions and quality of life after nerve-sparing radical hysterectomy: a multicenter comparative study. Anticancer Res. 2012;32(2):581-8.

40. Tseng CJ, Shen HP, Lin YH, Lee CY, Wei-Cheng CW. A prospective study of nerve-sparing radical hysterectomy for uterine cervical carcinoma in Taiwan. Taiwan J Obstet Gynecol. 2012;51(1):55-9.

41. Chang Y-Y, Hwang T-L, Lin W-C. Follow-up of clinical outcome of laparoscopic radical hysterectomy and laparoscopy nerve-sparing radical hysterectomy. Journal of Minimally Invasive Gynecology. 2013;Conference: 42nd Global Congress of Minimally Invasive Gynecology:November-December 2013.

42. Prajwala R, Tsang J, Thangavelu A, Abu JI. Feasibility of laparoscopic nerve sparing radical hysterectomy in the management of early cervical cancer. International Journal of Gynecological Cancer. 2013;Conference: 18th International Meeting of the European Society of Gynaecological Oncology:October 2013.

43. Bogani G, Cromi A, Uccella S, Serati M, Casarin J, Pinelli C, et al. Nerve-sparing versus conventional laparoscopic radical hysterectomy: a minimum 12 months' follow-up study. Int J Gynecol Cancer. 2014;24(4):787-93.

44. Bogani G, Serati M, Nappi R, Cromi A, di NE, Ghezzi F. Nerve-Sparing Approach Reduces Sexual Dysfunction in Patients Undergoing Laparoscopic Radical Hysterectomy. J Sex Med. 2014.

45. Dermenzhy T, Svintitskiy V, Yatsina A. Functioning of urinary and reproductive systems in patients with infiltrative cervical after nerve-sparing radical hysterectomy. International Journal of Gynecological Cancer. 2014;Conference(var.pagings):533.

46. Dermenzhy T, Svintitskiy V, Stakhovskiy E, Yatsyna O. Evaluation of some indexes of urinary system function in patients with infiltrative cervical cancer and effect of nerve-sparing radical hysterectomy (RHE-C1). Annals of Oncology. 2014;25(suppl_4):iv319.

47. Kanao H, Fujiwara K, Ebisawa K, Hada T, Ota Y, Andou M. Various types of total laparoscopic nerve-sparing radical hysterectomies and their effects on bladder function. J Gynecol Oncol. 2014;25(3):198-205.

48. Makowski M, Nowak M, Szpakowski M, Władziński J, Serwach-Nowińska A, Janas Ł, et al. Classical radical hysterectomy and nerve-sparing radical hysterectomy in the treatment of cervical cancer. Menopausal Review / Przeglad Menopauzalny. 2014;13(3):180-5.

49. Rademaker M, van den Tillaart SA, van Poelgeest MI, Beltman JJ, Gaarenstroom KN, Peters AAW, et al. Long-term follow-up after nerve sparing radical hysterectomy in patients with stage IA-IIA cervical cancer. International Journal of Gynecological Cancer. 2014;Conference(var. pagings):3.

50. Sowa E, Kuhnt S, Hinz A, Schroder C, Deutsch T, Geue K. Postoperative Health-Related Quality of Life of Cervical Cancer Patients - A Comparison between the Wertheim-Meigs Operation and Total Mesometrial Resection (TMMR). Geburtshilfe Frauenheilkd. 2014;74(7):670-6.

51. Wang W, Li B, Zuo J, Zhang G, Yang Y, Zeng H, et al. Evaluation of pelvic visceral functions after modified nerve-sparing radical hysterectomy. Chin Med J (Engl). 2014;127(4):696-701.

52. Wenwen W, Bin L, Jing Z, Gongyi Z, Yeduo Y, Hongmei Z, et al. [Evaluation of postoperative bladder function and prognosis after modified nerve sparing radical hysterectomy]. Zhonghua Fu Chan Ke Za Zhi. 2014;49(5):341-7.

53. Wirawan JP, Hakim S, Prihartono J, Rohim AA. The efficacy of nerve sparing technique during radical hysterectomy in reducing post operative urinary retention: Experience in Jakarta, Indonesia. International Journal of Gynecological Cancer. 2014;Conference: 14th Biennial Meeting of the International Gynecologic Cancer Society:October 2012.

54. Shi R, Wei W, Jiang P. Laparoscopic Nerve-Sparing Radical Hysterectomy for Cervical Carcinoma: Emphasis on Nerve Content in Removed Cardinal Ligaments. Int J Gynecol Cancer. 2015.

55. Xie BG, Lu WY, Huang YH, Zhu WJ. Quality of life in cervical cancer treated with systematic nerve-sparing and modified radical hysterectomies. J Obstet Gynaecol. 2015;35(8):839-43.

56. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. Social science & medicine. 1995;41(10):1403-9.

57. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1993;11(3):570-9.

58. 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.

59. Sandadi S, Tanner EJ, Khoury-Collado F, Kostolias A, Makker V, Chi DS, et al. Radical surgery with individualized postoperative radiation for stage IB cervical cancer: oncologic outcomes and severe complications. Int J Gynecol Cancer. 2013;23(3):553-8.

60. Todo Y, Kuwabara M, Watari H, Ebina Y, Takeda M, Kudo M, et al. Urodynamic study on postsurgical bladder function in cervical cancer treated with systematic nerve-sparing radical hysterectomy. Int J Gynecol Cancer. 2006;16(1):369-75.

61. Roh J-W, Lee D-O, Chung J, Lim MC, Seo SS, Park S-Y. A prospective randomized trial for evaluation of therapeutic efficacy and safety of nerve-sparing radical hysterectomy in cervical cancer. International Journal of Gynecological Cancer. 2014;Conference: 14th Biennial Meeting of the International Gynecologic Cancer Society:October 2012.

62. Basch E, Torda P, Adams K. Standards for patient-reported outcome-based performance measures. Jama. 2013;310(2):139-40.

63. Plante M. [updated 14 April 2016. Available from: http://www.gcig.igcs.org/ClinicalTrials.html.

64. Fujii S, Takakura K, Matsumura N, Higuchi T, Yura S, Mandai M, et al. Anatomic identification and functional outcomes of the nerve sparing Okabayashi radical hysterectomy. Gynecol Oncol. 2007;107(1):4-13.

65. 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.

66. Hockel M, Konerding MA, Heussel CP. Liposuction-assisted nerve-sparing extended radical hysterectomy: oncologic rationale, surgical anatomy, and feasibility study. Am J Obstet Gynecol. 1998;178(5):971-6.

67. Colombo N, Carinelli S, Colombo A, Marini C, Rollo D, Sessa C, et al. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012;23 Suppl 7:vii27-32.

68. Angioli R, Plotti F, Aloisi A, Scaletta G, Capriglione S, Luvero D, et al. A randomized controlled trial comparing four versus six courses of adjuvant platinum-based chemotherapy in locally advanced cervical cancer patients previously treated with neo-adjuvant chemotherapy plus radical surgery. Gynecol Oncol. 2015;139(3):433-8.

69. Yan H, Liu Z, Fu X, Li Y, Che H, Mo R, et al. Long-term outcomes of radical vaginal trachelectomy and laparoscopic pelvic lymphadenectomy after neoadjuvant chemotherapy for the IB1 cervical cancer: A series of 60 cases. International journal of surgery. 2016;29:38-42.

70. Yao YY, Wang Y, Wang JL, Zhao C, Wei LH. Outcomes of fertility and pregnancy in patients with early-stage cervical cancer after undergoing neoadjuvant chemotherapy. European journal of gynaecological oncology. 2016;37(1):109-12.

Supplemental figure 2. Quality of life: urinary function.

				NSRH			
Data analysed		**Author**	**Year**	**N**	**n**	**(%)**	**mean ± SD †**
PVRV	unknown	Ju	2009	24		-	8.7 ± -
	< 100 ml	Ceccaroni	2012	25	0	(0%)	
	< 50 ml	Chang	2013	32		-	7.03 ± -
	< 100 ml	Wirawan	2014	15		-	23.3 ± -
Retention		Merlot	2011	19	2	(10.5%)	
Recovery of bladder function		Ditto	2011	185	175	(94.6%)	
		Prajwala	2013	5	2	(40%)	
		Prajwala	2013	5	5	(100%)	
		Bogani 1	2014	33	27	(82%)	
		Bogani 1	2014	33	32	(97%)	
		Ceccaroni	2012	25	23	(92%)	
		Tseng	2012	18	18	(100%)	
		Wenwen 2*	2014	85	65	(76.5%)	
		Wirawan	2014	15		-	
Satisfaction of micturition		Liang	2010	82	71	(86,6%)	
		Skret-Magierlo	2010	10		-	4.7 ± 2.7
Abnormal bladder sensation / bladder dysfunction / ISC		Wu	2010	14	0	(0%)	
		Dowaji 2	2011	60	3	(5%)	
		Mukhtarulina	2011	23	2	(8,7%)	
		Mukhtarulina	2011	23	0	(0%)	
		Mukhtarulina	2011	23	0	(0%)	
		Radlovic	2011	41	1.7	(4%)	
		Chen	2014	30	0	(0%)	
		Dermenzhy 2	2014	25	3	(12%)	
		Roh	2015	64	1	(1.6%)	
Dysuria		Ceccaroni	2012	25	0	(0%)	
		Tseng	2012	18	2.1	(12%)	
		Wenwen 2*	2014	85	9	(10.6%)	
		Shi	2015	64	1	(1.6%)	
		Chen	2012	30	1	(3.3%)	
Good sensation		Sakuragi	2005	22	22	(100%)	
		Chen	2009	37	35	(95%)	
		Liang	2010	82	74	(90.2%)	
Urinary symptom	urgency	Ceccaroni	2012	25	1	(4%)	
	stress	Ceccaroni	2012	25	1	(4%)	

	RH					
N	**n**	**(%)**	**mean ± SD †**	**p**	**Ratio [95% CI]**	**Moment of evaluation ‡**
69		-	14.8 ± -	<0.01	-	6
31	6	(19.3%)		<0.01	-	36
36		-	26.36 ± -	-	-	post op
19		-	18.4 ± -	>0.05	-	post op
28	7	(25%)		-	-	post op
302	267	(88.4%)		0.022	-	unknown
18	18	(100%)		-	-	post op
18	18	(100%)		-	-	3
63	37	(59%)		-	OR 0.3 [0.11-0.87]	post op
63	51	(81%)		0.03	-	12
31	19	(61,3%)		0.01	-	36
12	5	(41.7%)		-	-	3
167	102	(61.1%)		-	-	-
19		-		>0.05	-	post op
81	58	(71.6%)		<0.05	-	-
10		-	9.5 ± 4.1	>0.05	-	post op
15	5	(33.3%)		0.034	-	6, 12
40	6.4	(16%)		<0.005	-	-
17	10	(58.8%)		0.002	-	1
17	6	(35.3%)		0.005	-	3
17	5	(31.1%)		0.001	-	6
46	11.5	(25%)		-	-	5
35	7	(20.0%)		<0.005	-	12
25	15	(60%)		-	-	-
42	3	(7.5%)		<0.001	-	12
31	8	(25.8%)		-	-	36
12	6.6	(55%)		-	-	3
167	68	(40.7%)		<0.05	-	-
42	3	(7.1%)		-	-	12
35	9	(37.1%)		<0.05	-	12
5	2	(40%)		0.03	-	12
25	22	(88%)		-	-	-
81	61	(75,3%)		<0.05	-	-
31	9	(29%)		0.01	-	36
31	4	(12.9%)		0.24	-	-

Supplemental figure 2. Continued

				NSRH			
Data analysed		**Author**	**Year**	**N**	**n**	**(%)**	**mean ± SD †**
	freq/urge	Tseng	2012	18	2	(11.1%)	
	frequency	Wenwen 2*	2014	85	12	(14.1%)	
		Chen	2014	30	3	(10%)	
Incontinence	stress	Sakuragi	2005	22	0	(0%)	
	overflow	Asmussen	1987	13	0	(0%)	
		Ceccaroni	2012	25	2	(8%)	
		Ceccaroni	2012	25	1	(14%)	
		Tseng	2012	18	0	(0%)	
	severe	Pieterse **	2013	91	32	(35%)	
	severe	Pieterse**	2013	77	38	(49%)	
	urge, little	Pieterse**	2013	91	8	(9%)	
	urge, little	Pieterse**	2013	77	4	(5%)	
		Wenwen 2*	2014	85	31	(36.5%)	
		Chen	2014	30	5	(16.7%)	

NSRH, nerve sparing radical hysterectomy; RH, conventional radical hysterectomy; † Days; ‡ Months; PVRV, post voidal residual volume; ISC, intermittent self catheterisation; * N = Amount of patients with known results. Total amount of patients: 102 (NSRH), 204 (RH); ** N = Amount of patients with known results. Total amount of patients: 123 (NSRH), 106 (RH).

	RH					
N	**n**	**(%)**	**mean ± SD †**	**p**	**Ratio [95% CI]**	**Moment of evaluation ‡**
12	9	(75%)		0.001	-	3
167	56	(33.5%)		<0.05	-	-
35	15	(42,9%)		<0.01	-	12
5	3	(60%)		0.0034	-	12
5	5	(100%)		-	-	12
31	17	(54.8%)		-	-	post op
31	14	(45.1%)		-	-	36
12	5	(41.7%)		0.006	-	3
83	39	(47%)		-	RR 0.61 [0.33-1.13]	12
79	35	(44%)		-	RR 1.23 [0.65-2.30]	24
84	5	(6%)		-	RR 1.52 [0.48-4.85]	12
79	4	(5%)		-	RR 1.03 [0.25-4.26]	24
167	91	(54.5%)		<0.05	-	-
35	17	(48.6%)		<0.01	-	12

Supplemental figure 3. Quality of life: bowel function.

			NSRH			
Data analysed	**Author**	**Year**	**N**	**n**	**(%)**	**mean ± SD [range] †**
Defaecation	Ju	2009	24		-	2.9 ± -
	Chen	2012	12		-	3.3 ± 0.71 [2.5-4.7]
Flatus	Chen	2012	12		-	2.1 ± 0.57 [1.5-3.1]
	Chen	2014	30		-	1.67 ± 0.16
	Ditto	2011	185	0	(0%)	
Defaec/Flatus	Rodolakis	2008	15		-	
	Radlovic	2011	41	2.5	(6%)	
	Ceccaroni	2012	25	0	(0%)	
	Wenwen 1	2014	78	0	(0%)	
Constipation	Ceccaroni	2012	25	1	(4%)	
	Chang	2013	32	2	(6%)	
	Pieterse*	2013	90	20	(22%)	
	Pieterse*	2013	76	14	(18%)	
	Wenwen 1	2014	78	4	(5.1%)	
	Chen	2014	30	2	(7%)	
	Sowa	2014	74		-	7.21 ± 20.10
	Shi	2015	64	2	(4.76%)	
Diarrhoea	Pieterse*	2013	90	19	(21%)	
	Pieterse*	2013	76	18	(24%)	
	Wenwen 1	2014	78	2	(2.6%)	
	Sowa	2014	74		-	2.7 ± 13.24
Constip/Diarrh	Bogani 1	2014	33	0	(0%)	

NSRH, nerve sparing radical hysterectomy; RH, conventional radical hysterectomy; † Days; ‡ Months; * N = Amount of patients responding to questionnaire. Total amount of patients: 123 (NSRH), 106 (RH); # Mean time of evaluation, NSRH group 29.5 months vs 41.1 months.

	RH					
N	**n**	**(%)**	**mean ± SD [range] †**	**p**	**Ratio [95% CI]**	**Moment of evaluation ‡**
69	3.2			< 0.01	-	post op
13	-		4.1 ± 0.93 [3.1-7]	0.026	-	post op
13	-		2.6 ± 0.60 [1.5-4.3]	0.083	-	post op
35	-		2.4 ± 0.17	0.000	-	post op
311	9	(2.9%)		-	-	post op
30	-			0.276	-	12
46	10.6	(23%)		-	-	5
31	2	(26%)		-	-	> 12
160	3	(2%)		0.553	-	31
31	8	(26%)		0.02	-	> 12
36	11	(31%)		-	-	-
84	19	(23%)		-	RR 0.98 [0.48-2.00]	12
79	15	(19%)		-	RR 0.96 [0.43-2.16]	24
160	50	(31.2%)		< 0.01	-	-
35	3	(9%)		-	-	-
36	-		12.04 ± 26.61	0.584	-	-
42	4	(9.5%)		-	-	-
76	18	(24%)		-	RR 0.75 [0.37-1.52]	12
79	23	(29%)		-	RR 0.76 [0.37-1.55]	24
160	22	(13.8%)		< 0.01	-	31
36	-		14.29 ± 28.34	0.012	-	35.3#
63	61.5	(13%)		0.04	OR 10.2 [0.57-183.7]	< 12

Supplemental figure 4. Quality of life: sexual function.

				NSRH			
Data analysed		**Author**	**Year**	**N**	**n**	**(%)**	**mean ± SD †**
(Dis)satisfaction	*Satisfaction*	Ju	2009	24	7	(29%)	
		Ceccaroni*	2012	25	10	(40%)	
		Pieterse**	2013	91	11	(12%)	
		Pieterse**	2013	75	11	(15%)	
		Chen	2014	30		-	4.36 ± 0.81
	Dissatisfaction	Ceccaroni*	2012	25	7	(28%)	
	Positive responsive	Sowa	2014	74		-	70.18 ± 28.65
	Desire	Chen	2014	30		-	3.60 ± 0.8
	Arousal	Chen	2014	30		-	3.52 ± 0.85
Activity/frequency	*Active*	Ceccaroni*	2012	25	8	(32%)	
		Sowa	2014	74		-	40.83 ± 30.46
	Not active	Pieterse**	2013	106	23	(22%)	
		Pieterse**	2013	92	22	(24%)	
	Reduced frequency	Wenwen 1***	2014	32	25	(78.1%)	
		Chen	2014	30		-	4.33 ± 0.71
Dysfunction		Radlovic	2011	41		-	
		Dermenzhy 1	2014	23	5	(21.5%)	
		Ceccaroni*	2012	25	0	(0%)	
Dyspareunia		Ceccaroni*	2012	25	1	(4%)	
		Pieterse**	2013	82	11	(12%)	
		Pieterse**	2013	71	11	(16%)	
		Bogani 1****	2014	27	0	(0%)	
	Dyspareunia	Wenwen 1***	2014	32	11	(34.4%)	
	Pain during coitus	Wenwen 1***	2014	32	14	(43.8%)	
		Shi	2015	64	0	(0%)	
		Dermenzhy 1	2014	23	1	(4.3%)	
Vaginal dryness	*Dryness*	Ceccaroni*	2012	25	3	(12%)	
		Pieterse**	2013	91	17	(19%)	
		Pieterse**	2013	77	11	(14%)	
		Shi	2015	64	1	(1.6%)	
	Reduced lubrication	Pieterse**	2013	82	19	(23%)	
		Pieterse**	2013	71	15	(21%)	
		Wenwen 1***	2014	32	20	(62.5%)	
		Dermenzhy 1	2014	23	2	(8.6%)	

	RH					
N	**n**	**(%)**	**mean ± SD †**	**p**	**Ratio [95% CI]**	**Moment of Evaluation ‡**
69	6	(9%)		0.042	-	6
31	12	(38.7%)		-	-	> 12
68	12	(18%)		-	RR 0.64 [0.26-1.56]	12
65	13	(20%)		-	RR 0.69 [0.28-1.66]	24
35	-		2.63 ± 0.84	0.046	-	-
31	11	(35.4%)		-	-	> 12
36	-		73.91 ± 30.08	0.46	-	35.3#
35	-		2.60 ± 0.53	0.002	-	-
35	-		2.60 ± 0.74	0.016	-	-
31	8	(25.8%)		-	-	> 12
36	-		31.10 ± 30.95	0.73	-	30.5
85	21	(25%)		-	RR 0.85 [0.43-1.66]	12
80	21	(26%)		-	RR 0.88 [0.44-1.76]	24
82	64	(78%)		0.993	-	> 6
35	-		4.17 ± 0.67	0.583	-	12
46	-			NS	-	-
23	20	(86.5%)		< 0.05	-	-
31	7	(22.5%)		0.03	-	> 12
31	4	(12.9%)		-	-	> 12
63	12	(19%)		-	RR 0.57 [0.24-1.47]	12
60	10	(17%)		-	RR 0.92 [0.36-2.34]	24
23	3	(13%)		0.09	OR 9.3 [0.45-192.2]	-
82	29	(35.4%)		0.921	-	> 6
82	32	(39.5%)		0.644	-	> 6
42	2	(4.8%)		-	-	> 12
23	-			-	-	-
31	8	(25.8%)		-	-	> 12
70	4	(6%)		-	RR 3.79 [1.21-11.84]	12
69	10	(15%)		-	RR 0.98 [0.39-2.48]	24
42	3	(7.1%)		-	-	> 12
65	12	(19%)		-	RR 1.33 [0.59-2.99]	12
60	14	(23%)		-	RR 0.88 [0.39-2.01]	24
82	43	(52.4%)		0.332	-	> 6
23	7	(30.3%)		-	-	-

Supplemental figure 4. Continued

				NSRH			
Data analysed		**Author**	**Year**	**N**	**n**	**(%)**	**mean ± SD †**
	Lubrication	Chen	2014	30		-	3.95 ± 0.70
Numbness of labia		Pieterse**	2013	105	44	(42%)	
		Pieterse**	2013	79	54	(68%)	
Psychological	*Fear of intercourse*	Sowa	2014	74		-	24.76 ± 37.08
distress due to		Dermenzhy 1	2014	23	2	(8.6%)	
	Vaginal dryness	Ceccaroni*	2012	25	4	(16%)	
	Dyspareunia	Ceccaroni*	2012	25	2	(6.4%)	

NSRH, nerve sparing radical hysterectomy; RH, conventional radical hysterectomy; † Days; ‡ Months; * N = Amount of patients responding to questionnaire. Total amount of patients: 25 (NSRH), 46 (RH); ** N = Amount of patients responding to questionnaire. Total amount of patients: 123 (NSRH), 106 (RH); *** N = Amount of patients responding to questionnaire. Total amount of patients: 78 (NSRH), 160 (RH); **** N = Amount of patients responding to questionnaire. Total amount of patients: 33 (NSRH), 63 (RH); # Mean time of evaluation, NSRH group 29.5 months vs 41.1 months.

RH						
N	n	(%)	mean ± SD †	p	Ratio [95% CI]	Moment of Evaluation ‡
35	-		2.75 ± 0.78	0.001	-	12
84	62	(74%)		-	RR 0.26 [0.14-0.48]	12
90	31	(34%)		-	RR 0.24 [0.13-0.46]	24
36	-		15.0 ± 30.84	0.549	-	-
23	8	(34.6%)		-	-	-
31	13	(41.9%)		0.02	-	> 12
31	12	(38.7%)		< 0.01	-	-

Supplemental figure 5. Quality of life: general.

		NSRH	RH					
Author	**Year**	**N**	**N**	**Questionnaire**	**Data analysed**	**p**	**Favours**	**Moment of evaluation‡**
Wu	2010	14	15	FACT-Cx	Basic bodily fx	NS	-	
					Social and family life	<0.001	NSRH	
					Emotional wellbeing	<0.001	NSRH	12
					Working status	<0.001	NSRH	
					Symptoms correlated with operation field	<0.001	NSRH	
Ceccaroni	2012	25	31	Modified from Bergmark series	Deterioration QOL	0.03	NSRH	22
					Post operative QOL	0.03	NSRH	[range 12-38]
Sowa	2014	74	36	EORTC QLQC30	Physical fx	0.047	NSRH	
					Role fx	0.016	NSRH	
					Fatigue	0.028	NSRH	
					Pain	0.018	NSRH	
					Shortness of breath	0.034	NSRH	
					Lack of appetite	0.006	NSRH	
					QOL overall fx	NS	-	post op*
					Cognitive fx	NS	-	
					Social fx	NS	-	
					Nausea	NS	-	
					Sleeping disorders	NS	-	
					Financial problems	NS	-	

				EORTC QLQCX24	Symptom experience	NS	-	
					Body image	NS	-	
Xie	2015	52	54	EORTC QLQ-C30	Physical fx	NS	-	
				(Chinese version)	Role fx	0,087	NSRH	
					Emotional fx	NS	-	6
					Cognitive fx	NS	-	
					Social fx	NS	-	
					Global QoL	NS	-	

NSRH, nerve sparing radical hysterectomy; RH, conventional radical hysterectomy; ‡ Months; * Not otherwise specified.