Universiteit
Leiden
The Netherlands

Tailoring therapy in endometrial and cervical cancer

Gent, M.D.J.M. van

Citation
Gent, M. D. J. M. van. (2017, June 20). *Tailoring therapy in endometrial and cervical cancer*. Retrieved from https://hdl.handle.net/1887/51101

Version:	Not Applicable (or Unknown)
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/51101

Note: To cite this publication please use the final published version (if applicable).

Cover Page

Universiteit Leiden

The handle http://hdl.handle.net/1887/51101 holds various files of this Leiden University dissertation

Author: Gent, M.D.J.M. van
Title: Tailoring therapy in endometrial and cervical cancer
Issue Date: 2017-06-20

TAILORING THERAPY
IN ENDOMETRIAL AND CERVICAL CANCER

Cover: Prins Clausplein 1997, by Ap Sok
ISBN 978-94-028-0650-2
Printed by IPSKAMP printing
Lay-out by Alex Wesselink, Persoonlijkproefschrift.nl

Financial support for the printing of this thesis was provided by: Chipsoft BV, department of gynaecology, Leiden University Medical Center

© 2017 Mignon van Gent
All rights reserved. No part of this thesis may be reproduced or transmitted, in any form or by any means, without permission of the author.

TAILORING THERAPY IN ENDOMETRIAL AND CERVICAL CANCER

Proefschrift

Ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van de rector Magnificus prof.mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op dinsdag 20 juni 2017
klokke 15.00 uur

door

Mignon Dingena Johanna Maria van Gent

Geboren te Veghel
in 1980

Promotor:	Prof. Dr. J.B.M.Z. Trimbos
Co-promotores:	Dr. M.J. Kagie, Haaglanden Medisch Centrum Dr. C. D. de Kroon
Leden promotiecommissie:	Prof. Dr. F.W. Jansen Prof. Dr. F. Amant, Nederlands Kanker Instituut/KU Leuven Prof. Dr. M.J.E. Mourits, Universiteit Groningen Dr. H.M. Hazelbag, Haaglanden Medisch Centrum

To my family

"Als je patiënten geen mogelijkheid tot vervullen kinderwens kan bieden moet je ze misschien iets anders te wensen bieden" - Michiel Krol, † 2012

TABLE OF CONTENTS

CHAPTER 1

Introduction

INTRODUCTION – TAILORING THERAPY IN GYNAECOLOGICAL CANCER

Care for patients with cancer has changed over the past decades from a more paternalistic model towards a model in which shared decision-making is more prominent. The doctor used to decide what was best for the patient and started a treatment without always taking the patient's thoughts, wishes and values into consideration. In shared decision-making, the patient and doctor have a dialogue. Quality of life and wishes and values of the patient play an important role in determining which way to go. [1] This does not necessarily have to be the usual, golden standard treatment of which efficacy and safety have been proven in well performed, controlled trials. It can also be an adaptation or alteration of the golden standard, to accomplish maintenance of fertility in endometrial and cervical cancer or to decide to be more or less aggressive in radical hysterectomy surgery, depending on the individual need of the patient.
In this thesis, two types of gynaecological cancers will be addressed, namely low-grade/ early stage endometrial cancer and early stage cervical cancer. Since survival rates of these patients are good, quality of life after treatment is of great importance. This thesis provides evidence of the treatment options and recommendations and future goals to optimise individualised and tailored therapy in early stage endometrial and cervical cancer.

ENDOMETRIAL CANCER

Endometrial cancer is the most common form of cancer of the female genital tract in Western countries. It is the fourth most frequent form of cancer after breast-, lung- and colorectal cancer. [2, 3] The incidence of endometrial cancer in the Netherlands is 20 per 100.000. Four percent of the patients are younger than 40 years of age. [4] This means around 50 patients a year are diagnosed with endometrial cancer who may not have completed their family. [5] High Body Mass Index (BMI) and reduced physical activity increase the risk of developing endometrial cancer. [6] Obesity causes insulin resistance, excessive androgen production by the ovaries, anovulation, polycystic ovary syndrome and chronic shortage of progesterone. [7] Women with a BMI above 25 kg/m^2 have a double risk of getting endometrial cancer and women with a BMI above 30 kg/ m^2 have a triple risk compared to patients with a BMI under 25 kg/ m^2. [7] Because the mean BMI will rise during the coming years, the incidence of endometrial cancer in pre-menopausal women will also rise. [8] Since patients with the above-mentioned features have a higher chance of having fertility problems, they have a higher chance of getting pregnant relatively late. This makes the need for research in this field even greater. Most pre-menopausal women present with a low-grade endometrioid type adenocarcinoma, emerged from the background of endometrial hyperplasia and long lasting estrogen stimulation

without adequate counteraction by progesterones. [9] This type behaves less aggressively compared to other types of endometrial cancer. [10 11]
The standard treatment of stage I endometrial cancer is hysterectomy with bilateral salpingo-oophorectomy. [12] Consequently this means that women who have not completed their family are confronted with infertility as a result of cancer therapy.

Fertility-sparing treatment options

An alternative for surgery can be hormonal treatment with progesterones. Worldwide experiences with this kind of treatment have been described in order to evaluate effectiveness and safety. [13-21] In **chapter 2** of this thesis a review is presented on the effectiveness and safety of fertility sparing treatment of early stage, low-grade endometrial cancer.

While writing, it became clear that reporting of data is heterogeneous and that, since the incidence of endometrial cancer in pre-menopausal women is so rare, a uniform protocol was greatly needed. The review formed the basis of the Dutch protocol for fertility sparing treatment in endometrial cancer (appendix 1). Since the introduction of the protocol, data of patients treated according to the protocol have been collected in a clinical database providing an overview of the results in the Dutch population (appendix 2).

Pre-treatment patient selection

The question remains how to decide which patient will benefit from hormonal therapy and which patient will not. To reduce the risk of recurrence and failed therapy, predictors of persistent response need to be identified. In **chapter 3** thorough molecular analyses have been performed on sequential endometrial samples of pre-menopausal women with low-grade endometrial cancer. These patients were treated, in order to perceive fertility, with progesterones. The samples have been used for immunohistochemical and in-depth molecular analysis. We know from advanced endometrial cancer, in which progesterone receptor analysis is done routinely, that a positive progesterone receptor status is positively predicting response to progesterone therapy. [22, 23] Due to the low prevalence of endometrial cancer in pre-menopausal women we do not have substantial evidence that we can extrapolate this to the low-grade endometrial cancers in women who would consider fertility preserving therapy. Previous studies have suggested progesterone to have an anti- tumour effect by interacting with the Wingless (Wnt) and/or Phosphatidylinositol 3-kinase (PI3K)-Akt signal transduction pathways. [24, 25] These pathways induce cell proliferation and are turned "on" and "off" during a menstrual cycle under the influence of progesterone/estrogen changes. Wnt-signaling can be constitutively activated by mutations in the *CTNNB1* gene (β-catenin), APC gene or under influence (endogenous) estrogen. 30-85% of the endometrioid endometrial cancers has nuclear β-catenin staining. [26, 27] In vitro analyses have shown progesterone

to inhibit Wnt signaling by up-regulation of FOXO1 and DKK1 [24, 25], suggesting the anti-tumour effect of progesterone. PI3K/Akt is activated by hotspot mutations in *PIK3CA* and/or *KRAS*, or inactivation of tumour suppressor gene PTEN. Fifty to eighty percent of the endometrial cancers is known to show *PTEN* loss [28] and respectively 52 % and 17 % of the tumours have *PIK3CA* and *KRAS* mutated. [29, 30] In **chapter 3** sequential endometrial samples of women before and while on progesterone therapy are analysed to investigate whether genetic alterations in these pathways lead to non-responsiveness to progesterones. The thought was that if one performs these analyses on the tissue at diagnosis, it might be possible to distinguish responders from non-responders before treatment is initiated. This knowledge will result in important additional information and improve shared decision making in respective women.

CERVICAL CANCER

The second part of this thesis is about early stage cervical cancer. Cervical cancer is the second most frequent type of cancer in females worldwide. It is the fourth most lethal type of cancer after breast-, lung- and bowel cancer. [31] In 2010 worldwide 453.970 new patients were diagnosed with cervical cancer and 44 percent of these women were less than 50 years of age. The treatment of cervical cancer depends entirely on the stage of disease, which is determined by clinical examination. Microscopic disease (FIGO IA1) is mostly treated by conisation or simple hysterectomy. The so-called early stage cervical cancer (FIGO IA2, IB and IIA) is mostly treated with a radical hysterectomy in combination with pelvic lymphadenectomy. Adjuvant (chemo-) radiation can be administered in case of positive lymph nodes, extra-cervical growth and unfavourable tumour characteristics. [32-34] The prognosis of cervical cancer after a radical hysterectomy with pelvic lymphadenectomy depends on the aspects mentioned above. 5-Year survival rates vary between 88 and 97 %. [35, 36] A way to improve quality of life after treatment is to reduce therapy induced morbidity. Up to 25 % of the patients treated with radical hysterectomy have bladder, bowel or sexual dysfunction problems. [37-39] It is thought that part of this morbidity is due to peroperative damaging of the autonomic nerves in the pelvis. Maas et al. showed that the conventional radical hysterectomy (PIVER III) damages the hypogastric and splanchnic nerves by dissecting the sacro-uterine ligaments and the parametrium underneath the level of the deep uterine vein respectively. [40] These autonomic nerves innervate the bladder and bowel and regulate the lubrication-swelling response of the female genitals during sexual arousal. [41] Since 1960 general acceptance of the nerve-sparing radical hysterectomy as a standard of care for the surgical treatment of early stage cervical cancer is rising. However, the technique remains subject of discussion in the world of gynaecologic oncology. Proponents state the technique

is safe, it improves quality of life after surgery and survival outcomes are not impaired. Opponents say the literature is too heterogeneous to draw these conclusions.
In The Netherlands, nerve sparing surgery was initiated at the department of gynaecologic oncology of the Leiden University Medical Center (LUMC) and the technique has evolved over time. [40-45] First there was the Leiden Nerve Sparing Radical Hysterectomy (LNSRH) which was later adapted to the Swift procedure, resembling the total mesometrial resection (TMMR) as developed and advocated by Höckel et al.[46]. The Swift procedure is also a nerve sparing technique for radical hysterectomy, being more radical than the LNSRH but sparing the same nerves. To evaluate the safety of nerve sparing techniques for early stage cervical cancer, a systematic review and meta-analysis has been performed (**chapter 4**). It reviews studies comparing nerve sparing radical hysterectomies with non-nerve sparing radical hysterectomies for early stage cervical cancer. The review focuses on survival and quality of life. It was also performed to compare it with the findings of the observational study performed at the LUMC (**chapter 5**). This single centre observational study evaluates the results of 3 types of radical hysterectomies, namely the conventional radical hysterectomy (Wertheim Meigs, PIVER III), the Leiden Nerve Sparing Radical Hysterectomy and the Swift procedure. It clarifies what effect the introduction of nerve sparing techniques in radical hysterectomies has on the oncological outcomes.
Fertility preservation is an important issue in tailoring therapy in patients with cervical cancer as well. At the LUMC, a radical abdominal trachelectomy (RAT) with or without pre-operative chemotherapy has been performed in women with stage IA2-IB cervical cancer. Parallel to the introduction of the nerve-sparing technique for the radical hysterectomy, the principle of preservation of the autonomic nerves has been transferred to the RAT, ensuring the same fertility maintaining surgery, but also preserving the hypogastric and splanchnic nerves: nerve sparing radical abdominal trachelectomy (NSRAT). **Chapter 5** describes a comparative study evaluating oncological outcomes of the NSRAT versus the NSRH, concurrently describing the pregnancy outcomes of the NSRAT cohort (**chapter 6**). **Chapter 7** holds the general discussion and recommendations on fertility sparing treatment of endometrial cancer and nerve sparing surgery and fertility-sparing surgery for cervical cancer.

REFERENCES

1. Schain WS. Patients' rights in decision making: the case for personalism versus paternalism in health care. Cancer. 1980;46(4 Suppl):1035-41.
2. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014;64(1):9-29.
3. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55(2):74-108.
4. Lee NK, Cheung MK, Shin JY, Husain A, Teng NN, Berek JS, et al. Prognostic factors for uterine cancer in reproductive-aged women. Obstet Gynecol. 2007;109(3):655-62.
5. Treffers. Obstetrie en gynaecologie. 2e herziene druk ed1995. p. 672.
6. Schouten LJ, Goldbohm RA, van den Brandt PA. Anthropometry, physical activity, and endometrial cancer risk: results from the Netherlands cohort study. Int J Gynecol Cancer. 2006;16 Suppl 2:492.
7. Amant F, Moerman P, Neven P, Timmerman D, Van LE, Vergote I. Endometrial cancer. Lancet. 2005;366(9484):491-505.
8. Renehan AG, Soerjomataram I, Leitzmann MF. Interpreting the epidemiological evidence linking obesity and cancer: A framework for population-attributable risk estimations in Europe. Eur J Cancer. 2010;46(14):2581-92.
9. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol. 1983;15(1):10-7.
10. Cancer Genome Atlas Research N, Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497(7447):67-73.
11. Church DN, Stelloo E, Nout RA, Valtcheva N, Depreeuw J, ter Haar N, et al. Prognostic significance of POLE proofreading mutations in endometrial cancer. Journal of the National Cancer Institute. 2015;107(1):402.
12. Colombo N, Creutzberg C, Amant F, Bosse T, Gonzalez-Martin A, Ledermann J, et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: Diagnosis, Treatment and Follow-up. Int J Gynecol Cancer. 2016;26(1):2-30.
13. Ramirez PT, Frumovitz M, Bodurka DC, Sun CC, Levenback C. Hormonal therapy for the management of grade 1 endometrial adenocarcinoma: a literature review. Gynecol Oncol. 2004;95(1):133-8.
14. Niwa K, Tagami K, Lian Z, Onogi K, Mori H, Tamaya T. Outcome of fertility-preserving treatment in young women with endometrial carcinomas. BJOG. 2005;112(3):317-20.

15. Gallos ID, Yap J, Rajkhowa M, Luesley DM, Coomarasamy A, Gupta JK. Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis. Am J Obstet Gynecol. 2012;207(4):266-12.

16. Yamazawa K, Hirai M, Fujito A, Nishi H, Terauchi F, Ishikura H, et al. Fertility-preserving treatment with progestin, and pathological criteria to predict responses, in young women with endometrial cancer. Hum Reprod. 2007;22(7):1953-8.

17. Simpson AN, Feigenberg T, Clarke BA, Gien LT, Ismiil N, Laframboise S, et al. Fertility sparing treatment of complex atypical hyperplasia and low-grade endometrial cancer using oral progestin. Gynecol Oncol. 2014;133(2):229-33.

18. Gotlieb WH, Beiner ME, Shalmon B, Korach Y, Segal Y, Zmira N, et al. Outcome of fertility-sparing treatment with progestins in young patients with endometrial cancer. Obstet Gynecol. 2003;102(4):718-25.

19. Ota T, Yoshida M, Kimura M, Kinoshita K. Clinicopathologic study of uterine endometrial carcinoma in young women aged 40 years and younger. Int J Gynecol Cancer. 2005;15(4):657-62.

20. Ushijima K, Yahata H, Yoshikawa H, Konishi I, Yasugi T, Saito T, et al. Multicenter phase II study of fertility-sparing treatment with medroxyprogesterone acetate for endometrial carcinoma and atypical hyperplasia in young women. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2007;25(19):2798-803.

21. van Gent MDJM, Kagie MJ, Trimbos JB. No surgery for Low-Grade Endometrial Cancer in Women with a Desire to Preserve Fertility. Journal of gynecologic Surgery. 2012;28(6):389-98.

22. Kauppila A. Oestrogen and progestin receptors as prognostic indicators in endometrial cancer. A review of the literature. Acta Oncol. 1989;28(4):561-6.

23. Thigpen JT, Brady MF, Alvarez RD, Adelson MD, Homesley HD, Manetta A, et al. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1999;17(6):1736-44.

24. Wang Y, van der Zee M, Fodde R, Blok LJ. Wnt/Beta-catenin and sex hormone signaling in endometrial homeostasis and cancer. Oncotarget. 2010;1(7):674-84.

25. Wang Y, Hanifi-Moghaddam P, Hanekamp EE, Kloosterboer HJ, Franken P, Veldscholte J, et al. Progesterone inhibition of Wnt/beta-catenin signaling in normal endometrium and endometrial cancer. Clin Cancer Res. 2009;15(18):5784-93.

26. Scholten AN, Creutzberg CL, van den Broek LJ, Noordijk EM, Smit VT. Nuclear beta-catenin is a molecular feature of type I endometrial carcinoma. J Pathol. 2003;201(3):460-5.

27. Saegusa M, Okayasu I. Frequent nuclear beta-catenin accumulation and associated mutations in endometrioid-type endometrial and ovarian carcinomas with squamous differentiation. J Pathol. 2001;194(1):59-67.

28. Mutter GL, Lin MC, Fitzgerald JT, Kum JB, Baak JP, Lees JA, et al. Altered PTEN expression as a diagnostic marker for the earliest endometrial precancers. J Natl Cancer Inst. 2000;92(11):924-30.

29. Lee II, Kim JJ. Influence of AKT on Progesterone Action in Endometrial Diseases. Biol Reprod. 2014;91(3):63.

30. Spaans VM, Trietsch MD, Crobach S, Stelloo E, Kremer D, Osse EM, et al. Designing a high-throughput somatic mutation profiling panel specifically for gynaecological cancers. PLoS One. 2014;9(3):e93451.

31. 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.

32. Peters WA, 3rd, Liu PY, Barrett RJ, 2nd, Stock RJ, Monk BJ, Berek JS, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2000;18(8):1606-13.

33. Rotman M, Sedlis A, Piedmonte MR, Bundy B, Lentz SS, Muderspach LI, et al. A phase III randomized trial of postoperative pelvic irradiation in Stage IB cervical carcinoma with poor prognostic features: follow-up of a gynecologic oncology group study. Int J Radiat Oncol Biol Phys. 2006;65(1):169-76.

34. 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.

35. Rob L, Halaska M, Robova H. Nerve-sparing and individually tailored surgery for cervical cancer. Lancet Oncol.11(3):292-301.

36. 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.

37. 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.

38. Bergmark K, Avall-Lundqvist E, Dickman PW, Henningsohn L, Steineck G. Vaginal changes and sexuality in women with a history of cervical cancer. The New England journal of medicine. 1999;340(18):1383-9.

39. 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.

40. 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.

41. 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.

42. Maas CP, Kenter GG, Trimbos JB, Deruiter MC. Anatomical basis for nerve-sparing radical hysterectomy: immunohistochemical study of the pelvic autonomic nerves. Acta Obstet Gynecol Scand. 2005;84(9):868-74.

43. de Kroon CD, Gaarenstroom KN, van Poelgeest MI, Peters AA, Trimbos JB. Nerve sparing in radical surgery for early-stage cervical cancer: yes we should! Int J Gynecol Cancer. 2010;20(11 Suppl 2):S39-S41.

44. Trimbos JB, Maas CP, Deruiter MC, Kenter GG. [Nerve sparing radical hysterectomy in the case of cervical cancer]. Ned Tijdschr Geneeskd. 2003;147(28):1344-7.

45. 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.

46. 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.

CHAPTER 2

No Surgery for Low-Grade Endometrial Cancer in Women with a desire to Preserve Fertility

Mignon van Gent
Marjolein Kagie
Baptist Trimbos

Journal of gynecological surgery 2012 Oct; volume 28 (issue 6): 398-398

CHAPTER 2

No Surgery for Low-Grade Endometrial Cancer in Women with a desire to Preserve Fertility

2.1 ABSTRACT

Objective

The treatment of endometrial cancer is total hysterectomy including bilateral salpingo-oophorectomy. Standard treatment takes away the possibility for fertile women to conceive. This review studies the effectiveness and safety of conservative/hormonal therapy for stage I grade 1 and 2 endometrial cancer.

Materials and Methods

We searched Pubmed for publications from January 1968 to November 2008. Publications included retrospective studies, case reports, multicenter Phase II study, and literature reviews describing conservative treatment for women with type I endometrial cancer.

Results

Fifty-five studies described 245 patients with stage I endometrial cancer. The median age of the patients was 30.3 years. Two hundred and thirty-two patients had grade 1 disease, and 16 had grade 2 or more. Grading was unknown for five patients. Patients were treated with different progestatives. Three out of 245 patients did not receive any treatment for their disease. The mean number of months of treatment was 7 months. One hundred and ninety-three of the 245 patients responded initially to therapy. Progesterone receptor status was known in 86 of 245 patients. Seventy-seven patients (90%) were progesterone receptor positive. The mean follow-up was 47 months. No patient died of endometrial cancer. One hundred and twenty-seven pregnancies and 109 living births were described.

Conclusions

Conservative treatment of endometrial cancer may be considered in a well-selected group of patients: stage I, grade 1 and 2 endometrial cancer in women who want to preserve their fertility. The patients have to be treated according to a well-defined, preset protocol. The process should be well documented to improve the safety and effectiveness of the conservative treatment.

2.2 INTRODUCTION

The standard treatment for patients with endometrial cancer is total hysterectomy including bilateral salpingo-oophorectomy. However, this standard approach takes away the possibility for fertile women to conceive. We undertook this review to determine the effectiveness and safety of conservative/hormonal therapy for stage I grade 1 and 2 endometrial cancer.

2.3 OBJECTIVES

Conservative (hormonal) treatment of early stage endometrial cancer has been advocated as an alternative method of treatment in exceptional cases for young women who wish to preserve their fertility. The objectives of this review are (1) to determine the effectiveness and safety of conservative therapy for stage I grade 1 and 2 endometrial cancer, and (2) to formulate a protocol to save fertility in young patients with endometrial cancer.

2.4 MATERIALS AND METHODS

We searched Pubmed for publications from January 1968 to November 2008. Publications included retrospective studies, case reports, multicenter Phase II study, and literature reviews describing conservative treatment for women with type I endometrial cancer. Because of a lack of prospective studies, we collected all data available on the subject. Two investigators abstracted the data. Studies that were not available online were hand searched.

2.5 RESULTS

Literature on conservative treatment of endometrial cancer in women who want to preserve fertility is inconclusive with regard to the best treatment modality. There are many case reports, retrospective observational studies, some prospective studies, and many reviews. Jadoul [1] reported 38 patients being treated with progestagens. Rackow [2] studied 90 patients. Gotlieb [3] , Ramirez [4] and Boing 2006 [5] have written the most complete and clear reviews. Chiva has used most of this information and completed it with the last available data and described 133 patients. [6] We offer the most recent and complete review of the available literature. Receptor status and methods of therapy were previously not described as clearly as they are in this review. Table 1 shows all case reports and prospective observational studies published from 1986 to the end of 2008. [1, 3, 6-58]

Number of patients

We found 55 studies describing conservative treatment of endometrial cancer. We checked for double registration, and 245 patients remained. The median age of the patients is 30.3 years.

Grading

Two hundred and thirty-two patients with stage I endometrial cancer had grade 1 disease, and 16 patients had grade 2 or more. Grading was unknown for five patients.

Treatment

Patients were treated with medroxyprogesterone acetate (MPA), megestrol acetate (MA), hydroxyprogesterone caproate (OH-prog), norethisterone acetate (NA), dihydrosterone (DH), and norethindrone (NE). Three of 245 patients did not receive any treatment for their disease. Most patients were treated with MPA varying from 5 to 800mg per day. The duration of the treatment varied between 1 and 37 months. The mean duration was 7 months. One hundred and ninety-three out of 245 patients responded to therapy. Histology results for 143 patients were grade 1, five were grade 2, one was grade 3, and 21 were either grade 1 or 2, not specified by the authors.

Receptor status

Progesterone receptor status was only known in 86 of 245 patients. Seventy-seven (90%) were progesterone receptor positive. Nine patients were receptor negative. Receptor status for all other cases was unknown.

Follow-up

The mean follow-up was 47 months. One hundred and twenty-seven pregnancies and 109 living births were described. Six studies did not mention pregnancy rates, and the rest of the studies were incomplete. It was not stated if all patients wished to conceive. Not all of the studies report all pregnancies (including miscarriages). Three patients died after being treated conservatively: two died of ovarian cancer and one died of liver cirrhosis. A description of the mortality is provided.

Table 1. Studies on Conservative Treatment of Endometrial Cancer From 1986 Till 2008.

Author Year	N	Grade	Treatment/day	Duration treatment ‡	Response
Kempson 1968[6]	3	2-3	progestagen (2)	>1	1/2
		1-2	none (1)		
O'neill 1970[7]	1	1	NE 2mg/mo	2.5	1/1
			Mestranol 0.1 mg		
Eddy 1978[8]	1	1	OH-prog 1000 mg	2	1/1
			3/wk, MPA cycle		
Greenblatt 1982[9]	1	uk	uk	uk	0/1
Bokhman 1985[10]	19	1 (15)	OH-prog 25-83 gram	3.6	12/19
		2 (4)	+ chemo		
Thornton 1985[11]	1	uk	NA 20mg 21/28 days	13	1/1
			+NA 5mg	6	
Fahri 1986[12]	4	1	Progestogen	uk	3/4
Muechler 1986[13]	1	1	MPA	15	1/1
Lee 1989[14]	2	uk	uk	uk	1/2
Paulson 1990[15]	1	1	MA 160mg	6	1/1
Kimmig 1995[16]	1	1	MPA 200mg	2	1/1
Lai 1994[17]	1	uk	uk	6	1/1
Kim 1997[18]	7	1	MA 160mg	3	4/7
Kung 1997[19]	1	1	Tamoxifen 30 mg	6	1/1
			+MA 160 mg		
Randall 1997[20]	12	1	MA 40-160mg	9	9/12
			+MPA or Tamoxifen		
			or Platinum		
			bromocriptine10 mg		
Salha 1997[21]	1	1	MPA 60 mg	9	1/1
Zanetta 1997[22]	1	1	MPA 5 mg	3	1/1
Sardi 1998[23]	3	1	MPA 200-500 mg	4	3/4 (grade 1)
	1	2			
Schammel 1998[24]	3	uk	none (1)	6	2/3
			progesterone (2)		
Zuckerman 1998[25]	1	2	MPA 600 mg	5,5	1/1
Kowalczyk 1999[26]	1	1	uk	6	1/1
Vinker 1999[27]	1	1	MPA 400 mg/day	2.5	0/1
Shibahara 1999[28]	1	1	None	uk	1/1

Recurrence	Mean Age	Receptor status	Follow up mean (mo)	Gravity/ parity
none	27,3	uk	24	G2 P uk
none	17	uk	19	G1 P1
none	21	uk	50	G1 P1
none	31	uk	uk	uk
uk	28	uk	36-108	uk
none	23	uk	21	uk
none	17,5	uk	45 3 -120 1 LTFU	G2 P2
none	31	uk	54	G2/P1/A1
uk	19	uk	30	G1/P1
none	35	uk	15	G2/P1/A1
none	28	uk	21,5	G1/P1+2
uk	31	uk	30	G1/P1
2/4	32,4	uk	12,9	G uk/P0
none	22	+	uk	uk
1/9	30,5	uk	46	G9 P7 A2
1/1	32,0	uk	uk	G0
none	30	uk	52	G2/P2
none	31,8	uk	41	G3 P3
none	35	uk	39	G4 P4
none	26	uk	18	G3/P1+1
none	28	uk	18	G1
none	33	uk	48	G0
none	32	+	11	G1

Table 1. Continued

Author Year	N	Grade	Treatment/day	Duration treatment ‡	Response
Jobo 1999[29]	2	1	MPA 600 mg	6,5	2/2
Mitsushita 2000[30]	1	1	MPA 400 mg, 4mo MPA 600 mg, 6mo	12	1/1
Ogawa 2000[31]	1	1	MPA 400 mg	3	1/1
Kaku 2001[32]	12	1 (10) 2 (2)	MPA 200-800 mg	2-14	9/12 8 CR 1 PR
Pinto 2001[33]	1	1	MA 40 mg	uk	1/1
Imai 2001[34]	12 1 2	1 2 a	MPA 400-800 mg	>3	8/15
Duska 2001[35]	12	1	Progestin	uk	10/12
Wang 2002[36]	9	1	MA 30 mg tamoxifen gnRHa	>6	8/9
Lowe 2003[37]	2	1	MA 80 mg	3 6	2/2
Gotlieb 2003[3]	13	1 (11) 2 (2)	MA 160mg (8) MPA 200-600 mg OH-prog2-3gr/wk NA 5 mg	12.7 (3-37 mo)	13/13
Jadoul 2003 [1]	5	1	endometrium resection + GnRH agonist	3-6	5/5 3 CR 2 PR
Burnett 2004[38]	2	1	MPA 160 mg + arimidex 1 mg	8-….	2/2
Nakao 2004[39]	2	1	MPA 400 mg	7-9	2/2
Yarali 2004[40]	1	1	MA 160 mg MPA 10 mg	6 6	1/1
Niwa 2005[41]	12	1	MPA 400-600 mg	6-10	12/12
Ota 2005[42]	12	1	MPA 600 mg	uk	5 /12 CR
Ferrandina 2005[43]	1	1	DH 20 mg CD15-25	2	1/1

Recurrence	Mean Age	Receptor status	Follow up mean (mo)	Gravity/ parity
none	34	+	41,5	G2/P2+1
1/1	28	+	uk	G1 P1
none	31	uk	>9	G1/P1
2/9	31	uk	31,5 10-133	G2 P1
none	29	uk	6	G1/P1+2
3/8	30,2		59	G2 P2+1
3/12	31	uk	uk	G uk/P5
4/8	32	7 + 1 - 1 weak +	69	G6 P3+2 EUG 2/A1
none	32,5	uk	44	G2 P3+2
5/13	31	uk	82 6-258	G12 P9 A1 pregnant 2
uk	33,4	uk	6-72	G4 P3+1 A1
none	29,0	uk	19	uk
none	36	+	32,5	G2/P2
none	32	uk	uk	G1 P1
8/9 (long term follow up)	28,5	+	18	G7 P5+1/A1 IUFD 22 wks
1/12	30,9	11 +	52,7	G5/P3/Apla 1 p.i. 22 wk
1/1	30	+ (prim tumour) - (recurrence)	uk	G1 P1

Table 1. Continued

Author Year	N	Grade	Treatment/day	Duration treatment ‡	Response
Huang 2005[44]	1	1	MA 160 mg	1	0/1
			>1 mo tamoxifen	4	
			no response		
Mazzon 2005[45]	1	1	MA 160 mg	10	1/1
Yang 2005[46]	6	1	MA 160 mg	uk	4/6
Chang 2006[47]	1	1	MPA 500 mg	6	1/1
			twice/wk		
Park 2006[48]	1	1	MA	2	1/1
			600 mg		
			400 mg	1	
			320 mg	3	
Sparac 2006[49]	1	1	MPA 400 mg	3	1/1
Yahata 2006[50]	8	1	MPA 1800 mg	22	7/8
Gurgan 2007[51]	1	1	uk	uk	0/1
Minaguchi 2007[52]	19	1	MPA 400-600 mg	2-12	15/19
Shamshirsaz 2007[53]	1	1	MA 160 mg	6	1/1
			MPA 20 mg		
			14days/mo	6	
			MPA 30 mg		
			14/days/mo	continued	
Ushijima 2007[54]	22	1	MPA 600 mg	6.5	12/22 CR
			+ 81 mg aspirin		7/22 PR
Yamazawa 2007[55]	9	1	MPA 400 mg	>6	9/9
					7 CR
					2 PR
Hurst 2008[56]	1	1	MA 160 mg	6	1/1
Takahashi 2008[57]	1	1	MPA 600 mg+E37	4.5	1/1
Wu 2008[58]	1	1	MA 160 mg	2 x 6 mo	1/1

N, number of of patients; ‡ Month; MPA, medroxyprogesterone acetate; MA, megestrol acetate; OH-prog. Hydroxyprogesterone caproate; NA, norethisterone acetate; DH, dihydrosterone; NE, norethindrone; a, adenocanthoma; LTFU, lost to follow up.

Recurrence	Mean Age	Receptor status	Follow up mean (mo)	Gravity/ parity
none	36	-	uk	G0
none	31,0	+	33	G1/P1
2/4	33	4 +	48,8	G4
		2 -		P2
none	35	uk	12	uk
none	36	+	24	G1
				P1
none	30	uk	uk	G1/P1
7/7	31,9	7	76,5	G7
		-1		P2
none	39	uk	uk	G0
5/15	30,6	17 +	40,7	G10
		1 -	2-109	P 6+1
		1 doubt		A4
1/1	21	uk	9	G0
7/19	31,7	uk	47,9	G12
				P7+2/A5
2/9	36	7 + (CR)	39	G4
		2 - (PR)		P3
				A1
1/1	31	uk	uk	G0
1/1	39	+	uk	G0
1/1	35	+	24	G0

Recurrence

Fifty-nine out of 193 patients had recurrent disease after first responding (partially or completely) to the treatment. Recurrence was noted by hysteroscopy and biopsy or mini-curettage. Of all 59 patients with recurrences after complete or partial response, 45 hysterectomies with bilateral salpingo-oophorectomy were performed. Eleven patients were retreated with progestatives and responded completely to treatment. One study describing three patients did not give any further information about their pathology results. Of the 45 patients who underwent hysterectomy, no evidence of disease was seen in three patients. Definitive pathology results were not described for 11 patients with recurrence. One patient had hyperplasia with atypical cells. Thirty-three patients were diagnosed with endometrial cancer, as detailed in Table 2.

Table 2. Patients with endometrial cancer at recurrence

			Grade			
			1	**2**	**3**	**unknown**
Stage	I	-	-	-	-	3
		a	5	-	-	2
		b	7	-	-	-
		c	3	-	-	-
	II	a	-	1	-	-
		b	-	-	-	-
		c	-	-	-	-
	III	a	7	-	-	2
		b	-	-	-	-
		c	-	1	-	1
	IV		-	1	-	-

Details

Mortality

The first death was described by Ota. [42] A patient died after not responding to conservative treatment, choosing abdominal hysterectomy without bilateral salpingo-oophorectomy. She was treated with 600mg MPA. Twenty months after initial surgery, a site of recurrence was found in one of the ovaries. Surgery was performed where bilateral salpingo-oophorectomy, pelvic lymphadenectomy, and omentectomy was performed. She was treated with chemotherapy. The patient died 71 months after primary treatment with MPA. The second death is discussed by Ushijima. [59] After 26 weeks, the patient was in complete remission. She was treated with 600mg MPA and 81mg aspirin a day. She had three more treatments with MPA for repeated recurrences. Two years after initial MPA treatment, she got peritoneal carcinomatosis and grade 2 endometrioid adenocar-

cinoma in her ovary. She died 4 months after surgery. It is speculated that it must have been a secondary primary malignancy (endometrial cancer and ovarian cancer) because no signs of endometrial malignancy were found at hysteroscopy 3 months before development of peritoneal lesions. The third patient died of liver cirrhosis not expected to be due to this treatment, and one patient had progressive disease but showed no evidence of disease after hysterectomy and bilateral salpingo-oophorectomy. [60]

Receptor status

Only 18 studies described the receptorstatus; 37 did not. In the prospective studies of Yang [46], Minaguchi [60] and Yamazawa [61] the receptor status was known. Yang treated six patients with 160mg MA per day. Four patients showed response, but two had recurrent disease. The two non-responders and the two patients with recurrent disease underwent a hysterectomy and bilateral salpingo-oophorectomy. Histological findings were twice stage IIa, twice stage Ic, and once grade 2 endometrial cancer. All four specimens showed ovarian cancer. Two samples were proven to be a second primary tumor, but the other two were inconclusive. The two responders were receptor positive, and two other patients were receptor positive: one had recurrence and one failed any response. The two patients with a negative receptor status were a non-responder and a patient with recurrence. Minaguchi treated 19 patients with 400 to 600mg MPA per day for 2-12 months. [60] Seventeen patients were receptor progesterone receptor positive, one negative and one inconclusive. Fifteen patients responded, and five had recurrent disease, all of whom were receptor positive. Yamazawa included nine patients, all grade 1, with 400mg MPA, for at least 6 months. [61] All patients showed response—seven complete responses and two partial responses. Progesterone receptor was positive in the complete response group and negative in the specimen of the two patients with partial response. One patient underwent an additional 9-month treatment with chemotherapy after not showing remission after 6 months. Two patients with recurrent disease were treated surgically and both showed grade 1 ovarian cancer.

Side effects therapy

Ushijima et al. treated their patients with 81mg aspirin in addition to 600mg MPA per day to avoid thrombo-emobilic complications that can be theoretically expected. [59] No study proves a significant higher chance of thrombo-embolic or cardiovascular problems with varying amounts of progesterone. Only two authors described a side effect of progesterone. Park described a weight gain of 15 kg during treatment with 600mg MA (2 months), 400mg MA (1 month), and 320mg MA (3 months). [48] Complaints of nausea made one patient choose to stop the treatment in Randall's study. [20] This patient was not treated maximally with medication to diminish the emesis.

2.6 DISCUSSION

Two hundred and forty-five patients were treated conservatively with progestagens. Mostly they were treated with MPA. The recurrence rate was high: 31% of all 193 patients that (partially) responded to the treatment. However, the mortality rate was low—3 out of 245 patients—and no patient died of endometrial cancer. We conclude that there is still insufficient evidence to compare the conservative treatment of endometrial cancer with the gold standard. At the same time, there is an increasing demand for conservative treatment of many cancers. Patients demand a better quality of life by keeping the possibility of being able to conceive. The aim of the study was to provide a protocol for gynecologists to treat their patients uniformly and to clarify the conservative treatment of endometrial cancer. In addition, data were collected prospectively to improve the effectiveness and safety of this method further.

The Safety of Non-invasive Staging

Surgical–pathological staging is the gold standard. FIGO staging for endometrial cancer is done by observing myometrial invasion of the endometrium, intra-peritoneal growth, and adnexal metastasis. In our protocol, surgical staging cannot be done, so clinical judgment for staging has to be done as accurately as possible. Tran investigated that more than 50% myometrial invasion is seen in 24% of young patients versus 49% of older patients. [62] Approximately 7% to 10% of the patients with grade 1 endometrial cancer have deep myometrial invasion. [63, 64] The chance of myometrial invasion is small for patients with grade 1 endometrial cancer. During the development of our protocol, we considered the fact that a stage Ic has a less favorable prognosis than a stage Ia, and the diagnostic tools to judge the myometrial invasion are limited. The most accurate way of imaging the myometrial invasion is by (contrast-enhanced) magnetic resonance imaging. The accuracy varies between 68% and 82%. [65] Contrast MRI is the only possibility to approach the accuracy of surgical staging. However, because the accuracy varies between 68% and 82% and there is only a small chance of deep myometrial invasion in low-grade tumors of 7% to 19%, we decided to include all assumed stage I tumors and not leave out stage Ic. [62, 63, 64] The essence of performing a pre-treatment laparoscopy can be discussed. Twenty-two studies described recurrences, and 29 stated that no recurrences were noticed at follow-up. Four studies did not mention recurrences. In the first group, only one study described performing a laparoscopy. In the second group without recurrences, laparoscopy had been performed in 10 out of 29 studies, and one study described pre-treatment staging by laparotomy. No patients were excluded from treatment because of laparoscopic findings. We could suggest laparoscopy has been performed more often during fertility analyses before discovering endometrial cancer. However, it has not been recorded. In conclusion, from this review, we cannot conclude

whether a laparoscopy is necessary. However, if lesions are suspected by vaginal ultrasound or MRI, laparoscopy is mandatory.

Grading

Endometrioid adenocarcinoma is the most common histological type of endometrial cancer in young patients. Other histological types are papillary serous and clear cell carcinoma. These are high-grade tumors and are not included in our protocol. Transitional cell, squamous cell, mucinous, and small cell cancers account for fewer than 2% of all endometrial cancers and are also excluded.

Receptor status

Positive ER and PR receptor status is of great importance to the response to progesterone. Type I tumors are typically low-grade endometrioid carcinomas, with positive estrogen (ER) and progesterone receptors (PR) in 92% of cases. A dose–response study of the Gynecologic Oncology Group showed a response rate of 37% in PR receptor positive patients and 8% in PR receptor negative patients. Likewise, ER receptor positive patients had a 26% response rate and only 7% for ER receptor negative patients. [66]

Ovarian cancer

Ulbright writes that simultaneous presence of an ovarian tumor with the same histology is present in 8% of endometrial cancers. [67] The risk of synchronous primary ovarian cancer is approximately 5% for intrauterine disease. [68] The ovarian tumour should be considered as metastatic when it is small, bilateral, or multinodular with surface implants and angiolymphatic invasion in the ovarian cortex. [67]

Hereditary predisposition

Endometrial cancer originates in high endogenous or exogenous estrogen levels or genetic predisposition like type II Lynch syndrome. Type I is estrogen dependent, hormone sensitive, and low stage with a very good prognosis, and type II, the minority, is associated with endometrial atrophy, being high grade, and having a high rate of recurrence. [69] Lynch II syndrome is an autosomal-dominant inherited cancer susceptibility mainly associated with colorectal cancer or endometrial cancer. [70] Patients have a risk of approximately 20% of developing endometrial cancer before the age of 50. [69] The lifetime risk of getting ovarian cancer for this group is more than 12%. [71] Women diagnosed with endometrial cancer at a fertile age should be referred to a genetic counselor.

Biological factors

Exposure to either endogenous or exogenous excess of estrogens instigates an increased risk of developing endometrial carcinoma. Among the risk factors are obesity,

early menarche, late menopause, no pregnancies, and genetic disorders. The literature suggests that endometrial carcinoma in young women is less aggressive and biologically different from that of older women. [4, 5, 7] The fact that obese women have a higher chance of a miscarriage is of secondary value and can be considered for inclusion in the counselling but will not be part of the standard work up.

Therapy

Most studies used MPA as their treatment. Eighteen of these studies used a low dose of ≤ 200 mg, 11 studies about 400 mg, and 7 studies a high dose of 600mg or more. A study comparing the effects of MPA, NE, and norethynodrel on the endometrium showed a more intense response to progestin than to NE and norethynodrel. [72] MPA is free of estrogen action. Studies in recurrent endometrial cancer have shown 200mg of MPA to be superior to the higher dose of 1,000mg per day. It is less toxic and equally effective. [73] There is a 5–17% chance of thrombophlebitis while using MPA. [74, 75] A higher dose leads to an increased chance of adverse effects. Considering these arguments, we have proposed the use of 200mg per day for our protocol.

Fertility

Before starting the conservative treatment, normal work up for endometrial cancer should be performed, including contrast enhanced MRI. Most patients start conservative treatment because of a wish for offspring. For this reason, fertility analysis of the patient and her partner (if applicable) should be performed before starting the protocol.

Outcome

Three out of 245 patients died during the mean follow-up of 47 months: two died of ovarian cancer and one died of liver cirrhosis. No patient died of endometrial cancer. The low mortality rate might be because when patients are treated conservatively, the follow-up is strict and the possibility of switching to surgery is always available. Most patients showing recurrent disease were treated surgically. While looking at the results, the influence of publication bias should always be considered. We are supported in this idea, while looking at the data we can see a recurrence rate of 31% compared to 47% is the article of Ushijima and 40.9% in a more recent study by Hahn. [8, 75]

2.7 AUTHORS' CONCLUSIONS

From the results of our literature review, we can conclude that for a selected group of patients, following clear guidelines and protocols, conservative treatment with progesterone is a save method to treat endometrial cancer. Using the information we extracted from the literature, we propose the following protocol. The inclusion criteria

are patients with stage I grade 1 and 2 endometrial cancer, under the age of 40 years, progesterone receptor positive, wishing for offspring, and whose informed consent has been obtained for the treatment advice of total hysterectomy including bilateral salpingo-oophorectomy. The exclusion criteria are patients with recurrent endometrial cancer, endometrial cancer more than stage one and/or grade two, and high-risk cell types. Patients are treated with 200mg MPA per day for at least 6 months and no more than 12 months. The minimum duration of treatment is a 3-month-long treatment course and a 3-month-long consolidation course. Three monthly check-ups with hysteroscopy and endometrial sampling are performed to investigate the effectiveness. If a suspicious lesion is seen, it is resected. In cases of irregular bleeding, a hysteroscopy will be performed directly. After two negative endometrial samplings, conception may be pursued. Follow-up starts after two negative endometrial samplings. During a period of 5 years, a hysteroscopy with endometrial sampling will be performed every 6 months. After this period, check-ups are done yearly. Factors that must be reported in future case reports are: receptor status, drug use, body mass index, attempts for pregnancies, fertility problems, follow-up, and histology results. Treatment is stopped if (1) histology results show endometrial cancer after three cycles of 3 months of therapy; (2) one of the samplings shows endometrial cancer grade 3; or (3) imaging shows extra-uterine disease. If a patient is excluded from the protocol, she receives a total hysterectomy including bilateral salpingo-oophorectomy. The protocol is shown in Figure 1.

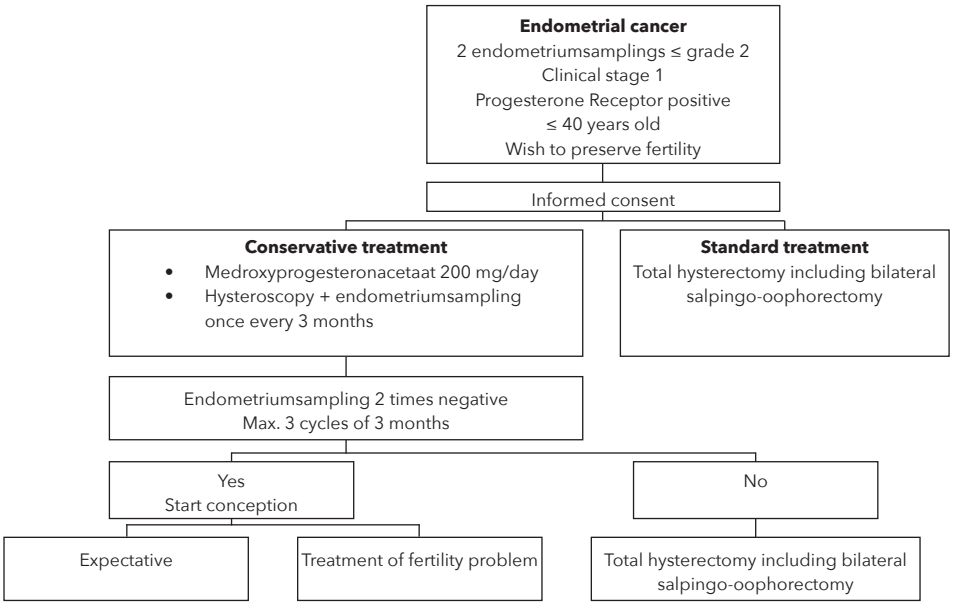


Figure 1. Flow chart showing conservative treatment of endometrial cancer

2.8 REFERENCES

1. Jadoul P, Donnez J. Conservative treatment may be beneficial for young women with atypical endometrial hyperplasia or endometrial adenocarcinoma. Fertil Steril. 2003;80(6):1315-24.
2. Rackow BW, Arici A. Endometrial cancer and fertility. Curr Opin Obstet Gynecol. 2006;18(3):245-52.
3. Gotlieb WH, Beiner ME, Shalmon B, Korach Y, Segal Y, Zmira N, et al. Outcome of fertility-sparing treatment with progestins in young patients with endometrial cancer. Obstet Gynecol. 2003;102(4):718-25.
4. Ramirez PT, Frumovitz M, Bodurka DC, Sun CC, Levenback C. Hormonal therapy for the management of grade 1 endometrial adenocarcinoma: a literature review. Gynecologic oncology. 2004;95(1):133-8.
5. Boing C, Kimmig R. Fertility-preserving treatment in young women with endometrial cancer. Gynakologisch-geburtshilfliche Rundschau. 2006;46(1-2):25-33.
6. Kempson RL, Pokorny GE. Adenocarcinoma of the endometrium in women aged forty and younger. Cancer. 1968;21(4):650-62.
7. O'Neill RT. Pregnancy following hormonal therapy for adenocarcinoma of the endometrium. Am J Obstet Gynecol. 1970;108(2):318-21.
8. Eddy WA. Endometrial carcinoma in Stein-Leventhal syndrome treated with hydroxyprogesterone caproate. Am J Obstet Gynecol. 1978;131(5):581-2.
9. Greenblatt RB, Gambrell RD, Jr., Stoddard LD. The protective role of progesterone in the prevention of endometrial cancer. Pathology, research and practice. 1982;174(3):297-318.
10. Bokhman JV, Chepick OF, Volkova AT, Vishnevsky AS. Can primary endometrial carcinoma stage I be cured without surgery and radiation therapy? Gynecol Oncol. 1985;20(2):139-55.
11. Thornton JG, Brown LA, Wells M, Scott JS. Primary treatment of endometrial cancer with progestagen alone. Lancet. 1985;2(8448):207-8.
12. Farhi DC, Nosanchuk J, Silverberg SG. Endometrial adenocarcinoma in women under 25 years of age. Obstet Gynecol. 1986;68(6):741-5.
13. Muechler EK, Bonfiglio T, Choate J, Huang KE. Pregnancy induced with menotropins in a woman with polycystic ovaries, endometrial hyperplasia, and adenocarcinoma. Fertil Steril. 1986;46(5):973-5.
14. Lee KR, Scully RE. Complex endometrial hyperplasia and carcinoma in adolescents and young women 15 to 20 years of age. A report of 10 cases. Int J Gynecol Pathol. 1989;8(3):201-13.
15. Paulson RJ, Sauer MV, Lobo RA. Pregnancy after in vitro fertilization in a patient with stage I endometrial carcinoma treated with progestins. Fertil Steril. 1990 54(4):735-6.

16. Kimmig R, Strowitzki T, Muller-Hocker J, Kurzl R, Korell M, Hepp H. Conservative treatment of endometrial cancer permitting subsequent triplet pregnancy. Gynecol Oncol. 1995;58(2):255-7.

17. Lai CH, Hsueh S, Chao AS, Soong YK. Successful pregnancy after tamoxifen and megestrol acetate therapy for endometrial carcinoma. Br J Obstet Gynaecol. 1994;101(6):547-9.

18. Kim YB, Holschneider CH, Ghosh K, Nieberg RK, Montz FJ. Progestin alone as primary treatment of endometrial carcinoma in premenopausal women. Report of seven cases and review of the literature. Cancer. 1997;79(2):320-7.

19. Kung FT, Chen WJ, Chou HH, Ko SF, Chang SY. Conservative management of early endometrial adenocarcinoma with repeat curettage and hormone therapy under assistance of hysteroscopy and laparoscopy. Hum Reprod. 1997;12(8):1649-53.

20. Randall TC, Kurman RJ. Progestin treatment of atypical hyperplasia and well-differentiated carcinoma of the endometrium in women under age 40. Obstetrics and gynecology. 1997;90(3):434-40.

21. Salha O, Martin-Hirsch P, Lane G, Sharma V. Endometrial carcinoma in a young patient with polycystic ovarian syndrome: first suspected at time of embryo transfer. Hum Reprod. 1997;12(5):959-62.

22. Zanetta G GA, Losa G, Cappellini A, Mangioni C. conservative management of endometrial carcinoma with prolonged preservation of the uterus in a young patient. Int J Gynecol Cancer. 1997;7:332-4.

23. Sardi J, Anchezar Henry JP, Paniceres G, Gomez Rueda N, Vighi S. Primary hormonal treatment for early endometrial carcinoma. Eur J Gynaecol Oncol. 1998;19(6):565-8.

24. Schammel DP, Mittal KR, Kaplan K, Deligdisch L, Tavassoli FA. Endometrial adenocarcinoma associated with intrauterine pregnancy. A report of five cases and a review of the literature. Int J Gynecol Pathol. 1998;17(4):327-35.

25. Zuckerman B LO, Neumann M, et al. Endometrial carcinoma Stage I-Grade II. Conservative treatment followed by a healthy twin pregnancy. Int J Gynecol Cancer. 2002;8(2):172-4.

26. Kowalczyk CL, Malone J, Jr., Peterson EP, Jacques SM, Leach RE. Well-differentiated endometrial adenocarcinoma in an infertility patient with later conception. A case report. J Reprod Med. 1999;44(1):57-60.

27. Vinker S, Shani A, Open M, Fenig E, Dgani R. Conservative treatment of adenocarcinoma of the endometrium in young patients. Is it appropriate? Eur J Obstet Gynecol Reprod Biol. 1999;83(1):63-5.

28. Shibahara H, Shigeta M, Toji H, Wakimoto E, Adachi S, Ogasawara T, et al. Successful pregnancy in an infertile patient with conservatively treated endometrial adenocarcinoma after transfer of embryos obtained by intracytoplasmic sperm injection. Hum Reprod. 1999;14(7):1908-11.

29. Jobo T, Imai M, Kawaguchi M, Kenmochi M, Kuramoto H. Successful conservative treatment of endometrial carcinoma permitting subsequent pregnancy: report of two cases. Eur J Gynaecol Oncol. 2000;21(2):119-22.

30. Mitsushita J, Toki T, Kato K, Fujii S, Konishi I. Endometrial carcinoma remaining after term pregnancy following conservative treatment with medroxyprogesterone acetate. Gynecol Oncol. 2000;79(1):129-32.

31. Ogawa S, Koike T, Shibahara H, Ohwada M, Suzuki M, Araki S, et al. Assisted reproductive technologies in conjunction with conservatively treated endometrial adenocarcinoma. A case report. Gynecol Obstet Invest. 2001;51(3):214-6.

32. Kaku T, Yoshikawa H, Tsuda H, Sakamoto A, Fukunaga M, Kuwabara Y, et al. Conservative therapy for adenocarcinoma and atypical endometrial hyperplasia of the endometrium in young women: central pathologic review and treatment outcome. Cancer Lett. 2001;167(1):39-48.

33. Pinto AB, Gopal M, Herzog TJ, Pfeifer JD, Williams DB. Successful in vitro fertilization pregnancy after conservative management of endometrial cancer. Fertil Steril. 2001;76(4):826-9.

34. Imai M, Jobo T, Sato R, Kawaguchi M, Kuramoto H. Medroxyprogesterone acetate therapy for patients with adenocarcinoma of the endometrium who wish to preserve the uterus-usefulness and limitations. Eur J Gynaecol Oncol. 2001;22(3):217-20.

35. Duska LR, Garrett A, Rueda BR, Haas J, Chang Y, Fuller AF. Endometrial cancer in women 40 years old or younger. Gynecol Oncol. 2001;83(2):388-93.

36. Wang CB, Wang CJ, Huang HJ, Hsueh S, Chou HH, Soong YK, et al. Fertility-preserving treatment in young patients with endometrial adenocarcinoma. Cancer. 2002;94(8):2192-8.

37. Lowe MP, Cooper BC, Sood AK, Davis WA, Syrop CH, Sorosky JI. Implementation of assisted reproductive technologies following conservative management of FIGO grade I endometrial adenocarcinoma and/or complex hyperplasia with atypia. Gynecol Oncol. 2003;91(3):569-72.

38. Burnett AF, Bahador A, Amezcua C. Anastrozole, an aromatase inhibitor, and medroxyprogesterone acetate therapy in premenopausal obese women with endometrial cancer: a report of two cases successfully treated without hysterectomy. Gynecol Oncol. 2004;94(3):832-4.

39. Nakao Y, Nomiyama M, Kojima K, Matsumoto Y, Yamasaki F, Iwasaka T. Successful pregnancies in 2 infertile patients with endometrial adenocarcinoma. Gynecol Obstet Invest. 2004;58(2):68-71.

40. Yarali H, Bozdag G, Aksu T, Ayhan A. A successful pregnancy after intracytoplasmic sperm injection and embryo transfer in a patient with endometrial cancer who was treated conservatively. Fertil Steril. 2004;81(1):214-6.

41. Niwa K, Tagami K, Lian Z, Onogi K, Mori H, Tamaya T. Outcome of fertility-preserving treatment in young women with endometrial carcinomas. BJOG. 2005;112(3):317-20.

42. Ota T, Yoshida M, Kimura M, Kinoshita K. Clinicopathologic study of uterine endometrial carcinoma in young women aged 40 years and younger. Int J Gynecol Cancer. 2005;15(4):657-62.

43. Ferrandina G, Zannoni GF, Gallotta V, Foti E, Mancuso S, Scambia G. Progression of conservatively treated endometrial carcinoma after full term pregnancy: a case report. Gynecol Oncol. 2005;99(1):215-7.

44. Huang SY, Jung SM, Ng KK, Chang YC, Lai CH. Ovarian metastasis in a nulliparous woman with endometrial adenocarcinoma failing conservative hormonal treatment. Gynecol Oncol. 2005;97(2):652-5.

45. Mazzon I, Corrado G, Morricone D, Scambia G. Reproductive preservation for treatment of stage IA endometrial cancer in a young woman: hysteroscopic resection. Int J Gynecol Cancer. 2005;15(5):974-8.

46. Yang YC, Wu CC, Chen CP, Chang CL, Wang KL. Reevaluating the safety of fertility-sparing hormonal therapy for early endometrial cancer. Gynecologic oncology. 2005;99(2):287-93.

47. Chang WH, Chen CH, Yu MH. Conservative therapy of stage I endometrial adenocarcinoma and atypical endometrial hyperplasia for the preservation of fertility. Int J Gynaecol Obstet. 2006;92(2):137-8.

48. Park JC, Cho CH, Rhee JH. A successful live birth through in vitro fertilization program after conservative treatment of FIGO grade I endometrial cancer. Journal of Korean medical science. 2006;21(3):567-71.

49. Sparac V, Ujevic B, Ujevic M, Pagon-Belina Z, Marton U. Successful pregnancy after hysteroscopic removal of grade I endometrial carcinoma in a young woman with Lynch syndrome. Int J Gynecol Cancer. 2006;16 Suppl 1:442-5.

50. Yahata T, Fujita K, Aoki Y, Tanaka K. Long-term conservative therapy for endometrial adenocarcinoma in young women. Hum Reprod. 2006;21(4):1070-5.

51. Gurgan T, Bozdag G, Demirol A, Ayhan A. Preserving fertility before assisted reproduction in women with endometrial carcinoma: case report and literature review. Reproductive biomedicine online. 2007;15(5):561-5.

52. Minaguchi T, Nakagawa S, Takazawa Y, Nei T, Horie K, Fujiwara T, et al. Combined phospho-Akt and PTEN expressions associated with post-treatment hysterectomy after conservative progestin therapy in complex atypical hyperplasia and stage Ia, G1 adenocarcinoma of the endometrium. Cancer Lett. 2007;248(1):112-22.

53. Shamshirsaz AA, Withiam-Leitch M, Odunsi K, Baker T, Frederick PJ, Lele S. Young patients with endometrial carcinoma selected for conservative treatment: a need for vigilance for synchronous ovarian carcinomas, case report and literature review. Gynecol Oncol. 2007;104(3):757-60.

54. Ushijima K, Yahata H, Yoshikawa H, Konishi I, Yasugi T, Saito T, et al. Multicenter phase II study of fertility-sparing treatment with medroxyprogesterone acetate for endometrial carcinoma and atypical hyperplasia in young women. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2007;25(19):2798-803.

55. Yamazawa K, Hirai M, Fujito A, Nishi H, Terauchi F, Ishikura H, et al. Fertility-preserving treatment with progestin, and pathological criteria to predict responses, in young women with endometrial cancer. Hum Reprod. 2007;22(7):1953-8.

56. Hurst SA, Hartzfeld KM, Del Priore G. Occult myometrial recurrence after progesterone therapy to preserve fertility in a young patient with endometrial cancer. Fertil Steril. 2008;89(3):724 e1-3.

57. Takahashi N, Hirashima Y, Harashima S, Takekuma M, Kawaguchi R, Yamada Y, et al. A patient with stage 1a endometrial carcinoma in whom a solitary recurrent lesion was detected in the external iliac lymph node after MPA therapy. Arch Gynecol Obstet. 2008;278(4):365-7.

58. Wu HM, Lai CH, Huang HY, Wang HS, Soong YK. A successful live twin birth by in vitro fertilization after conservative treatment of recurrent endometrial cancer. Chang Gung medical journal. 2008;31(1):102-6.

59. Ushijima K, Yahata H, Yoshikawa H, Konishi I, Yasugi T, Saito T, et al. Multicenter phase II study of fertility-sparing treatment with medroxyprogesterone acetate for endometrial carcinoma and atypical hyperplasia in young women. J Clin Oncol. 2007;25(19):2798-803.

60. Minaguchi T, Nakagawa S, Takazawa Y, Nei T, Horie K, Fujiwara T, et al. Combined phospho-Akt and PTEN expressions associated with post-treatment hysterectomy after conservative progestin therapy in complex atypical hyperplasia and stage Ia, G1 adenocarcinoma of the endometrium. Cancer letters. 2007;248(1):112-22.

61. Yamazawa K, Hirai M, Fujito A, Nishi H, Terauchi F, Ishikura H, et al. Fertility-preserving treatment with progestin, and pathological criteria to predict responses, in young women with endometrial cancer. Human reproduction (Oxford, England). 2007;22(7):1953-8.

62. Tran BN, Connell PP, Waggoner S, Rotmensch J, Mundt AJ. Characteristics and outcome of endometrial carcinoma patients age 45 years and younger. American journal of clinical oncology. 2000;23(5):476-80.

63. Boronow RC, Morrow CP, Creasman WT, Disaia PJ, Silverberg SG, Miller A, et al. Surgical staging in endometrial cancer: clinical-pathologic findings of a prospective study. Obstetrics and gynecology. 1984;63(6):825-32.

64. Larson DM, Connor GP, Broste SK, Krawisz BR, Johnson KK. Prognostic significance of gross myometrial invasion with endometrial cancer. Obstetrics and gynecology. 1996;88(3):394-8.

65. Ben-Shachar I, Vitellas KM, Cohn DE. The role of MRI in the conservative management of endometrial cancer. Gynecologic oncology. 2004;93(1):233-7.

66. Thigpen JT, Brady MF, Alvarez RD, Adelson MD, Homesley HD, Manetta A, et al. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1999;17(6):1736-44.

67. Ulbright TM, Roth LM. Metastatic and independent cancers of the endometrium and ovary: a clinicopathologic study of 34 cases. Human pathology. 1985;16(1):28-34.

68. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. Cancer. 1987;60(8 Suppl):2035-41.

69. Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, Vergote I. Endometrial cancer. Lancet. 2005;366(9484):491-505.

70. Sorosky JI. Endometrial cancer. Obstetrics and gynecology. 2008;111(2 Pt 1):436-47.

71. Prat J, Ribe A, Gallardo A. Hereditary ovarian cancer. Human pathology. 2005;36(8):861-70.

72. Moyer DL, Felix JC. The effects of progesterone and progestins on endometrial proliferation. Contraception. 1998;57(6):399-403.

73. Amant F, Leunen K, Neven P, Berteloot P, Vergote I. Endometrial cancer: predictors of response and preferred endocrine therapy. Int J Gynecol Cancer. 2006;16 Suppl 2:527-8.

74. Evans-Metcalf ER, Brooks SE, Reale FR, Baker SP. Profile of women 45 years of age and younger with endometrial cancer. Obstetrics and gynecology. 1998;91(3):349-54.

75. Bafaloukos D, Aravantinos G, Samonis G, Katsifis G, Bakoyiannis C, Skarlos D, et al. Carboplatin, methotrexate and 5-fluorouracil in combination with medroxyprogesterone acetate (JMF-M) in the treatment of advanced or recurrent endometrial carcinoma: A Hellenic cooperative oncology group study. Oncology. 1999;56(3):198-201.

CHAPTER 3

Exploring morphologic and molecular aspects of endometrial cancer under progesterone treatment in the context of fertility preservation

Mignon van Gent
Alina Nicolae-Cristea (shared first author)
Cor de Kroon
Michelle Osse
Marjolein Kagie
Baptist Trimbos
Hans Marten Hazelbag
Vincent Smit
Tjalling Bosse

International Journal of Gynecological Cancer. 2016 Mar; 26(3):483-90

CHAPTER 3

Exploring morphologic and molecular aspects of endometrial cancer under progesterone treatment in the context of fertility preservation

3.1 ABSTRACT

Objective

The standard treatment of early stage (FIGO I) endometrioid endometrial cancer (EEC) is a hysterectomy with bilateral salpingo-oophorectomy. An alternative approach for younger women with low-grade EEC who wish to preserve fertility may be hormonal treatment. Previous studies have suggested that progesterone may elicit its anti-tumour effect in EEC by interacting with the Wnt and/or PI3K/Akt pathways. Therefore, we explored whether common activating genetic alterations in Wnt and PI3K/Akt signaling correlated with non-responsiveness to progesterone therapy for low-grade EEC. Additionally, we investigated whether benign morphology under progesterone treatment is accompanied by absence of genetic changes.

Materials and Methods

We analysed molecular alterations in the Wnt and PI3K/Akt signaling in 84 serial endometrial samples from 11 premenopausal patients with progesterone receptor (PR) positive, low-grade EEC conservatively treated with progesterone and correlated these with histological and clinical follow-up.

Results

There were six responders and five non-responders to progesterone treatment. The response rate to progesterone treatment was 55% and the relapse rate 83%. All responders had alterations in both the Wnt and PI3K/Akt pathway prior to treatment. In the non-responder group, tumours inconsistently showed alterations in none, one or both pathways. Normalisation of the endometrium morphology under progesterone treatment is accompanied by absence of the genetic changes found in the specimen prior to treatment.

Conclusions

We found that activating molecular alterations in either Wnt or PI3K/Akt signaling pathways did not predict resistance to progesterone treatment. It seems that morphological response goes along with disappearance of the established mutations. This exploratory study suggests that Wnt or PI3K/Akt status is unable to predict response to progesterone treatment in patients with EEC.

3.2 INTRODUCTION

Endometrial cancer is the most common cancer of the female genital tract in most Western countries, with an incidence of 20 in 100.000 and is the fourth most common cancer in women after breast, lung, and colorectal cancer. [1, 2] A minority (4%) of the patients is younger than 40 years of age at diagnosis. [3] Standard treatment in early stage endometrial cancer is total hysterectomy with bilateral salpingo-oophorectomy (BSO). Hormonal treatment with progesterone may also be an option in women with well-differentiated endometrioid endometrial cancer (EEC) who wish to preserve their fertility. The initial response rate to hormonal treatment is generally good (76.2%). However, there is a high risk of relapse. [4]

The premise for progesterone treatment is the concept that unopposed estrogen stimulation is the driver for both initiation and progression of EEC. [5] In advanced endometrial cancer, progesterone receptor (PR) expression has a strong predictive value for response to progesterone therapy. [6, 7] In these patients it is possible to identify progesterone resistant tumours with an accuracy of about 90%, by determining the PR expression. Therefore, pre-treatment PR expression analysis is commonly used in the selection of patients prior to initiating progesterone therapy. [6-8] Whether PR expression is as accurate in predicting responsiveness to progesterone in low-grade EEC is unknown.

The mechanism by which progesterone induces involution of EEC is not fully understood. There is data suggesting involvement of the Wingless (Wnt) and Phosphatidylinositol 3-kinase (PI3K)-Akt signal transduction pathways. Both Wnt and PI3K/Akt signaling are frequently altered during endometrial tumourigenesis and act additively and synergistically in inducing cell proliferation. [9, 10] Constitutive activation of the Wnt-signaling can be the result of a mutation in the *CTNNB1* gene, alterations in the *APC* gene or functionally, under influence of (endogenous) estrogen. [9, 11] Nuclear β-catenin staining, indicative of active Wnt signaling, has been demonstrated in 30-85% of EECs. [12, 13] Furthermore, endogenous activation of the Wnt and PI3K/Akt pathways occurs throughout the normal menstrual cycle following changes of estrogen and progesterone levels and induces proliferation of the endometrium. [9, 14] High levels of progesterone have been shown to result in inhibition of Wnt signaling *in vitro* through up-regulation of FOXO1 and DKK1. [9, 11], thereby providing a possible mechanism for the anti-tumour effect of progesterone.

Activation of the PI3K/Akt pathway in EECs is most frequently due to inactivation of the tumour suppressor gene *PTEN* or by activating hotspot mutations in *PIK3CA* and/or *KRAS*. In EEC, loss of PTEN has been reported in 50 to 80% of cases. [15, 16] *PIK3CA* and *KRAS* have been shown to be mutated in up to 52% and 17% of EECs, respectively. [17, 18] One study of serial endometrial samples of patients with complex atypical hyperplasia (CAH), which is considered the precursor of EEC, shows significant decrease in phospho-Akt during

progesterone treatment. [19] This suggests that anti-tumour effect of progesterone may be mediated by inhibiting the PI3K/Akt signaling through dephosphorylation of Akt.
The aim of our study was to evaluate the morphological and molecular changes in sequential biopsies obtained prior to, during and after progesterone treatment in 11 women with EEC. We focussed on the Wnt and PI3K/Akt signaling pathways and explored whether activation of these pathways was related to response to therapy and recurrence.

3.3 MATERIALS AND METHODS

Patients

Between 2002 and 2012, pre-treatment specimens of eleven patients treated with progesterone for EEC were sent in for central pathological review at our institution. We retrospectively collected the clinical data of these patients and obtained all available consecutive endometrial specimens for histopathological review and molecular analysis. Patient data is administered according to the principles of the Declaration of Helsinki on the ethics of research with humans. Clinical, pathological and follow-up data are summarised in table 1. All patients were diagnosed as having well-differentiated (grade 1) EEC according to the criteria stated by the WHO Classification of Tumours of the Female Genital Tract. [15] All tumours showed PR expression by immunohistochemistry (IHC) in their pre-treatment samples. Myometrial invasion and extra-uterine disease were evaluated by transvaginal ultrasound and contrast enhanced magnetic resonance imaging, revealing <50% myometrium invasion and no extra-uterine disease in all cases. All patients were treated with high-dose progesterone followed by three-monthly hysteroscopy with curetting and/or biopsy. Ten patients received medroxyprogesterone (MPA) with a median dosage of 250 mg/day (range 100-600 mg) and 1 patient was treated with megestrol acetate 200 mg/day. In addition to MPA, two patients received a levonorgestrel-releasing intrauterine system (LNG-IUS). During follow up, if responders had completed family or revised their wish for offspring, hysterectomy with BSO was advised.

Pathology evaluation

We examined 84 curettings or biopsies and 5 hysterectomy specimens. Samples were handled in a coded fashion and all procedures were performed according to the ethical guidelines as outlined in the "Code for Proper Secondary Use of Human Tissue in The Netherlands" (Dutch Federation of Medical Scientific Societies). Formalin fixed paraffin embedded (FFPE) blocks of at least 6 consecutive samples were available for each patient (range 6 - 10, median 8). All slides and immunohistochemical stains were evaluated by one senior pathology resident (A.N.) and two gynaecopathologists (T.B. en V.S.) independently. Evaluation of the specimen was performed while unaware of

patient characteristics and clinical outcome. Discordant findings were reviewed until consensus was reached. The following parameters were evaluated on haematoxylin and eosin slides: architectural abnormalities, cytological atypia and presence of progesterone induced changes (atrophy of glands, secretory changes of the epithelium and pseudodecidualisation of stroma). Complete pathological response to progesterone therapy was defined as proliferative, secretory, inactive or atrophic endometrium without hyperplasia or atypia, as previously described [20] and according to the criteria stated by the WHO Classification of Tumours of the Female Genital Tract. [15] Absence of response was defined as persistence of well-differentiated EEC or CAH/endometrial intraepithelial neoplasia (EIN).

Endometrial sampling

63% of the pre-hysterectomy samples were taken by conventional dilatation and curetting or micro-curetting, 13% by biopsy/hysteroscopic resection, and 17% by both. The sampling method was unknown in 7% of the samples.

Table 1. Clinicopathological findings and follow-up of 11 patients with low-grade EEC treated with progesterone

Case no.	Age at Diagnosis, y	BMI	Menstrual cycle Prediagnosis	Indication Analysis	MRI	Prediagnosis GxPx
1	27	31.1	Oligomenorrhea	Polyp	normal	G1P1
2	30	38	Irregular	Fertility analysis	-	G0
3	35	20.8	Regular	Fertility analysis	normal	G0
4	37	30	Regular	Fertility analysis	normal	G0
5	35	20	Oligomenorrhea	Fertility analysis	-	G0
6	36	33.2	Irregular	Thickened endometrium	-	G0
7	38	22.8	Regular	Fertility analysis/ polyp	< 50% myometrium	G0
8	27	27	-	Fertility analysis/ polyp	normal	G0
9	31	23.9	Irregular	Metrorrhagia	normal	G0
10	33	28.7	Irregular	Fertility analysis/ polyp	-	G1P0A1
11	28	39	Irregular	Irregular bleeding	normal	G0

MPA. Medroxyprogesterone; mo. months; G, gravida; P, para; A, abortion; LNG-IUS, Levenogestrel-releasing intrauterine sysem; * But relapsed and responded again. † Complete family. ‡ After relapse.

Immunohistochemistry

Immunohistochemistry for PTEN and β-catenin was performed as described previously. [21] PTEN was scored positive if it showed cytoplasmic staining in the entire tumour or the majority of the tumour cells, and negative if it showed no cytoplasmic staining in the tumour cells. [22] Adjacent stromal cells or normal endometrial glands served as positive internal controls. Activated Wnt signaling was defined as nuclear beta-catenin staining in > 1% of the tumour cells, in accordance with previous studies. [12, 23] PR staining was performed using clone PGR 636, DAKO, 1: 100 dilution and ER staining using clone 1D5, DAKO, 1:100 on each sample. Nuclear PR and ER positivity in tumour cells was scored using a continuous percentage scale.

DNA isolation

From FFPE blocks containing sufficient tissue (curettings), two whole sections of 10 µm were used for DNA isolation with the Tissue Preparation System (Siemens Healthcare Diagnostics). From samples with a small amount of tissue (micro-curettings or biopsies), 5 whole sections of 10 µm were used. Endometrium from hysterectomy specimens was micro dissected from five whole sections of 10 um, to avoid contamination with normal myometrium.

Treatment, mg/d	Duration of Treatment, mo	No. Curettages	Response	Hysterectomy	Follow-up, mo	GxPx at End of Follow-up
MPA 200	17.5	10	Yes*	No	47	G3P1A2
MPA 600 (10 mo) + MPA 300 (4 mo) +LNG-IUS post tx	17	8	Yes*	Yes†	128	G3P2A1
MPA 200	18	9	Yes*	No	38	G1P0A1
MPA 200	19	6	No	Yes	32	G0
Megace 200	17	7	No	No	25	G0
MPA 100 + LNG-IUS (4 mo) + MPA 500	10	8	No	Yes	42	G0
MPA 400	9	6	No	Yes	22	G0
MPA 200	15	8	Yes	No	22	G0
MPA 200	8.5	7	Yes	Yes‡	23	G0
MPA 300 (3 mo) + MPA 200 (3 mo)	6	7	Yes	No	75	G2P1A1
MPA 500 + LNG-IUS	12	6	No	No	19	G0

Allele specific PCR (KRAS and PIK3CA)

Allele specific PCR was performed to identify the seven *KRAS* and three *PIK3CA* hot spot mutations most frequently encountered in EEC, using a custom-made panel of hydrolysis probe assays as described previously. [21, 24]

Sanger sequencing

CTNNB1 exon 3 was amplified using the following primers: forward: GATTTGATGGAGTTGGACATGG, reverse: TGTTCTTGAGTGAAGGACTGA. Sanger sequencing was performed on purified PCR products (Macrogen, Amsterdam, the Netherlands). Sequences of the forward and reverse strands were analysed with Mutation Surveyor software (Softgenetics, State College, PA, USA).

Genetic susceptibility exclusion

According to the clinical data there was no suspicion of Lynch syndrome. MLH1 immunohistochemistry was performed in all patients and showed no loss of expression, thereby excluding the possibility of sporadic EEC with microsatellite instability.

3.4 RESULTS

Clinical aspects

Eleven patients diagnosed with grade 1 EEC were included. The mean BMI was 25.8 (median 27.9, range 20-39). None of the patients suffered from diabetes. The duration of treatment varied between 6 and 19 months, with a median of 15 months. The median follow up was 32 months (range 19-128 months). Based on the aforementioned definition of complete response (CR) there were 5 non-responders (45%) and 6 responders (55%), of whom 5 patients (83%) relapsed during the follow-up of our study. All responders showed CR within the first 12 months of treatment, with a median time to response of 6 months (table 3). Four of the responders became pregnant with a total of 7 pregnancies (4 miscarriages, 3 term deliveries of healthy neonates). All pregnancies were achieved by assisted fertility treatment through intrauterine insemination (IUI) (n = 4) or in vitro fertilisation (IVF) (n = 3). Five responders had recurrent disease after discontinuation of progesterone and 4 of them responded again after restarting hormonal treatment. Two of the responders underwent hysterectomy after completion of their pregnancies (table 1). The non-responders continued treatment up to a follow up of respectively 15, 18, 24, 24 and 27 months. Of these, three have undergone hysterectomies and two are awaiting hysterectomy. In the 5 non-responders, there was persistence of residual disease in every curetting and in the hysterectomy specimen. Histological analysis of none of the available hysterectomy specimens showed upgrading or upstaging of the presumed stage of disease. Nine patients are alive without evidence of disease (table 1). Two are awaiting hysterectomy.

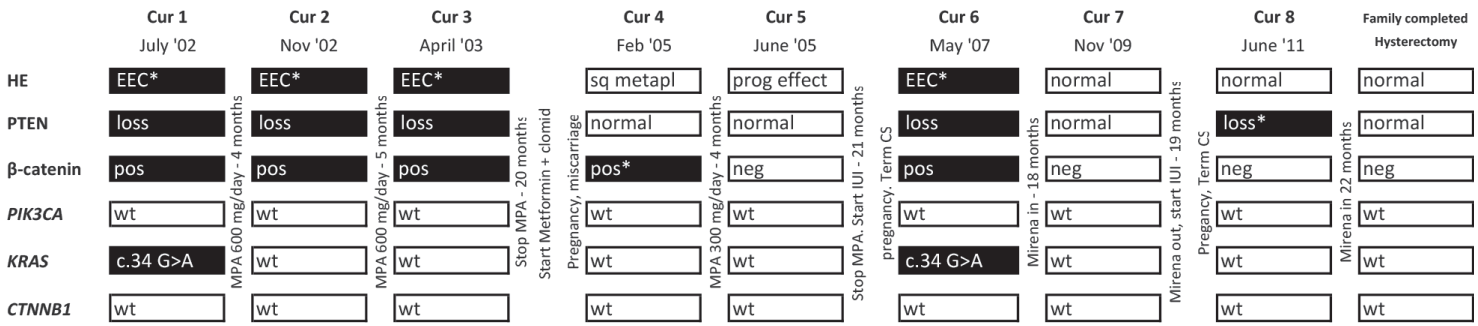


Figure 1. Histological changes and molecular findings in sequential endometrium samples under progesterone treatment, patient 2: response, recurrent disease, response.

Legend: Sq metapl, squamous metaplasia; prog effect, progesterone effect; wt, wild type; * focally present

Histology

During treatment, the tumours showed prominent architectural as well as cellular changes. Decrease of the gland-to-stroma ratio was observed. All patients showed decreased glandular cellularity, decreased mitotic activity of glandular epithelium and decreased cellular atypia during treatment. Atrophy of pre-existing glandular epithelium and pseudodecidualisation of stroma were present in the first curetting after initiation of hormonal treatment in most patients (82%). Figure 1 displays the HE and molecular findings of an initial responder, who relapsed and responded again. In samples with residual disease under progesterone treatment, glandular confluence with a cribriform growth pattern persisted at least focally (supplement 1).

Hormone receptor status

All patients had PR and ER expression in 90-100% of tumour cells in the initial curetting and maintained positivity during treatment.

Molecular changes

All 6 responders had both pathways activated. In the non-responder group, tumours inconsistently showed alterations in none, one or both pathways. An overview of alterations in the PI3K/Akt and Wnt signaling pathways in the pre-treatment (diagnostic) samples in relation to the clinical response is listed in table 2. The genetic aberrations in subsequent curettings are summarised in table 3.

Wnt signaling

Nuclear staining of β-catenin by IHC, consistent with Wnt activation, was seen in 9 patients in the pre-treatment samples, all 6 responders and 3 non-responders (table 3). Residual foci of EEC in subsequent samples showed the same β-catenin staining as the initial tumour. In pre-treatment samples of four of these 9 patients (44%) a *CTNNB-1* exon 3 mutation could be demonstrated; 3 of them were missense mutations (p.D32V, p.S33C and p.S37C) and one was an in-frame deletion (p.D32del4(DSGI)). In two non-responders the same *CTNNB-1* mutation was found in subsequent samples with residual disease, indicating persistence of the malignant clone. Moreover, in one patient with relapse after complete response, the same *CTNNB-1* mutation as demonstrated in the initial specimen was found in the relapse specimen (case 9, table 3).

Table 3. Pathway alterations in the pretreatment endometrial specimen (EEC), responders versus nonresponders

	Responders	Nonresponders
Wnt activation only	0	1
PI3K/Akt activation only	0	1
Wnt + PI3K/Akt activation	6	2
No detected pathway alterations	0	1

Wnt activation was defined as nuclear β-catenin by immuno-histochemistry (with or without *CTNNB-1* exon 3 mutation), PIK3/Akt activation as PTEN loss and/or PIK3CA or KRAS mutations.
All responders showed activation of both pathways. In the non-responders, the molecular alterations vary.

PI3K/Akt signaling pathway

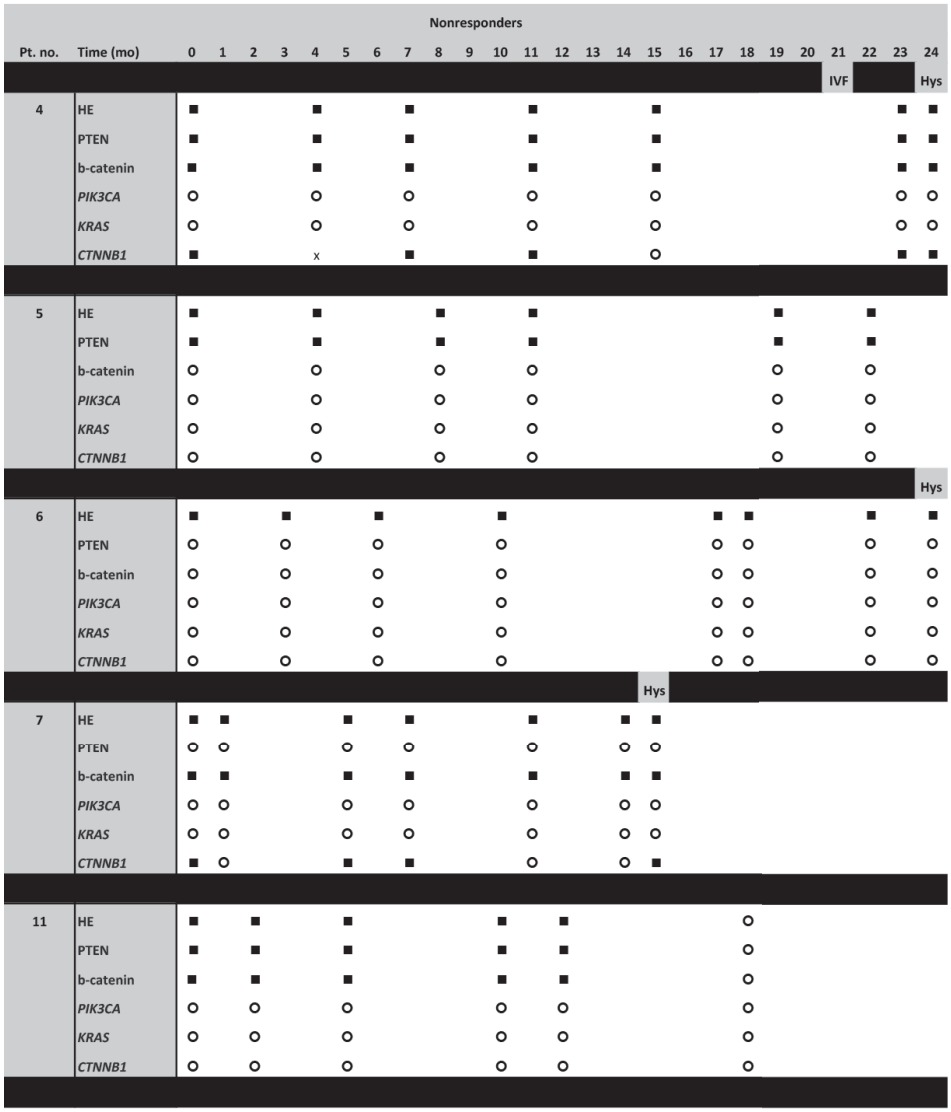
The PI3K/Akt pathway showed alterations in the pre-treatment samples in 8 patients (72%, table 2). Four of these had PTEN loss alone, one had simultaneous loss of PTEN and a *KRAS* exon 2 (p.G12S) mutation, and three had a *PIK3CA* mutation alone as activating event. Two of the *PIK3CA* mutations were located in exon 20 (H147R) and one in exon 9 (E542K). Residual foci of EEC in following samples had an identical PTEN-profile as the primary carcinoma. The same mutation (in *PIK3CA* and *KRAS*) was found in subsequent samples in two of the four patients, indicating persistence of the mutated clone. The same *KRAS* exon *2* mutation as in the initial specimen was found in one patient who relapsed after complete response followed by discontinuation of the treatment (table 3). None of the tumours harboured both *KRAS* and *PIK3CA* mutations simultaneously. In one of the non-responders no molecular alterations in Wnt or PI3K/Akt pathways were identified (table 2).

Samples without (pre)malignancy

Samples without histomorphological evidence of disease showed no *KRAS*, *PIK3CA or CTNNB-1* exon 3 mutations (N=32). In 6 of these samples, isolated benign looking glands showed nuclear beta-catenin positivity surrounded by strong pseudo-decidualized stroma. In 4 of the curettings without malignancy, sparse isolated PTEN negative glands with normal morphology were seen (PTEN null glands [25]).

Table 2. Histological and molecular findings in the first 24 months of follow-up, responders versus nonresponders

		Responders																							
Pt. no.	Time (mo)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
																							IVF	MC		
1	HE	■						○			○				○			■			○					○
	PTEN	○						○			○				○			○			○					○
	b-catenin	■						■			■				■			■			■					■
	PIK3CA	■						○			○				○			○			○					○
	KRAS	○						○			○				○			○			○					○
	CTNNB1	○						○			○				○			○			○					○
																				MC						
2	HE	■				■					■															
	PTEN	■				■					■															
	b-catenin	■				■					■															
	PIK3CA	○				○					○															
	KRAS	■				○					○															
	CTNNB1	○				○					○															
																							IUI	MC		
3	HE	■		■			■			○			○					○								
	PTEN	○		■			■			○			○					○								
	b-catenin	■		■			■			○			○					○								
	PIK3CA	■		x			○			○			○					○								
	KRAS	○		x			○			○			○					○								
	CTNNB1	■		x			○			○			x					○								
														IUI											IUI	
8	HE	■			○			○					○						○		■			○		
	PTEN	■			○			○					○						○		■			○		
	b-catenin	■			○			○					○						○		■			○		
	PIK3CA	○			○			○					○						○		xx			xx		
	KRAS	○			○			○					○						○		xx			xx		
	CTNNB1	■			○			○					○						○		xx			xx		
																										Hys
9	HE	■	○				○			○			○				■							■		■
	PTEN	○	○				○			○			○				○							○		○
	b-catenin	■	○				○			■			■				■							■		■
	PIK3CA	■	○				○			○			○				xx							xx		■
	KRAS	○	○				○			○			○				xx							xx		○
	CTNNB1	■	○				○			○			○				xx							xx		■
10	HE	■				■	■						■						○							
	PTEN	■				○	■						■						■							
	b-catenin	■				■	■						■						○							
	PIK3CA	○				○	○						○						○							
	KRAS	○				○	○						○						○							
	CTNNB1	○				○	○						○						○							


Nonresponders
Pt. no.
Time (mo)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
IVF
Hys
4
5
6
7
11
HE
PTEN
b-catenin
PIK3CA
KRAS
CTNNB1
x
Hys
HE ■ Ca/CAH ○ normal
PTEN ■ loss ○ normal
b-catenin ■ positive ○ negative
PIK3CA ■ mutant ○ wildtype
KRAS ■ mutant ○ wildtype
CTNNB1 ■ mutant ○ wildtype
x Not enough tissue for analysis
xx Not available
MC Miscarriage
Hys Hysterectomy
IVF IVF attempt
IUI IUI attempt

3.5 DISCUSSION

This study is the first to explore whether alterations in the Wnt and PI3K/Akt signaling pathways in the pre-treatment endometrial sample are predictive for progesterone non-responsiveness in women with low-grade, FIGO I, PR positive EEC. Moreover we evaluated the alteration in these signaling pathways during treatment and follow-up. In contrast to most previous work concentrating on morphological changes alone [20, 26, 27], our study describes molecular genetic alterations in combination with the morphologic appearance in subsequent endometrium samples from progesterone treated patients with low-grade EEC. According to our results, molecular alterations in Wnt and/or PI3K/Akt pathways do not necessarily induce resistance to progesterone treatment.

Alterations in the Wnt or PI3K/Akt signaling pathways are the most frequent genetic abnormalities in low-grade EEC. [15] Previous studies have suggested that progesterone might rely on the Wnt or PI3K/Akt signaling pathways to elicit its therapeutic effect in EEC. [11, 19] We hypothesised that if somatic mutations activate one or both signaling pathways constitutively, that might lead to resistance to progesterone therapy. All six responders in our series had concomitant activation of both Wnt and PI3K/Akt signaling pathways suggesting that alterations in these important pathways in endometrial cancer may not be predictive of resistance to progesterone treatment.

Our findings indicate that the progesterone effect may at least partially be independent of alterations in the Wnt and/or PI3K/Akt signaling pathways. Other non-mutually exclusive hypotheses may explain how progesterone bypasses the Wnt and PI3K/Akt signaling pathways. First, progesterone may induce apoptosis through up regulation of Fas/FasL or decreasing Bcl-2 protein expression. [28-30] According to this hypothesis, progesterone induces apoptosis in all endometrial glands including those with Wnt and PI3K/Akt activation, followed by replacement with new glands without genetic defects. [19] Additionally, there may be a role for endometrial stroma in endometrial carcinogenesis and response to progesterone therapy through PR receptor or hypermethylation of the tumour suppressor *HAND2* in stromal cells. Epigenetic *HAND2* inactivation in stromal cells seems to induce resistance to progesterone in hyperplastic endometrium. [31] As *HAND2* hypermethylation was observed in 90% of EEC, it seems unlikely to be the only factor of progesterone resistance, knowing the response rate in grade 1 EEC reaches up to 75%. [4] Future studies on these alternative mechanisms will be required to evaluate their potential role in predicting progesterone responsiveness in EEC.

We also observed that normalisation of the endometrium morphology under progesterone treatment is accompanied by absence of the pre-treatment genetic changes. The absence of genetic alterations in most morphologically normal endometrium under progesterone treatment could support the hypothesis that progesterone acts through induction of apoptosis followed by replacement with wild-type glands. The significance

of sparse PTEN null glands and single glands with nuclear beta-catenin positivity in a few of the morphologically normal samples is not clear. The significance of sparse PTEN null glands and single glands with nuclear beta-catenin positivity in a few of the morphologically normal samples is not clear. It is unknown whether this implies residual disease, *de novo* (pre)malignant disease after complete response or functional increase of beta-catenin/ decrease of PTEN under hormonal influence. [9, 14]

Previous research identified persistent architectural abnormalities and/or cellular atypia after 7-9 months of treatment as predictive of treatment failure. [20] Another study found that presence of at least three out of five given unfavourable architectural features in the pre-treatment specimen, in combination with the Body Mass Index (BMI) could predict the likelihood of response. [26] The tumour PR status before initiating the treatment was assessed in only one of the previous studies that tried to identify predictive markers in conservative treated low-grade EEC before initiating treatment, but correlation with response was not stated. [19] Most low-grade EECs express PR [32], but only approximately 75% of these patients do indeed respond to fertility sparing progesterone therapy, indicating that other prognostic biomarkers are required in this subset of patients. [4, 33] Studies investigating the value of PR positivity in predicting response in conservatively treated, low-grade presumed FIGO IA EEC are lacking, most likely due to the low number of patients and the high prevalence of PR positivity of these tumours. [32, 34] In all our patients the tumours were PR positive.

This work has some limitations. Although we analysed a large collection of serial endometrial samples, the number of patients we were able to include was small. The sampling method varied among patients during follow-up, resulting in potential under sampling in selected cases, which might explain negative findings in some curettings (figure 1). This notion is supported by the fact that the same genetic alterations were found in recurrences after 'negative' curettings. Thus, 'field cancerisation' in which new clones would arise under unopposed estrogen stimulation is not sustained by our results. Furthermore, despite a national treatment advice, the patients of whom the endometrial samples were included in the study did not receive uniform treatment nor follow up regime.

In conclusion, we describe an in-depth morphologic and molecular analysis of a large collection of serial endometrium samples from EEC patients undergoing progesterone treatment for preservation of fertility. In contrast to the initial hypothesis, our findings indicate that activation of the Wnt and/or PI3K/Akt pathways does not result in lack of response to progesterone treatment. Studying a cohort with more homogenous data, taking bio-physical profiles into account, and performing large scale analyses using targeted next generation sequencing may allow selection of EEC patients who will benefit from progesterone treatment. Young women with low-grade early stage EEC and desire to conceive should be offered progesterone treatment while risks are explained exten-

sively and response is monitored according to a strict protocol. We suggest to include these patients in an international registration study and treat them according to the 2015 ESMO-ESGO-ESTRO guidelines presented at the 19th ESGO meeting.

ACKNOWLEDGMENTS

The authors thank all participating gynaecologists: K.A.M. Peters, Hospital Group Twente; C.A.G. Holleboom, H.T.C. Nagel and J.P.T. Rhemrev, MCHaaglanden-Bronovo Hospital, The Hague; H.J.M.A.A. Zijlmans, Antoni van Leeuwenhoek hospital, Amsterdam; M. van den Berg, University Medical Center Groningen, Groningen, C.A. van Meir, Groene Hart Hospital, Gouda; M.J.Janssen, Maasziekenhuis Pantein, Beugen; M. den Ouden, Alrijne Hospital, Leiderdorp; J. de Waard, Sint Franciscus Gasthuis, Rotterdam, K.N. Gaarenstroom and A.A.W Peters, Leiden University Medical Center, Leiden, J.M.A. Pijnenborg, TweeSteden Hospital, Tilburg, for their contribution to the treatment of the patients and providing the tissue for analysis.

3.6 REFERENCES

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014;64(1):9-29.
2. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55(2):74-108.
3. Lee NK, Cheung MK, Shin JY, Husain A, Teng NN, Berek JS, et al. Prognostic factors for uterine cancer in reproductive-aged women. Obstet Gynecol. 2007;109(3):655-62.
4. Gallos ID, Yap J, Rajkhowa M, Luesley DM, Coomarasamy A, Gupta JK. Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis. Am J Obstet Gynecol. 2012;207(4):266-12.
5. Yang S, Thiel KW, Leslie KK. Progesterone: the ultimate endometrial tumor suppressor. Trends Endocrinol Metab. 2011;22(4):145-52.
6. Kauppila A. Oestrogen and progestin receptors as prognostic indicators in endometrial cancer. A review of the literature. Acta Oncol. 1989;28(4):561-6.
7. Thigpen JT, Brady MF, Alvarez RD, Adelson MD, Homesley HD, Manetta A, et al. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1999;17(6):1736-44.
8. Nyholm HC, Nielsen AL, Lyndrup J, Dreisler A, Thorpe SM. Estrogen and progesterone receptors in endometrial carcinoma: comparison of immunohistochemical and biochemical analysis. Int J Gynecol Pathol. 1993;12(3):246-52.
9. Wang Y, van der Zee M, Fodde R, Blok LJ. Wnt/Beta-catenin and sex hormone signaling in endometrial homeostasis and cancer. Oncotarget. 2010;1(7):674-84.
10. van der Zee M, Jia Y, Wang Y, Heijmans-Antonissen C, Ewing PC, Franken P, et al. Alterations in Wnt-beta-catenin and Pten signalling play distinct roles in endometrial cancer initiation and progression. J Pathol. 2013;230(1):48-58.
11. Wang Y, Hanifi-Moghaddam P, Hanekamp EE, Kloosterboer HJ, Franken P, Veldscholte J, et al. Progesterone inhibition of Wnt/beta-catenin signaling in normal endometrium and endometrial cancer. Clin Cancer Res. 2009;15(18):5784-93.
12. Scholten AN, Creutzberg CL, van den Broek LJ, Noordijk EM, Smit VT. Nuclear beta-catenin is a molecular feature of type I endometrial carcinoma. J Pathol. 2003;201(3):460-5.
13. Saegusa M, Okayasu I. Frequent nuclear beta-catenin accumulation and associated mutations in endometrioid-type endometrial and ovarian carcinomas with squamous differentiation. J Pathol. 2001;194(1):59-67.

14. Mutter GL, Lin MC, Fitzgerald JT, Kum JB, Eng C. Changes in endometrial PTEN expression throughout the human menstrual cycle. J Clin Endocrinol Metab. 2000;85(6):2334-8.

15. Kurman RJ, Carcangiu, M.L., Herrington, C.S., Young, R.H. WHO Classification of Tumours of Female Reproductive Organs. Fourth Edition2014 2014.

16. Mutter GL, Lin MC, Fitzgerald JT, Kum JB, Baak JP, Lees JA, et al. Altered PTEN expression as a diagnostic marker for the earliest endometrial precancers. J Natl Cancer Inst. 2000;92(11):924-30.

17. Lee II, Kim JJ. Influence of AKT on Progesterone Action in Endometrial Diseases. Biol Reprod. 2014;91(3):63.

18. Spaans VM, Trietsch MD, Crobach S, Stelloo E, Kremer D, Osse EM, et al. Designing a high-throughput somatic mutation profiling panel specifically for gynaecological cancers. PLoS One. 2014;9(3):e93451.

19. Minaguchi T, Nakagawa S, Takazawa Y, Nei T, Horie K, Fujiwara T, et al. Combined phospho-Akt and PTEN expressions associated with post-treatment hysterectomy after conservative progestin therapy in complex atypical hyperplasia and stage Ia, G1 adenocarcinoma of the endometrium. Cancer Lett. 2007;248(1):112-22.

20. Wheeler DT, Bristow RE, Kurman RJ. Histologic alterations in endometrial hyperplasia and well-differentiated carcinoma treated with progestins. Am J Surg Pathol. 2007;31(7):988-98.

21. Nout RA, Bosse T, Creutzberg CL, Jurgenliemk-Schulz IM, Jobsen JJ, Lutgens LC, et al. Improved risk assessment of endometrial cancer by combined analysis of MSI, PI3K-AKT, Wnt/beta-catenin and P53 pathway activation. Gynecol Oncol. 2012;126(3):466-73.

22. Garg K, Broaddus RR, Soslow RA, Urbauer DL, Levine DA, Djordjevic B. Pathologic scoring of PTEN immunohistochemistry in endometrial carcinoma is highly reproducible. Int J Gynecol Pathol. 2012;31(1):48-56.

23. Saegusa M, Hashimura M, Yoshida T, Okayasu I. beta- Catenin mutations and aberrant nuclear expression during endometrial tumorigenesis. Br J Cancer. 2001;84(2):209-17.

24. van Eijk R, Licht J, Schrumpf M, Talebian YM, Ruano D, Forte GI, et al. Rapid KRAS, EGFR, BRAF and PIK3CA mutation analysis of fine needle aspirates from non-small-cell lung cancer using allele-specific qPCR. PLoS One. 2011;6(3):e17791.

25. Mutter GL, Ince TA, Baak JP, Kust GA, Zhou XP, Eng C. Molecular identification of latent precancers in histologically normal endometrium. Cancer Res. 2001;61(11):4311-4.

26. Penner KR, Dorigo O, Aoyama C, Ostrzega N, Balzer BL, Rao J, et al. Predictors of resolution of complex atypical hyperplasia or grade 1 endometrial adenocarcinoma in premenopausal women treated with progestin therapy. Gynecol Oncol. 2012;124(3):542-8.

27. Kamoi S, Ohaki Y, Mori O, Kurose K, Fukunaga M, Takeshita T. Serial histologic observation of endometrial adenocarcinoma treated with high-dose progestin until complete disappearance of carcinomatous foci--review of more than 25 biopsies from five patients. Int J Gynecol Cancer. 2008;18(6):1305-14.

28. Amezcua CA, Lu JJ, Felix JC, Stanczyk FZ, Zheng W. Apoptosis may be an early event of progestin therapy for endometrial hyperplasia. Gynecol Oncol. 2000;79(2):169-76.

29. Wang S, Pudney J, Song J, Mor G, Schwartz PE, Zheng W. Mechanisms involved in the evolution of progestin resistance in human endometrial hyperplasia--precursor of endometrial cancer. Gynecol Oncol. 2003;88(2):108-17.

30. Vereide AB, Kaino T, Sager G, Orbo A. Bcl-2, BAX, and apoptosis in endometrial hyperplasia after high dose gestagen therapy: a comparison of responses in patients treated with intrauterine levonorgestrel and systemic medroxyprogesterone. Gynecol Oncol. 2005;97(3):740-50.

31. Jones A, Teschendorff AE, Li Q, Hayward JD, Kannan A, Mould T, et al. Role of DNA methylation and epigenetic silencing of HAND2 in endometrial cancer development. PLoS Med. 2013;10(11):e1001551.

32. Reid-Nicholson M, Iyengar P, Hummer AJ, Linkov I, Asher M, Soslow RA. Immunophenotypic diversity of endometrial adenocarcinomas: implications for differential diagnosis. Mod Pathol. 2006;19(8):1091-100.

33. Ramirez PT, Frumovitz M, Bodurka DC, Sun CC, Levenback C. Hormonal therapy for the management of grade 1 endometrial adenocarcinoma: a literature review. Gynecol Oncol. 2004;95(1):133-8.

34. Gent van MDJM, Kagie MJ, Trimbos BJB. No surgery for Low-grade Endometrial Cancer in Women with a Desire to Preserve Fertility. Journal of gynecologic surgery. 2012;28(6):389-98.

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.

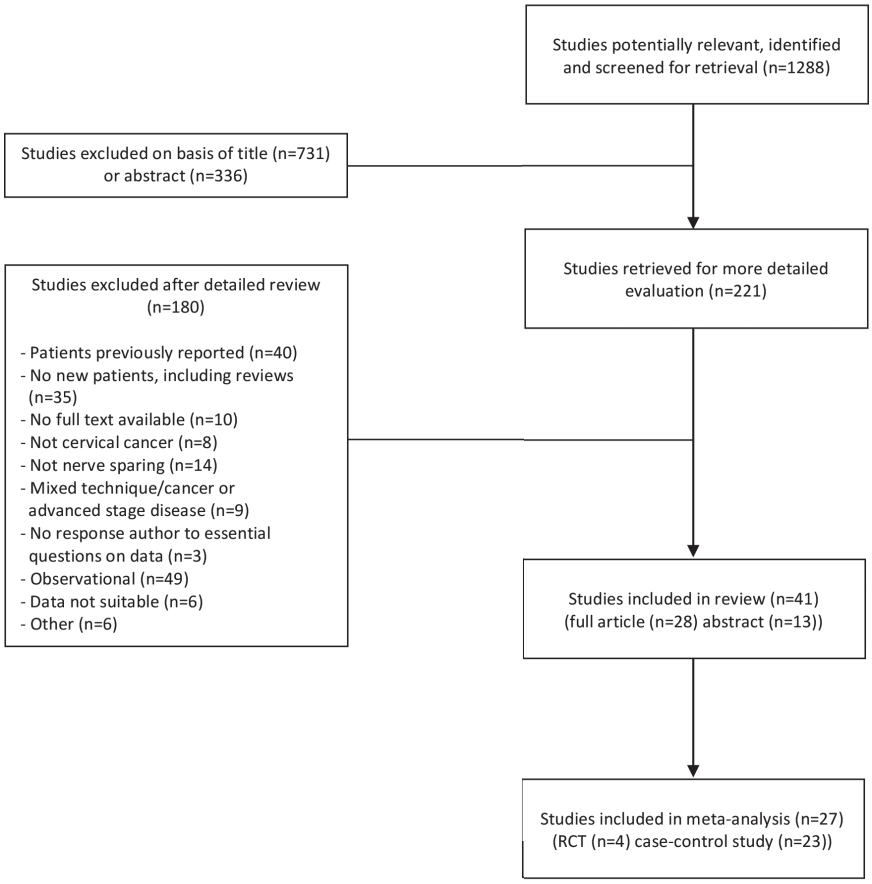


Figure 1. Flowchart review.

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

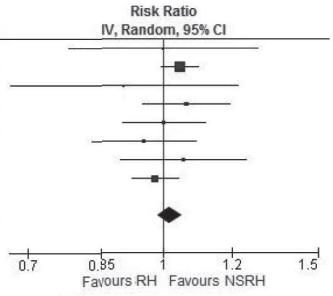
NSRH: nerve sparing radical hysterectomy; RH: conventional radical hysterectomy; * controle group retrospective.

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			

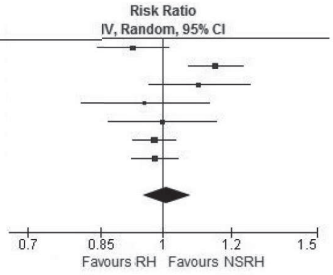
Heterogeneity: Tau² = 0.00; Chi² = 5.07, df = 7 (P = 0.65); I² = 0%
Test for overall effect: Z = 1.09 (P = 0.28)



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)

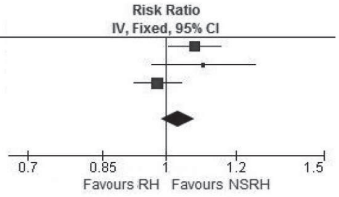
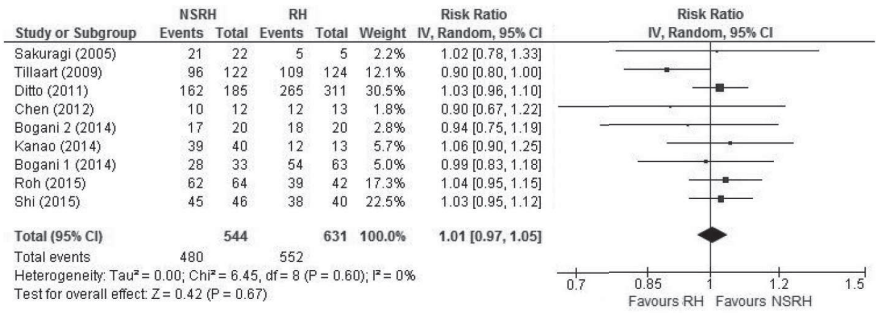


Figure 2. Meta-analysis: Survival.

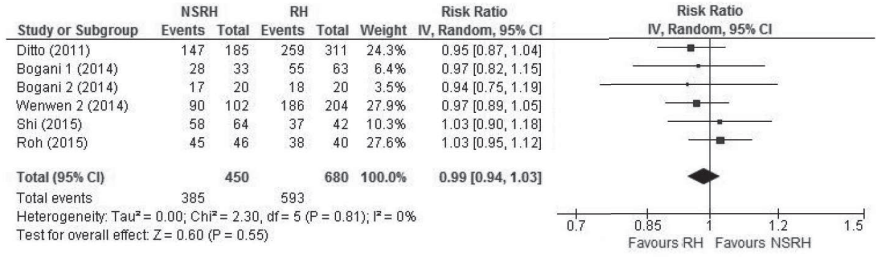
NSRH = nerve sparing radical hysterectomy; RH = conventional radical hysterectomy; Events = number of surviving patients; Total = number of patients in group; IV = inverse variance; CI = confidence interval.

Disease-free Survival

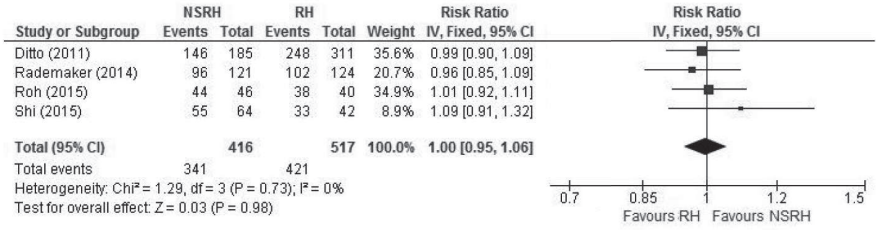
2 year



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.

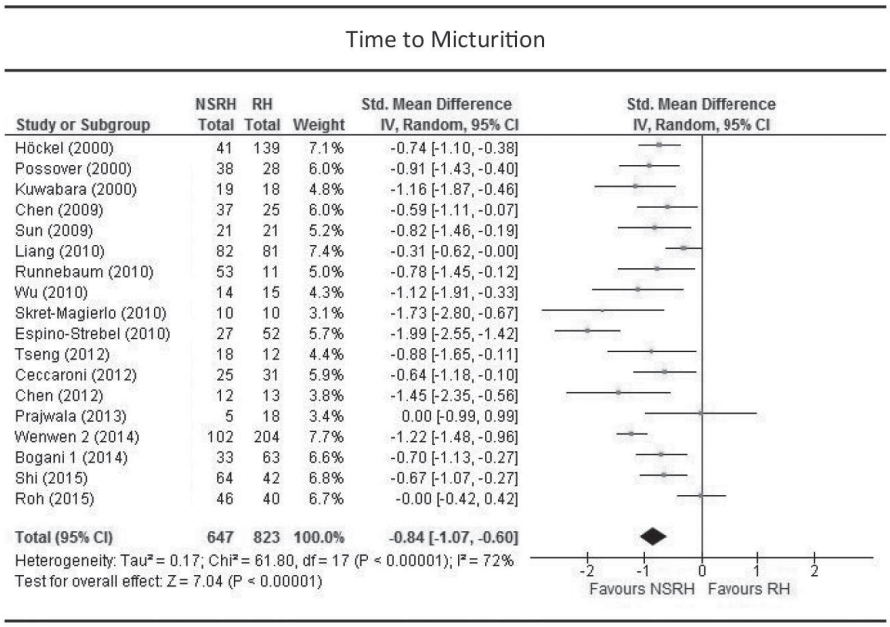


Figure. 3. Meta-analysis: Quality of life.

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

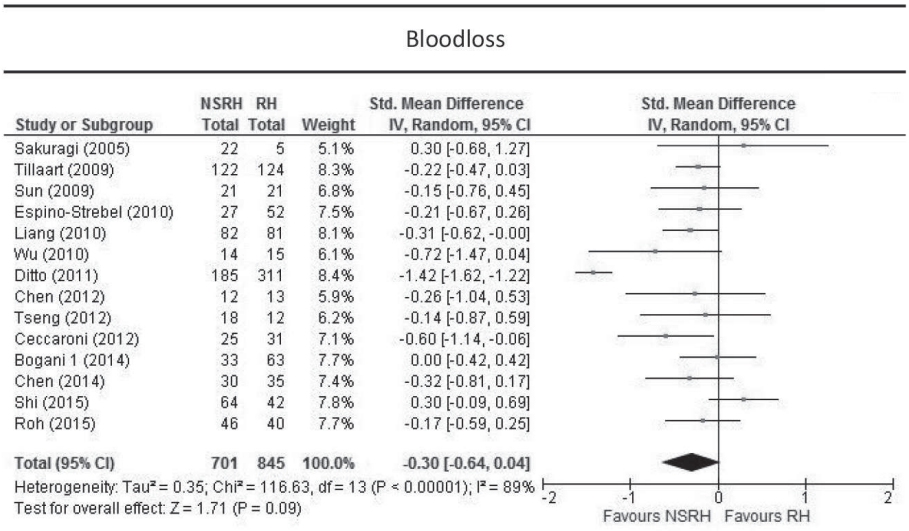


Figure. 4. Meta-analysis: Feasibility/Safety.

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

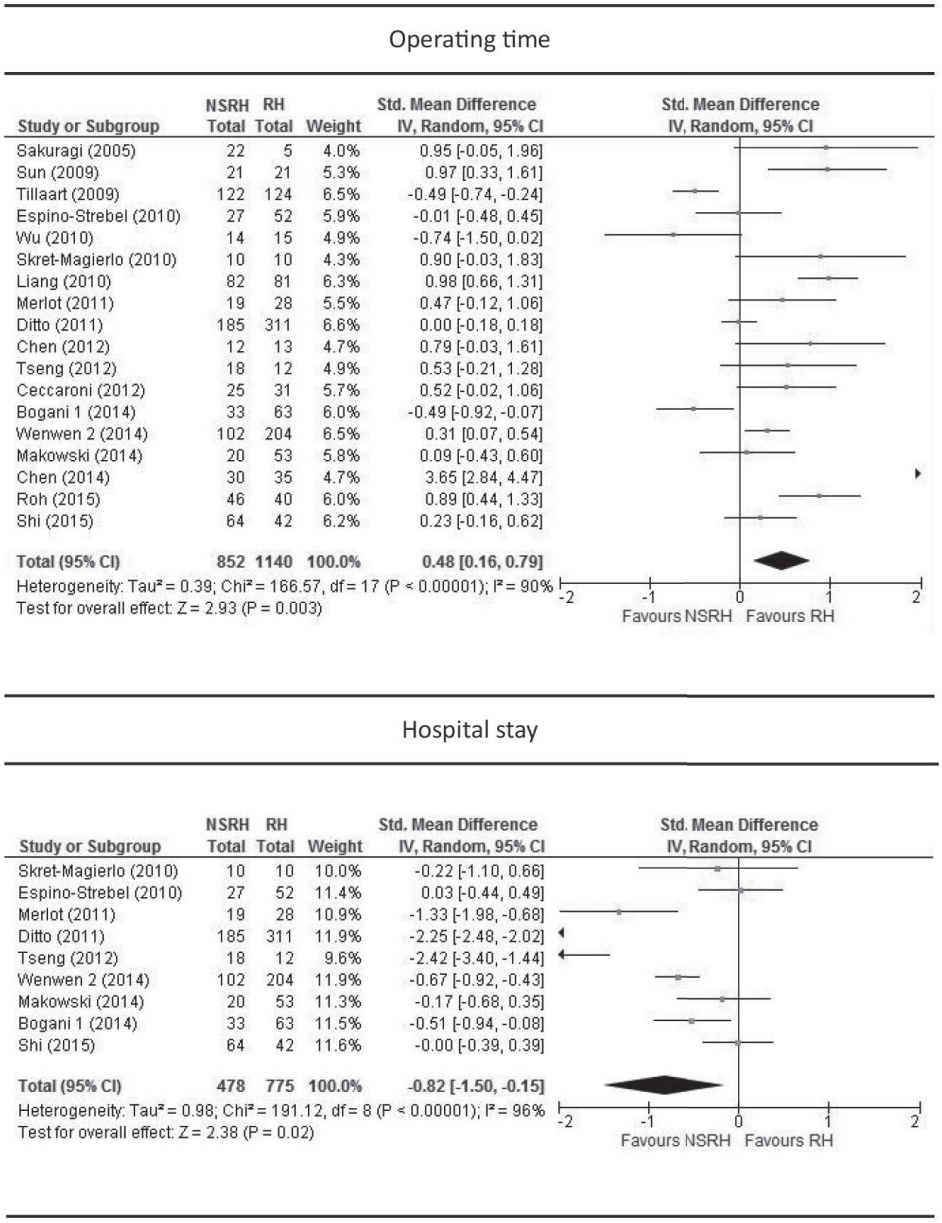


Figure. 4. Continued

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.

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

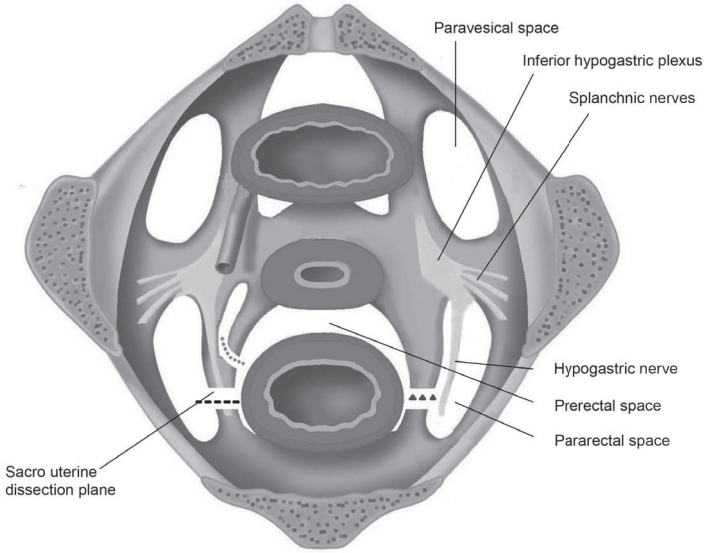


Diagram of the pelvic autonomic nerves in radical hysterectomy: transversal section through the pelvis showing the bladder, uterine cervix, and rectum within the pelvic connective tissues. Autonomic nerves are in yellow.

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)

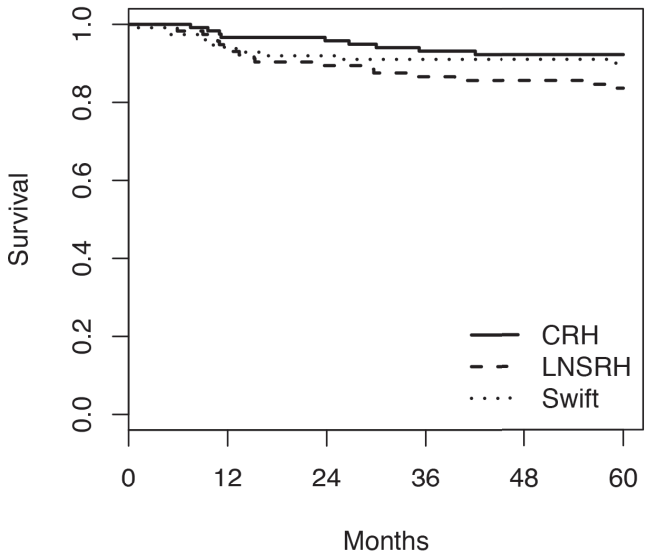
CRH versus LNSRH versus Swift

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

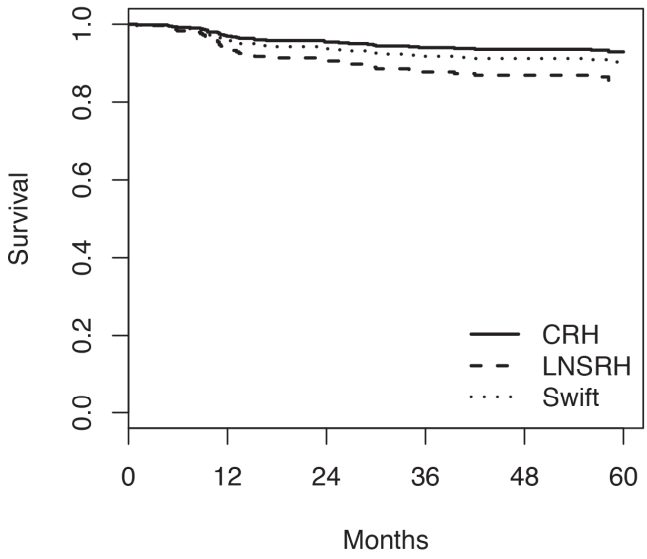
Legend: CRH: conventional radical hysterectomy; LNSRH: Leiden nerve sparing radical hysterectomy; PR: pelvic relapse; EPR: extra pelvic relapse; PRFS: pelvic relapse free survival; OS: overall survival. * comparing CRH, LNSRH and Swift; *** comparing CRH to Swift.** comparing LNSRH to Swift;



2A. Kaplan-Meier curve of PRFS

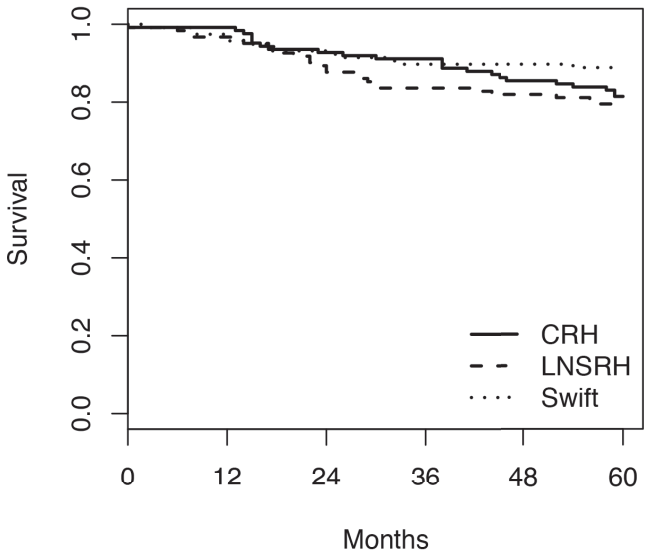
Log-Rank comparing all 3 cohorts: p = 0.116

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



2C. Cox-model based survival curve of PRFS

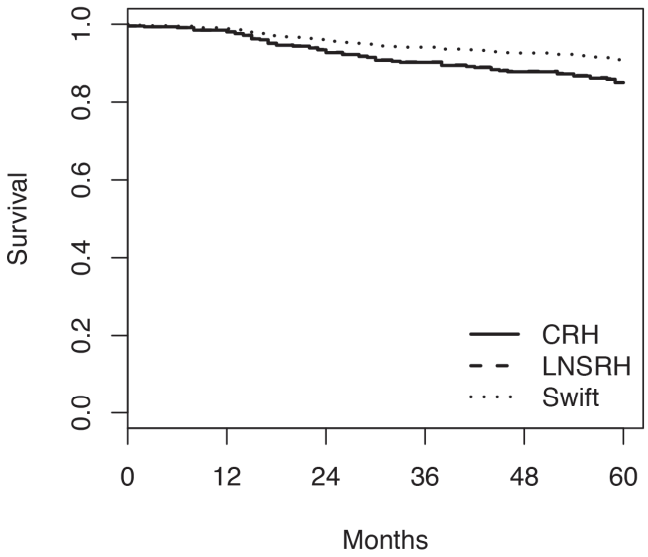
Figure 2. Survival curves of the radical hysterectomy cohorts with respect to 5 year pelvic relapse free survival (PRFS) and 5 year overall survival (OS).



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.

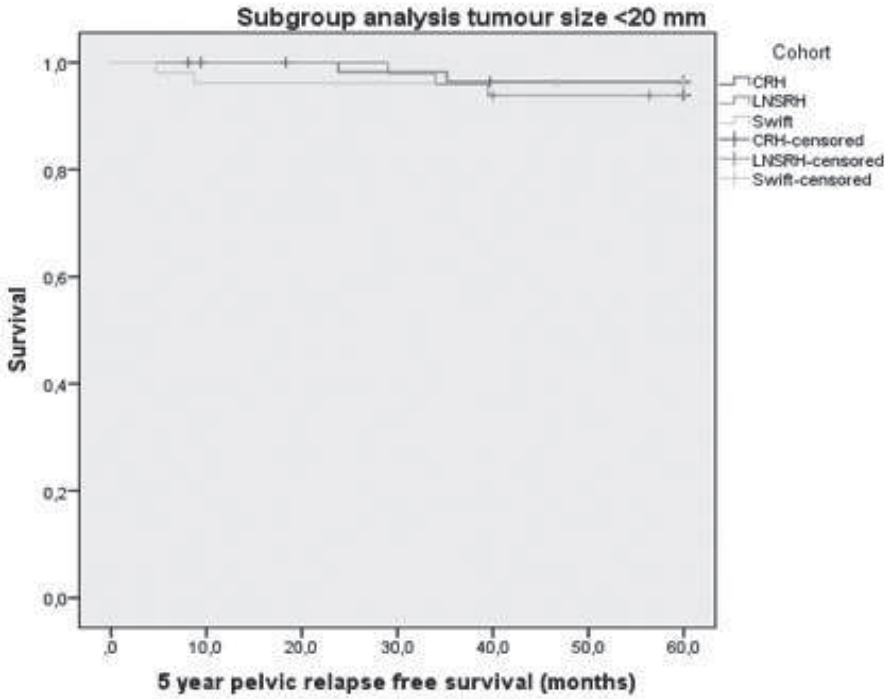
23. Bakker RM, Pieterse QD, van Lonkhuijzen LRCW, Trimbos JBMZ, Creutzberg CL, Kenter GG, et al., editors. An observational controlled study on vaginal blood flow and sexual functioning after early stage cervical cancer treatment. 18th International Psycho Oncology Society Congress; 2016; Dublin.

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

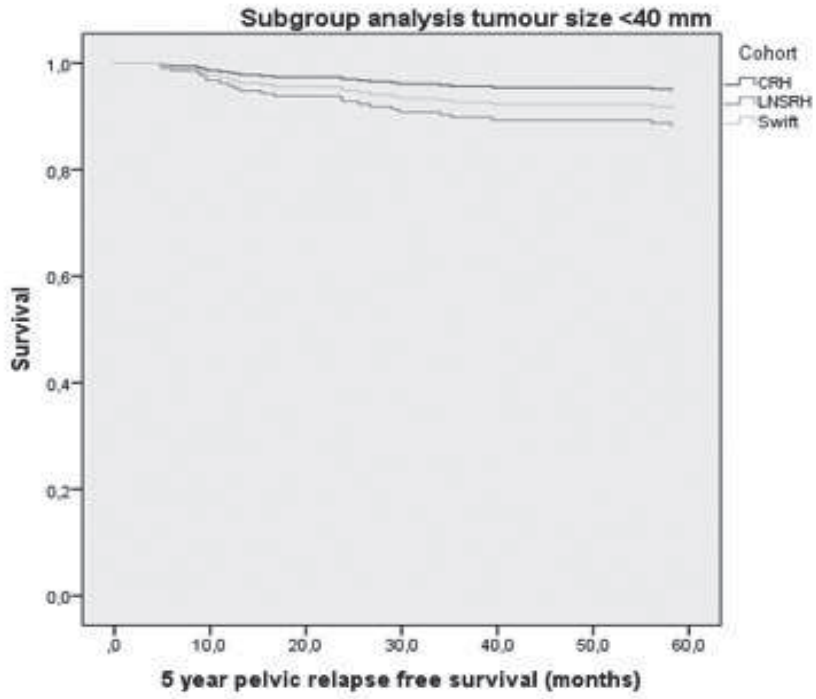


S1.b. Subgroup analysis by size: < 40mm

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

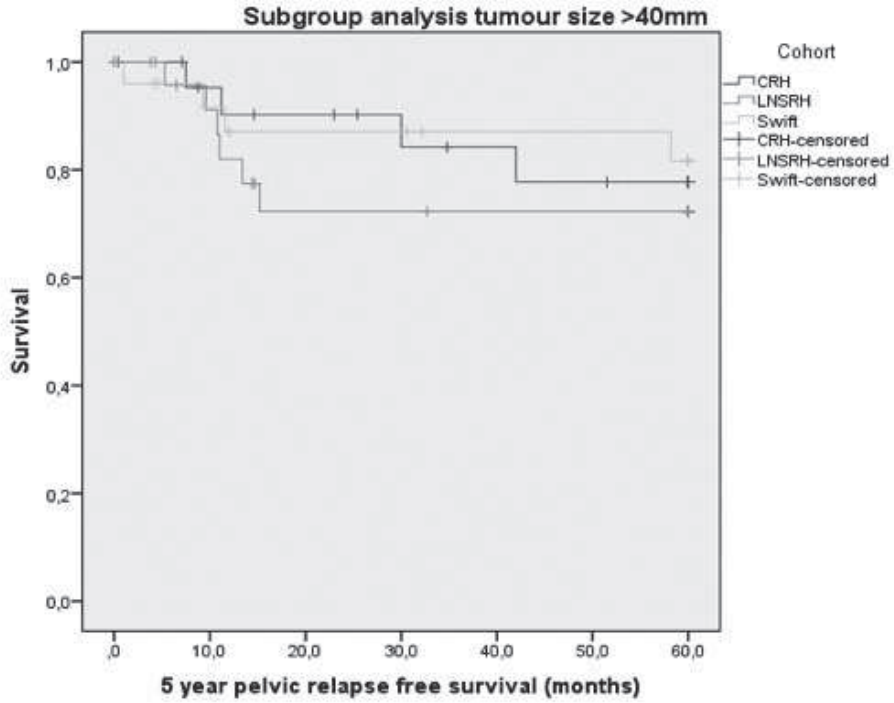


S1.c. Subgroup analysis by size: > 40mm

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

CHAPTER 6

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

A comparative study on feasibility and outcome

Mignon van Gent
Lukas van den Haak
Katja Gaarenstroom
Lex Peters
Mariette van Poelgeest
Baptist Trimbos
Cor de Kroon

International Journal of gynecological Cancer. 2014 May; 24(4): 735-43

CHAPTER 6

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

A comparative study on feasibility and outcome

6.1 ABSTRACT

Objectives

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

Methods

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

Results

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

Conclusions

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

6.2 OBJECTIVES

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

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

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

6.3 MATERIALS AND METHODS

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

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

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

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

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

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

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

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

6.4 RESULTS

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

Table 2. Patient and tumor characteristics and surgical data

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

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

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

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

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

Table 3. Recurrence and survival of NSRAT versus NSRH

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

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

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

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

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

NSRAT: nerve sparing radical abdominal trachelectomy

LVSI: lymph-vascular space invasion

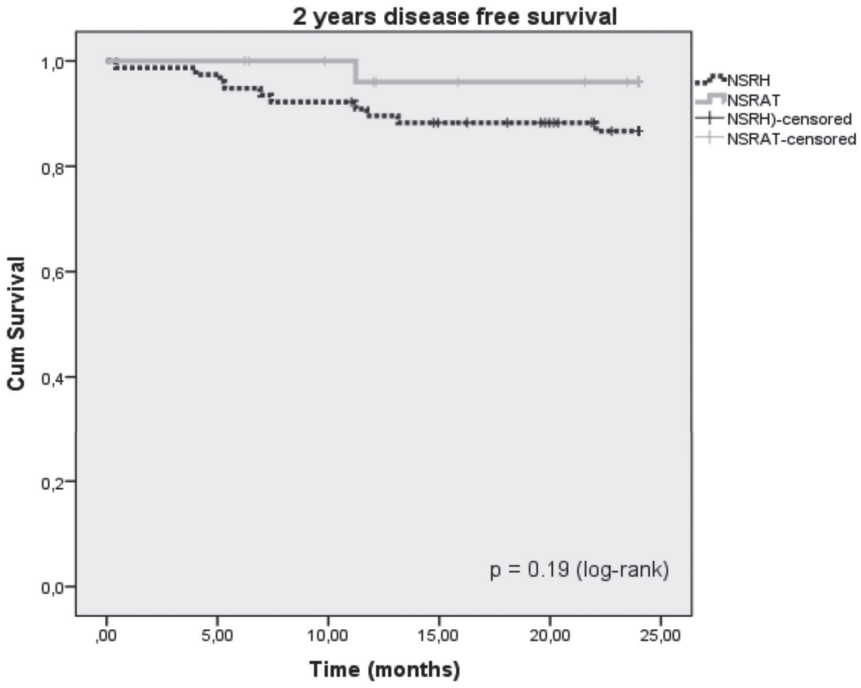


Figure 1. 2 years disease free survival curve

NSRAT: nerve sparing radical abdominal trachelectomy

NSRH: nerve sparing radical hysterectomy

6.5 DISCUSSION

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

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

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

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

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

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

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

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

6.6 REFERENCES

1. 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.
2. 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. Int J Gynecol Cancer. 2006;16(3):1119-29.
3. Bergmark K, Avall-Lundqvist E, Dickman PW, Henningsohn L, Steineck G. Vaginal changes and sexuality in women with a history of cervical cancer. The New England journal of medicine. 1999;340(18):1383-9.
4. Maas CP, Trimbos JB, DeRuiter MC, van de Velde CJ, Kenter GG. Nerve sparing radical hysterectomy: latest developments and historical perspective. Critical reviews in oncology/hematology. 2003;48(3):271-9.
5. 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.
6. Trimbos JB, Maas CP, Deruiter MC, Kenter GG. [Nerve sparing radical hysterectomy in the case of cervical cancer]. Nederlands tijdschrift voor geneeskunde. 2003;147(28):1344-7.
7. Rob L, Halaska M, Robova H. Nerve-sparing and individually tailored surgery for cervical cancer. The lancet oncology. 2010;11(3):292-301.
8. Raspagliesi F, Ditto A, Fontanelli R, Solima E, Hanozet F, Zanaboni F, et al. Nerve-sparing radical hysterectomy: a surgical technique for preserving the autonomic hypogastric nerve. Gynecologic oncology. 2004;93(2):307-14.
9. de Kroon CD, Gaarenstroom KN, van Poelgeest MI, Peters AA, Trimbos JB. Nerve sparing in radical surgery for early-stage cervical cancer: yes we should! Int J Gynecol Cancer. 2010;20(11 Suppl 2):S39-41.
10. Plante M, Gregoire J, Renaud MC, Roy M. The vaginal radical trachelectomy: an update of a series of 125 cases and 106 pregnancies. Gynecologic oncology. 2011;121(2):290-7.
11. Diaz JP, Sonoda Y, Leitao MM, Zivanovic O, Brown CL, Chi DS, et al. Oncologic outcome of fertility-sparing radical trachelectomy versus radical hysterectomy for stage IB1 cervical carcinoma. Gynecologic oncology. 2008;111(2):255-60.
12. Abu-Rustum NR, Sonoda Y, Black D, Levine DA, Chi DS, Barakat RR. Fertility-sparing radical abdominal trachelectomy for cervical carcinoma: technique and review of the literature. Gynecologic oncology. 2006;103(3):807-13.

13. Cibula D, Velechovska P, Slama J, Fischerova D, Pinkavova I, Pavlista D, et al. Late morbidity following nerve-sparing radical hysterectomy. Gynecologic oncology. 2010;116(3):506-11.

14. Hong DG, Lee YS, Park NY, Chong GO, Park IS, Cho YL. Robotic uterine artery preservation and nerve-sparing radical trachelectomy with bilateral pelvic lymphadenectomy in early-stage cervical cancer. Int J Gynecol Cancer. 2011;21(2):391-6.

15. Martin A, Torrent A. Laparoscopic nerve-sparing radical trachelectomy: surgical technique and outcome. Journal of minimally invasive gynecology. 2010;17(1):37-41.

16. Li J, Wang LJ, Zhang BZ, Peng YP, Lin ZQ. Neoadjuvant chemotherapy with paclitaxel plus platinum for invasive cervical cancer in pregnancy: two case report and literature review. Archives of gynecology and obstetrics. 2011;284(3):779-83.

17. de Jongh FE, de Wit R, Verweij J, Sparreboom A, van den Bent MJ, Stoter G, et al. Dose-dense cisplatin/paclitaxel. a well-tolerated and highly effective chemotherapeutic regimen in patients with advanced ovarian cancer. Eur J Cancer. 2002;38(15):2005-13.

18. Benedetti-Panici P, Greggi S, Colombo A, Amoroso M, Smaniotto D, Giannarelli D, et al. Neoadjuvant chemotherapy and radical surgery versus exclusive radiotherapy in locally advanced squamous cell cervical cancer: results from the Italian multicenter randomized study. J Clin Oncol. 2002;20(1):179-88.

19. Delgado G, Bundy B, Zaino R, Sevin BU, Creasman WT, Major F. Prospective surgical-pathological study of disease-free interval in patients with stage IB squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecologic oncology. 1990;38(3):352-7.

20. Trimbos JB, van den Tillaart SA, Maas CP, Peters AA, Gaarenstroom KN, deRuiter MC, et al. The Swift operation: a modification of the Leiden nerve-sparing radical hysterectomy. Gynecol Surgery. 2008;5:193-8.

21. Querleu D, Morrow CP. Classification of radical hysterectomy. Lancet Oncol. 2008;9(3):297-303.

22. Nishio H, Fujii T, Kameyama K, Susumu N, Nakamura M, Iwata T, et al. Abdominal radical trachelectomy as a fertility-sparing procedure in women with early-stage cervical cancer in a series of 61 women. Gynecologic oncology. 2009;115(1):51-5.

23. Bernardini M, Barrett J, Seaward G, Covens A. Pregnancy outcomes in patients after radical trachelectomy. American journal of obstetrics and gynecology. 2003;189(5):1378-82.

24. Pareja R, Rendon GJ, Sanz-Lomana CM, Monzon O, Ramirez PT. Surgical, oncological, and obstetrical outcomes after abdominal radical trachelectomy - a systematic literature review. Gynecologic oncology. 2013;131(1):77-82.

25. Beiner ME, Hauspy J, Rosen B, Murphy J, Laframboise S, Nofech-Mozes S, et al. Radical vaginal trachelectomy vs. radical hysterectomy for small early stage cervical cancer: a matched case-control study. Gynecologic oncology. 2008;110(2):168-71.

26. Lanowska M, Morawietz L, Sikora A, Raber G, Mangler M, Speiser D, et al. Prevalence of lymph nodes in the parametrium of radical vaginal trachelectomy (RVT) specimen. Gynecologic oncology. 2011;121(2):298-302.

27. Speiser D, Mangler M, Kohler C, Hasenbein K, Hertel H, Chiantera V, et al. Fertility Outcome After Radical Vaginal Trachelectomy: A Prospective Study of 212 Patients. Int J Gynecol Cancer. 2011.

28. Fagotti A, Gagliardi ML, Moruzzi C, Carone V, Scambia G, Fanfani F. Excisional cone as fertility-sparing treatment in early-stage cervical cancer. Fertility and sterility. 2011;95(3):1109-12.

29. Covens A, Rosen B, Murphy J, Laframboise S, DePetrillo AD, Lickrish G, et al. How important is removal of the parametrium at surgery for carcinoma of the cervix? Gynecologic oncology. 2002;84(1):145-9.

30. Rob L, Pluta M, Skapa P, Robova H. Advances in fertility-sparing surgery for cervical cancer. Expert review of anticancer therapy. 2010;10(7):1101-14.

31. Maneo A, Sideri M, Scambia G, Boveri S, Dell'anna T, Villa M, et al. Simple conization and lymphadenectomy for the conservative treatment of stage IB1 cervical cancer. An Italian experience. Gynecologic oncology.

32. Maas CP, Kenter GG, Trimbos JB, Deruiter MC. Anatomical basis for nerve-sparing radical hysterectomy: immunohistochemical study of the pelvic autonomic nerves. Acta obstetricia et gynecologica Scandinavica. 2005;84(9):868-74.

33. 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.

34. Soderini A. Is the nerve sparing (NS) a new standard in radical hysterectomy (NSRH) for cervical cancer (CC)? International Gynecological Cancer Society 12th Biennial Meeting, Bangkok, Thailand; 25 October 2008.

35. 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.

36. Neoadjuvant Chemotherapy for Cervical Cancer Meta analysis Collaboration. Neoadjuvant chemotherapy for locally advanced cervical cancer: a systematic review and meta-analysis of individual patient data from 21 randomised trials. Eur J Cancer. 2003;39(17):2470-86.

37. Plante M, Lau S, Brydon L, Swenerton K, LeBlanc R, Roy M. Neoadjuvant chemotherapy followed by vaginal radical trachelectomy in bulky stage IB1 cervical cancer: case report. Gynecologic oncology. 2006;101(2):367-70.

38. Rydzewska L, Tierney J, Vale CL, Symonds PR. Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer. Cochrane database of systematic reviews (Online). 2010(1):CD007406.

6

CHAPTER 7

General discussion and recommendations

GENERAL DISCUSSION AND RECOMMENDATIONS

The idea of tailoring therapy for early stage gynaecological cancers was formed on the basis of the disruption of quality of life of a specific group of young patients after treatment. Patients with low-grade endometrial cancer derailed psychologically after having a hysterectomy without fulfilling their child wish. These patients represent a group of young women suffering from gynaecological cancer. The cancer is not only worsening the life expectancy on the long run of these women, but also influences their here and now. This group of patients is a vulnerable group of women, for whom therapy according to default may not automatically be the best choice. In these women fertility and sexuality are traditionally among substantial elements of perceived quality of life.
The fact that life after treatment is of importance was emphasized by Michael Porter of the Harvard Business School, who introduced the concept of value based healthcare. Value is herein defined as the patient health outcomes per dollar spent. He states that outcomes of treatment should be seen in a wider perspective than survival only, and should be evaluated over the full cycle of care. The degree of health after treatment, the kind of recovery achieved and the prices in life patients have had to pay, need to be evaluated on an individual basis. Once these considerations are taken into account prospectively at the time of discussing treatment options, and decisions are made, it will result in a completely different and innovative kind of healthcare: value based healthcare. [1]
There are plenty of developments in improving quality of life for patients with early stage cancer, without compromising survival outcomes. The next step is to invest in knowledge on patient related outcome measurements that are really significant for each individual patient. [2] In doing so, the focus should not be directed at maintaining physiological functions, but also on self-assesed functioning and individually specified quality of life. In this thesis we aimed to study this practice, the possibilities of this practice and the oncological outcome of this practice in order to take a step forward in tailoring therapy for young women suffering from gynaecologic malignancies.

PART 1 - LOW-GRADE LOW STAGE ENDOMETRIAL CANCER.

In the search to improve quality of life after treatment for young women with endometrial cancer literature is scarce and information scattered. Conservative treatment of endometrial cancer in which the uterus is left in situ and the tumour is treated with hormones is the most widely used way of fertility preserving therapy. The available literature shows several promising papers, but it lacks an overview to establish a treatment plan. This lack of fundament has led to performing such a review and it is described in **chapter 2.**

In over 600 patients, described in more than 35 studies, the response rate to hormonal treatment was 78 %. However, the recurrence rate was still 30 to 40 %. [3-5] Recurrences were usually treated by hysterectomy and in some cases by repeating progesterone treatment with promising results. [6, 7] Despite these rather optimistic figures there were 6 patients with progressive diseases and four women died of disease after being treated with progesterones. [8-13] Unfortunately, pregnancy outcomes were not systematically reported. The most complete overview was written by Gallos et al., showing a pooled live birth rate of 28% [95% CI 21.6-36.3] with better outcomes for patients treated with assisted reproduction techniques compared to patients with spontaneous conception: 39.4% versus 14.9% respectively. [3]
Most patients were treated with medroxyprogesterone (MPA).
Synthetic progestins, given continuously or cyclically, suppress epithelial proliferation. The rate of mitosis decreased due to the inhibition of glandular proliferation, which is thought to be the treatment effect of progesterone on endometrial intra-epithelial neoplasia (EIN) and low-grade endometrial cancer. [14] We must conclude that the literature is scarce and that the available studies are mostly case-series. Moreover, we were not able to exclude publication bias. However, the results of the literature review in **chapter 2** give a complete overview, providing the best evidence available to serve as a basis for a Dutch protocol to treat early endometrial cancer conservatively (appendix 1). Since conservative treatment was already incidentally administered to patients, the protocol, from that moment on, could guide the clinician through the steps of this therapy, therewith tailoring it in a more controlled and uniform way. The protocol was introduced to the Dutch Gynaecologic Oncology Society and adopted nationwide, and further research was initiated as can be seen in **chapter 3**. Since publication bias is lurking and randomised controlled trials and case-control studies are lacking, international collaboration and concomitant registration is mandatory. Since improving quality of life after treatment is the reason for deviating from the golden standard, registration of these results cannot be omitted. Fortunately, some promising initiatives have been introduced lately. One of these initiatives is the international collaboration through the release of the ESMO-ESGO-ESTRO guideline in 2015 [15], which has great similarities to the Dutch protocol that was written in 2008. The specifics of the collaboration are to be evaluated and discussed.

Progesterone

The dosage and administration method of progesterone remains subject of debate. For medroxyprogesterone (MPA) we know 200 milligrams daily are just as effective and cause less side effects compared to 1000 milligrams a day. [16] Because this study was studied on advanced endometrial cancer, we should be careful extrapolating these findings for early stage low-grade endometrial cancers since the response might be differ-

ent. The ESMO-ESGO-ESTRO guideline proposes to use 400 – 600 milligrams a day. [15, 17] However, no evidence is provided to justify this. Penner suggests to adjust the dosage of progesterone to the patient's BMI. [18] A dose of more than 500 milligrams a day leads to inhibition of the adrenal cortex resulting in less production of Adrenocorticotropic hormone (ACTH) and hydrocortisone. This in turn, results in a risk of fluid retention and Cushing's syndrome. [19] Progesterone treatment can lead to reduced glucose tolerance. Endometrial cancer patients suffer from a disease which is by nature thrombogenic. However, no studies were found describing thrombo-embolic events among patients on progesterone, but the side effects were not extensively described in all studies. Only one study added prophylactic aspirin to the progesterone treatment. [8] A positive family history and obesity lead to a higher chance of thrombosis. [20] The risk of thrombosis has to be weighed on an individual basis in making the decision for progesterone therapy and considerations for prophylactic medication can be made.

Choice of treatment modality

Dose response studies are lacking for progesterones in endometrial cancer, but in most studies, patients are treated with medroxyprogesterone. Experience with medroxyprogesterone for other indications is abundant. Therefore, our protocol and also the ESMO-ESGO-ESTRO guideline continue advising medroxyprogesterone until a study proves otherwise. [15] Previous mouse model studies have proven to be useful to perform a detailed investigation on the biological behaviour, resistance to and hormonal modulation of progesterone therapy. There is a need to conduct more of these studies to improve and increase knowledge of the effect of progesterone in humans. [21] Other options besides medroxyprogesterone and megestrol acetate (both so called C21 steroids) are norethisteron (NET) and lynestrenol (LYN) (C19 steroids) since they have the same effect on mitosis as MPA. [14] Cyclic administration of C19 steroids leads to destruction of the whole endometrium including the stratum basale. This results in removing stem cell as well. This may allow lower dosages. [22] However, these C19 steroids have not been evaluated for the indication of fertility preservation in endometrial cancer.

The role of the levonorgestrel releasing intra uterine device (IUD) is still to be investigated in more detail but results show potential. [23, 24] Whether it will be able to replace oral progesterone treatment or better serves as adjuvant therapy, during or after oral progesterone therapy, is still under investigation: The (KGOG) 2006 (NCT01234818) run by the Korean Gynecologic Oncology Group investigates levonorgestrel IUD for the treatment of endometrial intraepithelial neoplasia [25] and the KGOG2009 (NCT01594879) investigates MPA + levonorgestrel IUD to treat early stage endometrial cancer. [26] At the MDAnderson Cancer Center, a Phase II study is conducted (NCT 00788671), analysing 70 patients treated with levonorgestrel IUD for complex atypical hyperplasia and grade 1 endometrial cancer.

In this thesis the costs of the treatment with progesterones have not been evaluated. Progesterone itself is a low cost medicine and as such fits well into the idea of value based healthcare as described by Porter where acquired benefits and costs of therapy should be weighed on an individual basis. [1]

Pre-treatment clinical staging

It is important to minimize risks before treatment is started. Fertility preserving therapy should, at this stage, only be offered to women with low-grade, clinically estimated stage IA endometrial cancer. Imaging, like trans-vaginal ultrasound and contrast enhanced Magnetic Resonance Imaging (MRI), can help with assessing myometrial involvement and excluding both adnexal masses and pathological enlarged lymph nodes. [27, 28] One can consider performing a diagnostic laparoscopy to exclude adnexal disease, since the chances of having a simultaneous ovarian cancer is 4.3 %. [27] However, this remains controversial at this moment since this procedure can have false negative results and taking ovarian biopsies carries a significant risk of sampling error. [29]

Histopathological analysis

Diagnosis is done by histopathological analysis, obtained at diagnostic hysteroscopy in the in- or outpatient clinic. An abnormal lesion can be resected and abnormal areas of the endometrium can be biopsied. Afterwards a (micro)-curetting is performed. To increase the reliability of the histopathological result, central pathological revision of the tissue sample should be performed by a gynae-pathologist. [30]

Since the Dutch protocol was published [31], many clinicians have acknowledged to be satisfied by using the protocol, admitting being unsecure and reluctant to treat endometrial cancer patients conservatively, before. Patients are registered centrally and if needed patients can be referred to specialised centres. In our experience patients who received explicit counselling and strict guidance, do very well understand the implications of their choice. In the Netherlands, using this approach, a small cohort of patients treated with progesterone only was established, enabling the start of the search for response predictors at a molecular level.

Response predictors

Previous celline models have suggested that the therapeutic effect of progesterone relies on the pro-proliferative Wnt or PI3K/Akt signaling pathways. The hypothesis in **chapter 4** of this thesis was that the Wnt- and PI3K/Akt pathways are constitutively activated if genetically altered, and therefore progesterone will not be effective. Data was collected from 11 patients treated with progesterone for low-grade endometrial cancer. Tissue analysis was performed, before, during, and after treatment, resulting in a unique

collection of serial endometrial tissue under treatment. Our results showed that, despite the presence of activating mutations in Wnt- and/or PI3K/Akt-pathways, patients still responded to progesterone treatment. This finding in a small series indicates that progesterone treatment, at least in part, acts through mechanisms independent of these oncogenic pathways. An alternative explanation for these findings may be that progesterone has pro-apoptotic effect on the proliferative cancer cell clone that is dominant as compared to the anti-proliferative action. Previous studies have provided mechanistic evidence on how progesterone induces apoptosis through upregulation of Fas/FasL or decreasing Bcl-2 protein expression and function. [32] Therefore, it would be of interest to direct future studies towards genes involved in the apoptotic pathway. It is plausible that alterations in this pathway influence the action of progesterone and therefore these may turn out to be as informative as predictive markers.
In addition to the molecular analysis, we have also performed a comprehensive morphologic description of sequential curettings in these women under progesterone treatment. This elucidated that morphological response is accompanied by disappearance of the earlier present genetic alterations. This finding would support a role for pro-apoptotic progesterone action, as treatment results in the disappearance of the malignant clone and consequent replacement of endometrial glands without genetic alterations. A significance limitation of this study is the variety of treatment regimes, which makes it hard to draw firm conclusions. Therefore, this pilot study was descriptive in nature. However, it does form a basis for further investigations.

The way forward

For follow-up work, it appears essential to start with establishing a uniform treatment regime including uniform follow up procedures. We have therefore provided the above described protocol that can serve this purpose. Use of this protocol will result in a uniform cohort of patients of whom tumour tissue will be very valuable for translational studies directed at identifying predictive markers. This will enable us to move the field of fertility sparing treatment in endometrial cancer from an experience based approach towards an evidence based approach, with opportunities for further improvement of tailored therapy.

FUTURE RESEARCH DIRECTION

In 2016 Wan et al. published a research agenda on endometrial cancer. [33] They followed a priority setting methodology starting with an online survey yielding endometrial cancer survivors, caretakers and professionals. The reason for performing this research was the rising incidence of endometrial cancer, while experiencing a lack of public awareness and consequently a shortage of funding for research in this field. Personalising

care and quality of life after treatment were of top priority for the patients. After the full selection process was followed, a top ten of research questions was formed. One of these questions was: Can we predict at the time of diagnosis which endometrial cancers and precancerous lesions will respond to hormone treatment? These data support our research line and show that our main objective is considered relevant by health care professionals and endometrial cancer patients alike.

The above-mentioned proposition to form an internationally uniform treatment will support the goal of making it possible to distinguish responders from non-responders. Modern biobanks holding both fresh frozen tissue and paraffin fixed tissue and maybe even dissected stromal fraction from fresh tissue, will open doors to translational research. It will be possible to look at copy number alterations, methylation profiles, and to perform whole genome sequencing and next generation sequencing.

The molecular landscape of endometrial cancer is receiving more and more road signs. For research questions focussing on a specific group of patients, e.g. fertility preservation, the doctor needs to find out which sign to follow. The former division between type I and II endometrial cancer might not suffice anymore. Different subheadings as seen in the TCGA data and data from Stelloo et al. change the view on subtypes of endometrial cancer. [34, 35] In the search to define which patient is suitable for fertility sparing treatment, new subtypes need attention.

It is important to find the markers that can help construct a prediction model in which negative and positive features of the patient and the disease can be incorporated. This will reduce treatment failure and incidence of recurrent disease before completed family has been reached.

Together with collecting tissue, patient characteristics will need to be uniformly registered. In this way, translational research can really build a bridge between basic science and the clinic where the patient and doctor are deciding how to tailor the therapy. Besides focussing on which medication is the best way to cure cancer with sparing fertility and how to improve the diagnostic track, other issues like life style changes (exercise and weight loss) will need attention. With the introduction of quality of life assessments and unifying reporting of data, research in this field will better reach its goal: tailoring therapy without compromising patients' safety.

PART 2 - NERVE - SPARING AND FERTILITY - SPARING SURGERY FOR EARLY STAGE CERVICAL CANCER.

As discussed in the introduction of this thesis, nerve-sparing surgery for early stage cervical cancer has supporters and opponents. Previously reviews on this topic have been published. Rob et al. [36] focussed mostly on the anatomy and the different techniques.

Basaran et al. calculated what statistical numbers needed to be reached for proof of non-inferiority of the nerve sparing radical hysterectomy compared to the non-nerve sparing modalities. [37] Finally and most recently, Long et al. [38] published an interesting review, proving better bladder function after nerve sparing surgery. These were all very valuable studies, but none of the reviews focussed on oncological outcomes like survival or disease-free survival. To be able to judge the oncological safety in tailoring therapy, survival outcomes need to be taken into account. This lack in literature has led to the systematic review and meta-analysis in **chapter 4**. In our meta-analysis we looked at both safety and feasibility of nerve sparing surgery. Secondarily we evaluated quality of life (QoL) issues. 41 Studies were selected for review, comparing conventional radical hysterectomy (RH) to nerve sparing radical hysterectomy (NSRH). 27 Studies were found suitable for meta-analysis. The 2, 3 and 5-year (disease-free) survival of conventional radical hysterectomy was equal to that of nerve-sparing radical hysterectomy. The operating time was 20 minutes longer for NSRH, but hospital stay was 2.4 days shorter. Post-operative time to spontaneous micturition was significantly shorter for the NSRH cohort, improving QoL and shortening the duration of hospital stay. All other data on QoL were found to be heterogeneous and therefore not suitable for meta-analysis. The meta-analysis also provides an overview of results on these issues as well as general QoL, that were too heterogeneously reported to perform a meta-analysis on.
To evaluate the oncological outcome of the nerve sparing procedures performed at our institution, a comparative cohort study has been performed and described in **chapter 5.** Before 2000 a PIVER III radical hysterectomy was performed for early stage cervical cancer. After extensive anatomy analysis on cadavers and learning from Japanese colleagues [39], in 2000 the Leiden Nerve Sparing Radical hysterectomy (LNSRH) was introduced. New insights and promising results of the resection of the morphogenetic unit described by Höckel, the idea of the total mesometrial resection (TMMR) [40] formed the basis to modify the LNSRH to the nerve sparing Swift procedure in 2006. The latter being more radical in the resection planes of the parametrium and the sacro-uterine ligaments, while allowing more accurate sparing of the hypogastric and splanchnic nerve fibers. Long term oncological outcomes were compared between 3 cohorts: the conventional RH (CRH) cohort, the LNSRH cohort and the Swift cohort. 362 Patients were analysed. There were no significant differences in 5 –year pelvic relapse free survival, nor in overall survival between the three cohorts ($p = 0.116$). In the multivariate analysis, correcting for FIGO > 1b2, LVSI, lymph node metastases, and infiltration depth of more than 15 mm, the two nerve sparing modalities did not influence the hazard on developing a pelvic recurrence when compared to the reference (CRH cohort). The hazard ratios for death within 5 years did not differ either: 0.989 ($p = 0.970$) for LNSRH and 0.590 ($p = 0.140$) for Swift. After performing a Cox-regression model analysis we found that the 5-year OS was significantly better for the Swift cohort compared to the former LNSRH

cohort (p = 0.040) although the PRFS was not (p= 0.202). The reason for this difference can not completely be deducted from the data available in the studies, but it might be explained by improvement of pre-operative staging (and consequently less women with distant metastases at time of surgery in the Swift cohort), or improvement of adjuvant therapy over time. Subgroup analysis with regard to tumour size (smaller than 2 cm, smaller than 4 cm or larger than 4 cm) showed a non-significant improved 5-year overall survival rate of 79.2% for the Swift cohort, versus 52.2% for CRH and 57.7% for LNSRH (p = 0.125) for tumours larger than 4 cm. From the data of the systematic review and meta-analysis in **chapter 4** and the cohort study in **chapter 5**, we conclude that nerve sparing surgery is safe in early stage cervical cancer. Preservation of nerves should not lead to a concession on oncological outcome. Since sparing the autonomic nerves in radical hysterectomy results in significantly better functional outcome with regard to sexual- and bladder function, as demonstrated in our review (**chapter 4**) and by many others, nerve sparing radical hysterectomy should be considered standard practise in women with early stage cervical cancer.

Like in endometrial cancer, fertility preservation is an important issue in young women with cervical cancer. This has, parallel to others sharing the same interest, resulted in the development of a nerve sparing radical abdominal trachelectomy (NSRAT). This surgical approach comprises two of the major QoL issues in patients with cancer and gynaecological cancer in particular: fertility and sexuality. In **chapter 6** the oncological and fertility outcomes of the NSRAT for fertility sparing treatment of early stage cervical cancer (FIGO Ia-Ib2). It is a case-control study in which a step-by-step description of the NSRAT is provided as it is performed at the LUMC. One part of the technique is to selectively spare the uterine artery. This is done with the idea to improve pregnancy outcomes by maintaining complete uterine vascularisation. More recently, however, some studies have not shown any benefit from preserving the artery, although numbers are low. [41, 42] Oncological outcomes of patients treated with the fertility sparing NSRAT were compared to the outcomes of patients receiving a NSRH in the same period. There was no significant difference in recurrence rates of 7.4 % versus 14.3% (p = 0.35) for NSRAT and NSRH respectively nor 2 and 5-year disease-free- and overall survival. In the NSRAT cohort 1 patient (1/28) died 15 months after surgery. In the NSRH cohort 2 women died of disease (2/77) after 14 and 28 months. We also looked at the pregnancy outcomes of the NSRAT cohort. The overall pregnancy rate for NSRAT patients who attempted to conceive was 52.9%. There were 14 pregnancies in 9 women, all resulting in term deliveries. The fact that there were no preterm deliveries is remarkable and is better than literature describes, reviving the idea that sparing the uterine arteries might positively influence pregnancy outcomes. Impaired blood supply is thought to be causal for less placental function, higher risk of premature rupturing of the membranes and premature labour.

[43, 44] Two miscarriages occurred in the patients who were pregnant at time of surgery, no miscarriage occurred in the pregnancies of the patients who conceived after surgery. At the time of closure of our follow-up, 8 patients were either within the process of in vitro fertilisation or awaiting spontaneous pregnancy. Three patients (tumour sizes: 40, 40 and 42 mm) were successfully treated with neo-adjuvant chemotherapy for reduction of tumour size before trachelectomy and two of them became successfully pregnant. Literature on survival outcomes and pregnancy rates after abdominal trachelectomy is relatively scarce. Pareja et al. has performed a literature review on this topic, identifying 485 patients treated by radical abdominal trachelectomy (RAT) with a median time to follow-up of 31.6 months (range 1-124). 3.5 % had recurrent disease and two patients (0.4%) died of disease. 38% attempted to conceive, of whom 59.3% got pregnant. [45] These data match with the results of our cohort presented in **chapter 6**. Plante et al. performed a literature review on tumours larger than 2 and smaller than 4 centimetres. [43] They compared the results of the RAT to upfront neo-adjuvant chemotherapy (NACT) followed by less radical cervical surgery (e.g. cone-excision or simple trachelectomy). They found 3 studies, comprising 136 patients treated with an abdominal radical trachelectomy. The recurrence rate was 4.1 % and death rate was 1.6%. 95 of these 136 patients (69%) were eventually successfully treated while having fertility preserved. Only 40 out of 95 patients (42%) attempted to conceive with 16 pregnancies leading to 8 babies born (2 preterm, 6 term). The 5 studies on NACT followed by fertility sparing surgery describe 77 patients. The recurrence rate was 7.2% and the death rate was 2.9%. 62 out of 77 (80%) had a successful fertility sparing treatment. 28 of these 62 (45%) tried to conceive resulting in 35 pregnancies and 24 take home babies (11 preterm, 13 term). Since recurrence and death rate do not differ, but successful fertility preservation is higher in the NACT- followed by less radical cervical surgery group, this approach is promising. The benefit of NACT on fertility and pregnancy outcomes is supported by the review by Bentivegna et al. [46] They found a pregnancy rate of 44 % versus 77 %, live birth rate of 68% versus 76 % and prematurity rate of 57% versus 15% for respectively RAT and NACT followed by fertility sparing surgery. The low percentages of patients attempting conception after fertility sparing treatment has never been thoroughly analysed, but should be included in future research.

We conclude that in the comparative study in **chapter 6** (28 patients in the NSRAT cohort) and in literature, the numbers are still small. The 100 % term birth rate in our cohort is remarkable and promising compared to the 15 – 57% described in literature. [43, 45, 46] Fertility sparing treatment for early stage cervical cancer is rare, and therefore it is important, as well as for low stage endometrial cancer, to collaborate on national and international level and to combine databases so results can be evaluated, leading to better care for the patient. In this light, it is promising to find several institutions collaborating in order to write a study protocol for fertility sparing treatment in patients with

early stage cervical cancer and the wish for fertility preservation. The results of this study are highly valuable in the so highly needed process of value based healthcare for this group of patients.

Considerations

Early stage cervical cancer and low-grade, low stage endometrial cancer in pre-menopausal women are rare tumours. Attempts to perform research with the goal to improve quality of life after surgery often result in frustration with the researcher, due to the fact that numbers needed for randomised controlled trials will almost certainly, never be reached. One needs to rely on reviews, observational studies, case-series and case reports. Despite strong efforts, results of these studies will not completely confirm safety of new treatment strategies. Within this framework, the focus of the research in this thesis on endometrial and cervical cancer is to improve quality of life after therapy without deteriorating the oncological outcomes.

It is known that surgeon and hospital volume of procedures are considered to enhance patient safety with regard to well established therapies. However, other aspects such as case mix, surgical skills, experience and innovation must be considered as well when measuring quality of care. [47] Recommendations regarding surgical innovation have been made to enhance safety, quality and efficiency in surgical care. [48] Moreover nationwide prospective registries, like the registries in the Dutch Institute for Clinical Auditing (DICA), are mandatory to improve quality of care and outcomes. The IDEAL collaboration tries to take innovation and quality of surgical care to a higher plan by, among other initiatives, surgical trials and registries. A recent editorial about the multiple benefits of surgical registries has stressed the need for national and international collaboration in improving quality of care as suggested in this thesis with regard to fertility preservation in both endometrial and cervical cancer. [49]

It would be interesting to evaluate what Value Based Healthcare means in The Netherlands for patients with endometrial and cervical cancer. What are the priorities for the patients, carers, doctors, researchers, insurers and last but not least, governmental bodies? [33] The results of this evaluation might draw focus and funding to a field of research with a multi supported goal to improve the patient's health, instead of it being drawn to the regularly funded fields.

Values in life are personal and therefore cannot be generalized. To be able to tailor therapy for patients with low-grade endometrial cancer and early stage cervical cancer, knowledge of individual patients' values in life is indispensable but knowledge about the outcome of different fertility and quality of life preserving therapies is of top priority. With this thesis, a small step has been taken, but there is still a long way to go.

REFERENCES

1. Porter ME. What is value in health care? The New England journal of medicine. 2010;363(26):2477-81.
2. Basch E, Torda P, Adams K. Standards for patient-reported outcome-based performance measures. Jama. 2013;310(2):139-40.
3. Gallos ID, Yap J, Rajkhowa M, Luesley DM, Coomarasamy A, Gupta JK. Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis. Am J Obstet Gynecol. 2012;207(4):266-12.
4. Park JY, Kim DY, Kim JH, Kim YM, Kim KR, Kim YT, et al. Long-term oncologic outcomes after fertility-sparing management using oral progestin for young women with endometrial cancer (KGOG 2002). Eur J Cancer. 2013;49(4):868-74.
5. Koskas M, Uzan J, Luton D, Rouzier R, Darai E. Prognostic factors of oncologic and reproductive outcomes in fertility-sparing management of endometrial atypical hyperplasia and adenocarcinoma: systematic review and meta-analysis. Fertil Steril. 2014;101(3):785-94.
6. Perri T, Korach J, Gotlieb WH, Beiner M, Meirow D, Friedman E, et al. Prolonged conservative treatment of endometrial cancer patients: more than 1 pregnancy can be achieved. Int J Gynecol Cancer. 2011;21(1):72-8.
7. Park JY, Lee SH, Seong SJ, Kim DY, Kim TJ, Kim JW, et al. Progestin re-treatment in patients with recurrent endometrial adenocarcinoma after successful fertility-sparing management using progestin. Gynecol Oncol. 2013;129(1):7-11.
8. Ushijima K, Yahata H, Yoshikawa H, Konishi I, Yasugi T, Saito T, et al. Multicenter phase II study of fertility-sparing treatment with medroxyprogesterone acetate for endometrial carcinoma and atypical hyperplasia in young women. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2007;25(19):2798-803.
9. Greenblatt RB, Gambrell RD, Jr., Stoddard LD. The protective role of progesterone in the prevention of endometrial cancer. Pathology, research and practice. 1982;174(3):297-318.
10. Wang CB, Wang CJ, Huang HJ, Hsueh S, Chou HH, Soong YK, et al. Fertility-preserving treatment in young patients with endometrial adenocarcinoma. Cancer. 2002;94(8):2192-8.
11. Ota T, Yoshida M, Kimura M, Kinoshita K. Clinicopathologic study of uterine endometrial carcinoma in young women aged 40 years and younger. Int J Gynecol Cancer. 2005;15(4):657-62.

12. Ferrandina G, Zannoni GF, Gallotta V, Foti E, Mancuso S, Scambia G. Progression of conservatively treated endometrial carcinoma after full term pregnancy: a case report. Gynecol Oncol. 2005;99(1):215-7.

13. Cormio G, Martino R, Loizzi V, Resta L, Selvaggi L. A rare case of choroidal metastasis presented after conservative management of endometrial cancer. International Journal of Gynecological Cancer. 2006;16(6):2044-8.

14. Moyer DL, Felix JC. The effects of progesterone and progestins on endometrial proliferation. Contraception. 1998;57(6):399-403.

15. Colombo N, Creutzberg C, Amant F, Bosse T, Gonzalez-Martin A, Ledermann J, et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: Diagnosis, Treatment and Follow-up. Int J Gynecol Cancer. 2016;26(1):2-30.

16. Thigpen JT, Brady MF, Alvarez RD, Adelson MD, Homesley HD, Manetta A, et al. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1999;17(6):1736-44.

17. Rodolakis A, Biliatis I, Morice P, Reed N, Mangler M, Kesic V, et al. European Society of Gynecological Oncology Task Force for Fertility Preservation: Clinical Recommendations for Fertility-Sparing Management in Young Endometrial Cancer Patients. Int J Gynecol Cancer. 2015;25(7):1258-65.

18. Penner KR, Dorigo O, Aoyama C, Ostrzega N, Balzer BL, Rao J, et al. Predictors of resolution of complex atypical hyperplasia or grade 1 endometrial adenocarcinoma in premenopausal women treated with progestin therapy. Gynecol Oncol. 2012;124(3):542-8.

19. Hug V, Kau S, Hortobagyi GN, Jones L. Adrenal failure in patients with breast carcinoma after long-term treatment of cyclic alternating oestrogen progesterone. Br J Cancer. 1991;63(3):454-6.

20. Stein PD, Beemath A, Olson RE. Obesity as a risk factor in venous thromboembolism. Am J Med. 2005;118(9):978-80.

21. Satyaswaroop PG. Development of a preclinical model for hormonal therapy of human endometrial carcinomas. Annals of medicine. 1993;25(2):105-11.

22. Ozdegirmenci O, Kayikcioglu F, Bozkurt U, Akgul MA, Haberal A. Comparison of the efficacy of three progestins in the treatment of simple endometrial hyperplasia without atypia. Gynecol Obstet Invest. 2011;72(1):10-4.

23. Laurelli G, Falcone F, Gallo MS, Scala F, Losito S, Granata V, et al. Long-Term Oncologic and Reproductive Outcomes in Young Women With Early Endometrial Cancer Conservatively Treated: A Prospective Study and Literature Update. Int J Gynecol Cancer. 2016.

24. Minig L, Franchi D, Boveri S, Casadio C, Bocciolone L, Sideri M. Progestin intrauterine device and GnRH analogue for uterus-sparing treatment of endometrial precancers and well-differentiated early endometrial carcinoma in young women. Ann Oncol. 2011;22(3):643-9.

25. Lee TS, Seong SJ, Kim JW, Ryu HS, Song ES, Nam BH. Management of endometrial hyperplasia with a levonorgestrel-releasing intrauterine system: single arm, prospective multicenter study: Korean gynecologic oncology group study (KGOG2006). Japanese journal of clinical oncology. 2011;41(6):817-9.

26. Kim MK, Seong SJ, Lee TS, Kim JW, Nam BH, Hong SR, et al. Treatment with medroxyprogesterone acetate plus levonorgestrel-releasing intrauterine system for early-stage endometrial cancer in young women: single-arm, prospective multicenter study: Korean gynecologic oncology group study (KGOG2009). Japanese journal of clinical oncology. 2012;42(12):1215-8.

27. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. Cancer. 1987;60(8 Suppl):2035-41.

28. Kinkel K, Kaji Y, Yu KK, Segal MR, Lu Y, Powell CB, et al. Radiologic staging in patients with endometrial cancer: a meta-analysis. Radiology. 1999;212(3):711-8.

29. Song T, Seong SJ, Bae DS, Suh DH, Kim DY, Lee KH, et al. Synchronous primary cancers of the endometrium and ovary in young women: a Korean Gynecologic Oncology Group Study. Gynecol Oncol. 2013;131(3):624-8.

30. Larson DM, Johnson KK, Broste SK, Krawisz BR, Kresl JJ. Comparison of D&C and office endometrial biopsy in predicting final histopathologic grade in endometrial cancer. Obstet Gynecol. 1995;86(1):38-42.

31. van Gent MDJM, Kagie MJ, Trimbos JBMZ. Conservatieve behandeling van endometriumcarcinoom bij patiënten met kinderwens. Nederlands Tijdschrift voor Obstetrie en Gynaecologie. 2009;122:33-6.

32. Amezcua CA, Lu JJ, Felix JC, Stanczyk FZ, Zheng W. Apoptosis may be an early event of progestin therapy for endometrial hyperplasia. Gynecol Oncol. 2000;79(2):169-76.

33. Wan YL, Beverley-Stevenson R, Carlisle D, Clarke S, Edmondson RJ, Glover S, et al. Working together to shape the endometrial cancer research agenda: The top ten unanswered research questions. Gynecol Oncol. 2016;143(2):287-93.

34. Stelloo E, Bosse T, Nout RA, MacKay HJ, Church DN, Nijman HW, et al. Refining prognosis and identifying targetable pathways for high-risk endometrial cancer; a TransPORTEC initiative. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc. 2015;28(6):836-44.

35. Cancer Genome Atlas Research N, Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497(7447):67-73.

36. Rob L, Halaska M, Robova H. Nerve-sparing and individually tailored surgery for cervical cancer. Lancet Oncol. 2010;11(3):292-301.

37. 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.

38. 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.

39. 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.

40. 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.

41. Makino H, Kato H, Furui T, Hayasaki Y, Morishige K, Kanematsu M. Assessment of uterine enhancement rate after abdominal radical trachelectomy using dynamic contrast-enhanced magnetic resonance imaging. Arch Gynecol Obstet. 2016;293(3):625-32.

42. Tang J, Li J, Wang S, Zhang D, Wu X. On what scale does it benefit the patients if uterine arteries were preserved during ART? Gynecol Oncol. 2014;134(1):154-9.

43. Plante M. Bulky Early-Stage Cervical Cancer (2-4 cm Lesions): Upfront Radical Trachelectomy or Neoadjuvant Chemotherapy Followed by Fertility-Preserving Surgery: Which Is the Best Option? Int J Gynecol Cancer. 2015;25(4):722-8.

44. Rob L, Pluta M, Skapa P, Robova H. Advances in fertility-sparing surgery for cervical cancer. Expert Rev Anticancer Ther. 2010;10(7):1101-14.

45. Pareja R, Rendon GJ, Sanz-Lomana CM, Monzon O, Ramirez PT. Surgical, oncological, and obstetrical outcomes after abdominal radical trachelectomy - a systematic literature review. Gynecol Oncol. 2013;131(1):77-82.

46. Bentivegna E, Maulard A, Pautier P, Chargari C, Gouy S, Morice P. Fertility results and pregnancy outcomes after conservative treatment of cervical cancer: a systematic review of the literature. Fertil Steril. 2016;106(5):1195-211 e5.

47. Twijnstra AR, Blikkendaal MD, van Zwet EW, van Kesteren PJ, de Kroon CD, Jansen FW. Predictors of successful surgical outcome in laparoscopic hysterectomy. Obstetrics and gynecology. 2012;119(4):700-8.

48. McCulloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, et al. No surgical innovation without evaluation: the IDEAL recommendations. Lancet. 2009;374(9695):1105-12.

49. Sedrakyan A, Campbell B, Graves S, Cronenwett JL. Surgical registries for advancing quality and device surveillance. Lancet. 2016;388(10052):1358-60.

7

CHAPTER 8

Dutch summary (Nederlandse samenvatting)

Dit proefschrift heeft als doel de mogelijkheden en uitkomsten van 'tailored therapy' voor laaggradig, vroeg stadium baarmoederslijmvlieskanker (endometriumcarcinoom) en vroeg stadium baarmoederhalskanker (cervixcarcinoom) te evalueren. De gouden standaard is niet per definitie voor elk individu de beste behandelmethode en er zal bij het maken van een gezamenlijk behandelplan ook gekeken moeten worden naar welke doelen en wensen de patiënt heeft.

Het eerste deel van het proefschrift betreft onder andere een inventarisatie van de huidige (methodes voor) fertiliteitsparende behandelingen van endometriumcarcinoom. In het tweede deel worden de mogelijkheden om de behandeling van cervixcarcinoom aan te passen aan de wensen van het individu onderzocht. In het tijdperk van value-based healthcare wordt het naast het nastreven van genezing, topprioriteit om aandacht te hebben voor behoud van kwaliteit van leven van de patiënt.
Hoofdstuk 1 is een algemene inleiding over fertiliteitsparende behandeling binnen endometriumcarcinoom en cervixcarcinoom.

DEEL 1: ENDOMETRIUMCARCINOOM

Endometriumcarcinoom is de meest voorkomende kankersoort van de tractus genitalis van de vrouw in veel westerse landen. Het is de vierde meest voorkomende vorm van kanker bij vrouwen na borst-, long- en darmkanker. [1, 2] De incidentie van endometriumcarcinoom is 20 per 100.000 en 4% van de patiënten is jonger dan 40 jaar. [3] Dat betekent dat in Nederland ongeveer 50 patiënten per jaar in de fertiele levensfase worden gediagnosticeerd met endometriumcarcinoom. [4] Hoge BMI en verminderde fysieke activiteit verhogen de kans op het ontstaan van endometriumcarcinoom. [5] Aangezien de gemiddelde BMI de komende jaren zal stijgen, zal ook de incidentie van fertiele vrouwen met endometriumcarcinoom stijgen. [6] Overgewicht zorgt voor insulineresistentie, overmatige androgeenproductie door de ovaria, anovulatie en chronisch progesterontekort. [7] De meeste vrouwen in de fertiele levensfase presenteren zich met een laaggradig, endometrioïd type adenocarcinoom. Deze ontstaat vanuit de achtergrond van endometriumhyperplasie en langdurige oestrogeenstimulatie zonder tegenwerking van voldoende progestageen. [8] Dit type gedraagt zich minder agressief dan andere types endometriumcarcinoom. [9-11] De standaardbehandeling van stadium I endometriumcarcinoom is uterusextirpatie met bilaterale adnexextirpatie. [12] Voor patiënten met kinderwens betekent dit definitieve sterilisatie. Een alternatief voor chirurgie zou hormonale behandeling met progestativa kunnen zijn.
Er zijn meerdere studies die hebben gekeken naar de effectiviteit en veiligheid van deze behandelmethode. [10, 11, 13-19]

Hormonale therapie met behulp van progestativa heeft een goede initiële respons van 76,2%, maar er is een relatief hoge kans op een recidief (32-40,6%), zonder dat dit gevolgen heeft voor de langetermijnprognose. [13, 19] Een strikte opvolging met behulp van hysteroscopie met biopten danwel afname van micro-curettement is noodzakelijk. [20]

Voor het starten van de behandeling is het belangrijk de risico's zo goed mogelijk in te schatten. Dit kan gedaan worden met behulp van beeldvorming.
Hormonale therapie dient alleen te worden voorgesteld bij een laaggradig, laag stadium endometriumcarcinoom. Het endometriumcarcinoom wordt pathologisch gestadieerd. Om pre-operatief een zo accuraat mogelijke inschatting te kunnen maken van het stadium waarin de ziekte zich bevindt, dienen een transvaginale echografie (TVE) en een MRI met contrast te worden verricht. [21] Men kan overwegen een diagnostische laparoscopie te verrichten in verband met een kans van 4,3% op een simultaan optredend ovariumcarcinoom. [22] De diagnostiek wordt verricht middels hysteroscopie. Een afwijkende lesie wordt gereseceerd en er zal tevens een micro-curettement af worden genomen. Als er geen of juist diffuus afwijkingen te zien zijn, wordt geadviseerd een micro-curettement af te nemen. Wij adviseren twee afnamen met een tussenpose van 2 weken en centrale revisie van het preparaat. [20] In de literatuur is gekeken naar de meest effectieve dosering van progestativa. Over het algemeen wordt gebruik gemaakt van medroxyprogesteron. In een dosis-responsstudie van Thigpen [23] zijn doseringen tussen de 200 en 1000 mg per dag vergeleken en bleek de effectiviteit van 200 mg per dag superieur ten opzichte van 1000 mg per dag met minder bijwerkingen. Er is echter nog geen dosis-responsstudie gedaan met lagere doseringen progestativa danwel een vergelijkende studie tussen de effectiviteit van orale progestativa en een intra uterien levonogestrel (LNG) houdend spiraal. [24]

Aangezien endometriumcarcinoom weinig voorkomt in de fertiele levensfase en daardoor het aantal patiënten in Nederland beperkt is, hebben wij de beschikbare literatuur over het onderwerp verzameld en de resultaten vergeleken. Dit doen we in **hoofdstuk 2.** Het blijkt dat de literatuur over het onderwerp beperkt is. Er waren case reports en kleine cohortstudies, maar geen grote studies beschikbaar voor analyse. Op het moment van het uitvoeren van de review waren er in totaal 55 studies die 245 patiënten beschreven met een laaggradig, vroeg stadium endometriumcarcinoom. Inmiddels is er informatie over 600 patiënten. Opvallend was het verschillende behandel- en opvolgregime. De gemiddelde behandelduur was 7 maanden. De gemiddelde follow-up duur 47 maanden. Er werden 127 zwangerschappen waarvan 109 levendgeborenen geregistreerd. De conclusie uit deze review was dat conservatieve behandeling van endometriumcarcinoom overwogen kan worden in een streng geselecteerde groep patiënten die een fertiliteitsparende behandeling wensen. Patiënten moeten behan-

deld worden volgens een goed afgebakend protocol en nauwe follow-up is een vereiste. De resultaten zullen goed geregistreerd moeten worden om het effect van deze behandelwijze te kunnen evalueren. Het grootste discussiepunt van deze review is het grote risico op publicatiebias.

Gezien het feit dat endometriumcarcinoom, wanneer behandeld met progestativa, in een relatief hoog percentage recidiveert, we nog niet goed kunnen voorspellen welke patiënten gaan reageren op de therapie en niet goed weten waarom sommigen recidiveren en anderen niet, zijn we op zoek gegaan naar precursors op moleculair en histologisch niveau. In **hoofdstuk 3** bespreken we onze hypothese dat mutaties in belangrijke moleculaire pathways die betrekking hebben op de ontwikkeling van endometriumcarcinoom uit precursor cellen, mogelijkerwijs voorspellend zijn voor hoe goed de patiënt gaat reageren op therapie.

Voorgaande studies hebben gesuggereerd dat progesteron effectief was doordat het anti-tumor effect ontstaat door de interactie met de Wingless (Wnt) en/of Phospohatidylinositol 3-kinase (PI3K)/Akt pathways. Deze pathways induceren celproliferatie en worden aan en uit gezet tijdens een menstruatiecyclus onder invloed van progesteron en oestrogeen veranderingen. Daarnaast hebben we gekeken of er in morfologisch normaal ogend endometrium na therapie, de eerder aanwezige genetische afwijkingen nog terug te vinden waren. Om deze hypothese te bewijzen hebben we moleculaire veranderingen geanalyseerd in de Wnt en PI3K/Akt signaling in 84 seriële endometrium afnames van 11 premenopausale patiënten met laaggradig endometriumcarcinoom met een positieve progesteron receptor, die zijn behandeld met progestativa. Deze resultaten hebben we naast de histologische en klinische follow-up-resultaten gezet.
Wij hebben gezien dat er in deze serie geen aanwijzingen zijn dat moleculaire veranderingen in Wnt danwel PI3K/Akt signaling voorspellend zijn voor wel of niet reageren op behandeling met progesteron. Het lijkt dat morfologische respons samengaat met het verdwijnen van eerder aanwezige mutaties. Een kanttekening op deze studie is dat het aantal curettementen dat in follow-up geanalyseerd is, uniek is in de literatuur. Echter, vanwege het heterogene doseringsbeleid van de progestativa en de verschillende follow-up regimes, is het niet mogelijk hier goed onderbouwde conclusies aan te verbinden.

Aangezien heterogeniteit en lage aantallen de twee grootste problemen zijn om de veiligheid van de fertiliteitsparende behandeling goed te kunnen analyseren en daarmee te kunnen verbeteren, is het van groot belang een internationaal samenwerkingsverband op te zetten. Dan kunnen met prospectieve dataverzameling en een gestandaardiseerd protocol resultaten worden gepoold. Naar aanleiding van dit pro-

motieonderzoek zal dit protocol worden geschreven, met als basis het reeds bestaande protocol dat tot op heden werd gehanteerd en het afgelopen jaar verschenen protocol gepresenteerd door de werkgroep fertiliteitsparende behandeling bij endometriumcarcinoom van de ESGO-ESMO-ESTRO task force. [25]

DEEL 2: CERVIXCARCINOOM

Het tweede deel van het proefschrift handelt over cervixcarcinoom. Cervixcarcinoom is wereldwijd het derde meest voorkomende type kanker bij vrouwen. Daarnaast is het 4e meest dodelijke type kanker na borst-, long- en darmkanker. [26] In 2010 werden wereldwijd 453.970 nieuwe patiënten gediagnostiseerd met cervixcarcinoom en 44 % van deze vrouwen was jonger dan 50 jaar. Behandeling van cervixcarcinoom hangt af van het stadium waarin de ziekte zich bevindt. Microscopische ziekte (FIGO IA1) wordt meestal behandeld met een conisatie dan wel een simpele baarmoederverwijdering (hysterectomie). Het zo genoemde 'vroeg stadium cervixcarcinoom' (FIGO IA2, IB, IIA en IIB) kan worden behandeld met een radicale hysterectomie. Met de bedoeling om lymfeklier-metastasen uit te sluiten wordt een pelviene lymfadenectomie verricht. Adjuvante (chemo-) radiatie wordt gegeven in het geval van positieve klieren, extra-cervicale groei en ongunstige tumorkarakteristieken. De prognose na een radicale hysterectomie hangt af van wel of geen aanwezigheid van de hiervoor genoemde ongunstige tumorkarakteristieken. De 5-jaars overlevingsgetallen variëren tussen de 88 en 97 %. [27, 28] Met deze overlevingsgetallen wordt kwaliteit van leven extra belangrijk.
Een manier om deze kwaliteit van leven te verbeteren is door de morbiditeit die door de ingreep wordt geïnduceerd, te verminderen. Tot wel 25 % van de patiënten die een radicale hysterectomie ondergaan lijdt aan blaas-, darm- of seksuele dysfunctieklachten. [29, 30] Het idee is dat deze morbiditeit onder andere komt door per operatieve beschadiging van de autonome zenuwen die in het kleine bekken lopen. Maas et al. toonde aan dat de conventionele radicale hysterectomie (Piver III) onvermijdelijk schade aan de nervus hypogastrica en de nervus splanchnicus toebrengt door respectievelijk het doornemen van de sacro-uteriene ligamenten en het doornemen van het parametrium onder de diepe vena uterina. [31] De autonome zenuwen innerveren de blaas en darm en zijn belangrijk voor de seksualiteit: ze reguleren de lubricatie-zwellingrespons van de genitalia van de vrouw tijdens seksuele opwinding. [32] Het is bekend dat onbedoelde schade aan de autonome zenuwen kan leiden tot urine-incontinentie, diarree of obstipatie en seksuele problematiek. [33] Sinds 1960 is de zenuwsparende radicale hysterectomie in opkomst. Echter, het blijft een onderwerp van discussie binnen de wereld van de gynaecologische oncologie. Voorstanders stellen dat de techniek veilig is, betere kwaliteit van leven geeft, in het licht van een even goede overlevingskans. Tegenstand-

ers zeggen dat de literatuur te heterogeen is om de oncologische veiligheid en het fysiologische voordeel met zekerheid vast te stellen.
Dit is de reden geweest voor de meta-analyse die in **hoofdstuk 4** is weergegeven. Het doel van het verrichten van de systematische review en meta-analyse was om het beste bewijs te geven waarbij naar zowel kwaliteit van leven als naar survival wordt gekeken bij patiënten die behandeld werden met een radicale hysterectomie voor vroeg-stadium cervixcarcinoom. We concludeerden dat de 2-,3- en 5-jaars (ziektevrije) overleving niet tussen de groepen verschilden. De postoperatieve tijd tot spontane mictie na chirurgie was significant korter voor de groep die zenuwsparend werd behandeld wat leidt tot kortere opnameduur en verminderde morbiditeit op het gebied van de mictie. De andere data over kwaliteit van leven zoals seksuele functie en darmfunctionaliteit waren te heterogeen om hierop een meta-analyse te verrichten. Deze data is verwerkt in supplemental figures bij hoofdstuk 4 en laat zien dat de kwaliteit van leven na een zenuwsparende ingreep over het algemeen beter is dan na een niet-zenuwsparende operatie. Concluderend kunnen we stellen dat een zenuwsparende hysterectomie een veilige optie is voor patiënten met een vroeg stadium cervixcarcinoom, terwijl de morbiditeit minder is ten opzichte van de conventionele radicale hysterectomieën.

Het nastreven van betere kwaliteit van leven moet niet leiden tot het doen van concessies op het gebied van overleving. Die gedachte heeft geleid tot het evalueren van de resultaten van onze eigen kliniek. **(hoofdstuk 5)** Aanvankelijk werden patiënten met een vroeg stadium cervixcarcinoom behandeld met de conventionele radicale hysterectomie. In de jaren ’90 werd de Leiden zenuwsparende radicale hysterectomie (LNSRH) ontwikkeld. Vanaf 2000 werd deze ingreep gemodificeerd naar de Swift-procedure waarbij beter rekening gehouden werd met de morfogenetische unit. We hebben de lokale recidief kansen en 5-jaars ziektevrije overleving tussen de 3 groepen vergeleken: conventionele radicale hysterectomie (CRH), Leiden zenuwsparende radicale hysterectomie (LNSRH) en de zenuwsparende Swift procedure. Er werd data van in totaal 362 patiënten geanalyseerd. In multivariate analyse was het type chirurgie geen voorspellende factor voor het krijgen van een lokaal recidief danwel 5-jaars ziektevrije overleving. Lymfeklierbetrokkenheid, vaso-invasie en tumorgrootte boven de 4 cm waren wel prognostische factoren voor een slechte uitkomst. Deze bevindingen bevestigen de resultaten uit de literatuur dat zenuwsparend opereren veilig is en geen slechtere overlevingsuitkomsten geeft.

Het laatste hoofdstuk, **hoofdstuk 6**, combineert het idee van een fertiliteitsparende behandeling, dat in deel een van dit proefschrift wordt behandeld, met het zenuwsparend opereren dat in deel 2 besproken wordt. Het gaat namelijk over de zenuwsparende

radicale trachelectomie voor patiënten met een vroeg-stadium cervixcarcinoom met wens tot behoud van fertiliteit.
Een trachelectomie kan via de abdominale danwel via de vaginale route plaats vinden. Het nadeel van de vaginale route is dat er geen mogelijkheid is tot zenuwsparend opereren en het niet mogelijk is tumoren van > 2 cm via deze route te benaderen. Vanwege de ervaring die er in Leiden is met het zenuwsparend opereren bij de radicale hysterectomie, is er besloten de zenuwsparende techniek ook in te voeren voor de abdominale radicale trachelectomie. Op deze manier kan er naast de mogelijkheid van behoud van fertiliteit, ook verbetering worden nagestreefd in de kwaliteit van leven. We hebben een case-control studie verricht waarbij we in detail de techniek van de zenuwsparende abdominale trachelectomie beschrijven, de klinische uitkomsten bekijken en deze vergelijken met de patiënten die een zenuwsparende radicale hysterectomie ondergingen in dezelfde periode. Daarnaast is er gekeken naar de zwangerschapsuitkomsten bij het cohort dat de fertiliteit sparende techniek onderging.
Deze studie toont aan dat het aantal recidieven en de overlevingsuitkomsten niet verschillen tussen de zenuwsparende radicale abdominale trachelectomie versus de zenuwsparende radicale hysterectomie. De kans op een zwangerschap was 53 %.
Daarnaast hebben we drie patiënten behandeld met neoadjuvante chemotherapie teneinde tumorload te laten doen afnemen, zodat een trachelectomie een behandeloptie werd. Wat opvalt aan de studie is dat de aantallen klein zijn en het daardoor nog onvoldoende bewezen is dat de trachelectomie als even veilig als de conventionele hysterectomie kan worden aangeboden. Ook in dit geval is het belangrijk dat er op nationaal en internationaal niveau samen gewerkt gaat worden en gezamenlijke databases zullen ervoor zorgen dat data uniformer kan worden geanalyseerd en bovendien het aantal patiënten fors zal toenemen waardoor de resultaten beter kunnen worden geëxtrapoleerd naar de patiënt als individu.

Samenvattend zijn er volop ontwikkelingen gaande om kwaliteit van leven van de patiënt met een vroeg-stadium oncologische aandoening te verbeteren met het oog op een even goede danwel betere overlevingsuitkomst. Overeenkomstig met de ontwikkelingen in de huidige geneeskunde waarbij patient related outcome measurements worden gebruikt om patiënttevredenheid vast te stellen [34], zou het volgende doel van onderzoek moet zijn om deze factoren te overkomen zodat niet alleen de fysiologie wordt behouden maar ook de self-assessed functie en kwaliteit van leven. Met dit proefschrift is een kleine stap gemaakt, maar er is nog een lange weg te gaan.

REFERENTIES

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014;64(1):9-29.
2. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55(2):74-108.
3. Lee NK, Cheung MK, Shin JY, Husain A, Teng NN, Berek JS, et al. Prognostic factors for uterine cancer in reproductive-aged women. Obstet Gynecol. 2007;109(3):655-62.
4. Treffers. Obstetrie en gynaecologie. 2e herziene druk ed1995. p. 672.
5. Schouten LJ, Goldbohm RA, van den Brandt PA. Anthropometry, physical activity, and endometrial cancer risk: results from the Netherlands cohort study. Int J Gynecol Cancer. 2006;16 Suppl 2:492.
6. Renehan AG, Soerjomataram I, Leitzmann MF. Interpreting the epidemiological evidence linking obesity and cancer: A framework for population-attributable risk estimations in Europe. Eur J Cancer. 2010;46(14):2581-92.
7. Amant F, Moerman P, Neven P, Timmerman D, Van LE, Vergote I. Endometrial cancer. Lancet. 2005;366(9484):491-505.
8. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol. 1983;15(1):10-7.
9. Boing C, Kimmig R. Fertility-preserving treatment in young women with endometrial cancer. Gynakol Geburtshilfliche Rundsch. 2006;46(1-2):25-33.
10. Ramirez PT, Frumovitz M, Bodurka DC, Sun CC, Levenback C. Hormonal therapy for the management of grade 1 endometrial adenocarcinoma: a literature review. Gynecol Oncol. 2004;95(1):133-8.
11. Niwa K, Tagami K, Lian Z, Onogi K, Mori H, Tamaya T. Outcome of fertility-preserving treatment in young women with endometrial carcinomas. BJOG. 2005;112(3):317-20.
12. oncoline 2014 [updated 7/1/2014]. Available from: www.oncoline.nl.
13. Gallos ID, Yap J, Rajkhowa M, Luesley DM, Coomarasamy A, Gupta JK. Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis. Am J Obstet Gynecol. 2012;207(4):266-12.

14. Yamazawa K, Hirai M, Fujito A, Nishi H, Terauchi F, Ishikura H, et al. Fertility-preserving treatment with progestin, and pathological criteria to predict responses, in young women with endometrial cancer. Hum Reprod. 2007;22(7):1953-8.

15. Simpson AN, Feigenberg T, Clarke BA, Gien LT, Ismiil N, Laframboise S, et al. Fertility sparing treatment of complex atypical hyperplasia and low-grade endometrial cancer using oral progestin. Gynecol Oncol. 2014;133(2):229-33.

16. Gotlieb WH, Beiner ME, Shalmon B, Korach Y, Segal Y, Zmira N, et al. Outcome of fertility-sparing treatment with progestins in young patients with endometrial cancer. Obstet Gynecol. 2003;102(4):718-25.

17. Ota T, Yoshida M, Kimura M, Kinoshita K. Clinicopathologic study of uterine endometrial carcinoma in young women aged 40 years and younger. Int J Gynecol Cancer. 2005;15(4):657-62.

18. Ushijima K, Yahata H, Yoshikawa H, Konishi I, Yasugi T, Saito T, et al. Multicenter phase II study of fertility-sparing treatment with medroxyprogesterone acetate for endometrial carcinoma and atypical hyperplasia in young women. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2007;25(19):2798-803.

19. van Gent MDJM, Kagie MJ, Trimbos JB. No surgery for Low-Grade Endometrial Cancer in Women with a Desire to Preserve Fertility. Journal of gynecologic Surgery. 2012;28(6):389-98.

20. Larson DM, Johnson KK, Broste SK, Krawisz BR, Kresl JJ. Comparison of D&C and office endometrial biopsy in predicting final histopathologic grade in endometrial cancer. Obstet Gynecol. 1995;86(1):38-42.

21. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. Cancer. 1987;60(8 Suppl):2035-41.

22. Song T, Seong SJ, Bae DS, Suh DH, Kim DY, Lee KH, et al. Synchronous primary cancers of the endometrium and ovary in young women: a Korean Gynecologic Oncology Group Study. Gynecol Oncol. 2013;131(3):624-8.

23. Thigpen JT, Brady MF, Alvarez RD, Adelson MD, Homesley HD, Manetta A, et al. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1999;17(6):1736-44.

24. Wheeler DT, Bristow RE, Kurman RJ. Histologic alterations in endometrial hyperplasia and well-differentiated carcinoma treated with progestins. Am J Surg Pathol. 2007;31(7):988-98.

25. Colombo N, Creutzberg C, Amant F, Bosse T, Gonzalez-Martin A, Ledermann J, et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: Diagnosis, Treatment and Follow-up. Int J Gynecol Cancer. 2016;26(1):2-30.

26. 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.

27. Rob L, Halaska M, Robova H. Nerve-sparing and individually tailored surgery for cervical cancer. Lancet Oncol.11(3):292-301.

28. 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.

29. 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.

30. Bergmark K, Avall-Lundqvist E, Dickman PW, Henningsohn L, Steineck G. Vaginal changes and sexuality in women with a history of cervical cancer. The New England journal of medicine. 1999;340(18):1383-9.

31. 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.

32. 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.

33. 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.

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

8

APPENDICES

BIBLIOGRAPHY

M.D.J.M. van Gent, M. Rademaker, J.C.B. van der Veer, MIE van Poelgeest, KN Gaarenstroom, JB Trimbos en CD de Kroon. Long term oncological outcome after conventional radical hysterectomy versus two nerve-sparing modalities for early stage cervical cancer 2017. Accepted

M.D.J.M. van Gent, H. Trum, F. Amant. Treatment of Advanced and Recurrent Endometrial Cancers. 2017. IGCS website.

M.D.J.M van Gent, L. Romijn, K. van Santen, C.D. de Kroon. 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 Dec.

M.D.J.M. van Gent, A. Nicolae-Cristina, C.D. de Kroon, J.B.M.Z. Trimbos, M.J. Kagie, H.M. Hazelbag, T. Bosse, V.T.H.B.M. Smit. Exploring morphologic and molecular aspects of endometrial cancer under progesterone treatment in the context of fertility preservation. Int J Gynecol Cancer. 2016 Mar; 26(3):483-90

M.D.J.M van Gent, L. W. van den Haak, K.N. Gaarenstroom, A.A.W. Peters, M.I.E. van Poelgeest, J.B.M.Z. Trimbos, C.D. de Kroon. 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 May; 24(4): 735-43

M.D.J.M van Gent. Dokter in Australië. NTOG, dec 2013; vol. 127: 506-508

M.D.J.M van Gent, M.J.Kagie, J.B. Trimbos. No Surgery for Low-Grade Endometrial Cancer in Women with a Desire to Preserve Fertility. Journal of gynecol surg, 2012 Oct; volume 28 (issue 6): 389-398

M.D.J.M van Gent, M.J.Kagie, J.B. Trimbos. Conservatieve behandeling van endometriumcarcinoom bij patiënten met kinderwens. NTOG. Vol 122, maart 2009: 33-6

M.D.J.M. van Gent, A. Clement, F.C.M. Twaalfhoven. Een verzuimde dwarsligging. NTOG. 2007 Sep; 120(07):24-5

M.D.J.M. van Gent, H.M. Oosterkamp, M.J. Kagie. Manifest carcinoma of the glandula vestibularis major (Bartholin's gland), detected one year after an inguinal lymph-node metastasis Ned Tijdschr Geneeskd. 2007 Jul 28; 151 (30): 1686-9

A

REFERENCES

Abu-Rustum NR, Sonoda Y, Black D, et al. Fertility-sparing radical abdominal trachelectomy for cervical carcinoma: technique and review of the literature. Gynecologic oncology. 2006;103(3):807-13.

Amant F, Leunen K, Neven P, Berteloot P, Vergote I. Endometrial cancer: predictors of response and preferred endocrine therapy. Int J Gynecol Cancer. 2006;16 Suppl 2:527-8.

Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, Vergote I. Endometrial cancer. Lancet. 2005;366(9484):491-505.

Amezcua CA, Lu JJ, Felix JC, Stanczyk FZ, Zheng W. Apoptosis may be an early event of progestin therapy for endometrial hyperplasia. Gynecol Oncol. 2000;79(2):169-76.

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.

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.

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

Axelsen SM, Petersen LK. Urogynaecological dysfunction after radical hysterectomy. Eur J Surg Oncol. 2006;32(4):445-9.

Bafaloukos D, Aravantinos G, Samonis G, Katsifis G, Bakoyiannis C, Skarlos D, et al. Carboplatin, methotrexate and 5-fluorouracil in combination with medroxyprogesterone acetate (JMF-M) in the treatment of advanced or recurrent endometrial carcinoma: A Hellenic cooperative oncology group study. Oncology. 1999;56(3):198-201.

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.

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.

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

Beiner ME, Covens A. Surgery insight: radical vaginal trachelectomy as a method of fertility preservation for cervical cancer. Nature clinical practice. 2007;4(6):353-61.

Beiner ME, Hauspy J, Rosen B, et al. Radical vaginal trachelectomy vs. radical hysterectomy for small early stage cervical cancer: a matched case-control study. Gynecologic oncology. 2008;110(2):168-71.

Ben-Shachar I, Vitellas KM, Cohn DE. The role of MRI in the conservative management of endometrial cancer. Gynecologic oncology. 2004;93(1):233-7.

Benedetti-Panici P, Greggi S, Colombo A, et al. Neoadjuvant chemotherapy and radical surgery versus exclusive radiotherapy in locally advanced squamous cell cervical cancer: results from the Italian multicenter randomized study. J Clin Oncol. 2002;20(1):179-88.

Bentivegna E, Maulard A, Pautier P, Chargari C, Gouy S, Morice P. Fertility results and pregnancy outcomes after conservative treatment of cervical cancer: a systematic review of the literature. Fertil Steril. 2016;106(5):1195-211 e5.

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.

Bergmark K, Avall-Lundqvist E, Dickman PW, Henningsohn L, Steineck G. Vaginal changes and sexuality in women with a history of cervical cancer. The New England journal of medicine. 1999;340(18):1383-9.

Bernardini M, Barrett J, Seaward G, et al. Pregnancy outcomes in patients after radical trachelectomy. American journal of obstetrics and gynecology. 2003;189(5):1378-82.

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.

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.

Boing C, Kimmig R. Fertility-preserving treatment in young women with endometrial cancer. Gynakologisch-geburtshilfliche Rundschau. 2006;46(1-2):25-33.

Bokhman JV, Chepick OF, Volkova AT, Vishnevsky AS. Can primary endometrial carcinoma stage I be cured without surgery and radiation therapy? Gynecol Oncol. 1985;20(2):139-55.

Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol. 1983;15(1):10-7.

Boronow RC, Morrow CP, Creasman WT, Disaia PJ, Silverberg SG, Miller A, et al. Surgical staging in endometrial cancer: clinical-pathologic findings of a prospective study. Obstetrics and gynecology. 1984;63(6):825-32.

Burnett AF, Bahador A, Amezcua C. Anastrozole, an aromatase inhibitor, and medroxyprogesterone acetate therapy in premenopausal obese women with endometrial cancer: a report of two cases successfully treated without hysterectomy. Gynecol Oncol. 2004;94(3):832-4.

Cancer Genome Atlas Research N, Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497(7447):67-73.

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.

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.

Chang WH, Chen CH, Yu MH. Conservative therapy of stage I endometrial adenocarcinoma and atypical endometrial hyperplasia for the preservation of fertility. Int J Gynaecol Obstet. 2006;92(2):137-8.

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.

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.

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.

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.

Chiva L, Lapuente F, Gonzalez-Cortijo L, et al. Sparing fertility in young patients with endometrial cancer. Gyecol Oncol 2008; 111 (2 Suppl): S101-4.

Church DN, Stelloo E, Nout RA, Valtcheva N, Depreeuw J, ter Haar N, et al. Prognostic significance of POLE proofreading mutations in endometrial cancer. Journal of the National Cancer Institute. 2015;107(1):402.

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.

Cibula D, Velechovska P, Slama J, et al. Late morbidity following nerve-sparing radical hysterectomy. Gynecologic oncology. 2010;116(3):506-11.

Neoadjuvant Chemotherapy for Cervical Cancer Meta-analysis Collaboration. Neoadjuvant chemotherapy for locally advanced cervical cancer: a systematic review and meta-analysis of individual patient data from 21 randomised trials. Eur J Cancer. 2003;39(17):2470-86.

Collaboration TC. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 2008 [updated September 2008. Available from: www.cochrane-handbook.org.

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.

Colombo N, Creutzberg C, Amant F, Bosse T, Gonzalez-Martin A, Ledermann J, et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: Diagnosis, Treatment and Follow-up. Int J Gynecol Cancer. 2016;26(1):2-30.

Cormio G, Martino R, Loizzi V, Resta L, Selvaggi L. A rare case of choroidal metastasis presented after conservative management of endometrial cancer. International Journal of Gynecological Cancer. 2006;16(6):2044-8.

Covens A, Rosen B, Murphy J, et al. How important is removal of the parametrium at surgery for carcinoma of the cervix? Gynecologic oncology. 2002;84(1):145-9.

Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. Cancer. 1987;60(8 Suppl):2035-41.

de Jongh FE, de Wit R, Verweij J, et al. Dose-dense cisplatin/paclitaxel. a well-tolerated and highly effective chemotherapeutic regimen in patients with advanced ovarian cancer. Eur J Cancer. 2002;38(15):2005-13.

de Kroon CD, Gaarenstroom KN, van Poelgeest MI, Peters AA, Trimbos JB. Nerve sparing in radical surgery for early-stage cervical cancer: yes we should! Int J Gynecol Cancer. 2010;20(11 Suppl 2):S39-S41.

Delgado G, Bundy B, Zaino R, et al. Prospective surgical-pathological study of disease-free interval in patients with stage IB squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecologic oncology. 1990;38(3):352-7.

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.

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.

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), Ann. Oncol. 25 (suppl. 4) (2014) iv319.

Diaz JP, Sonoda Y, Leitao MM, et al. Oncologic outcome of fertility-sparing radical trachelectomy versus radical hysterectomy for stage IB1 cervical carcinoma. Gynecologic oncology. 2008;111(2):255-60.

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.

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.

Duska LR, Garrett A, Rueda BR, Haas J, Chang Y, Fuller AF. Endometrial cancer in women 40 years old or younger. Gynecol Oncol. 2001;83(2):388-93.

Eddy WA. Endometrial carcinoma in Stein-Leventhal syndrome treated with hydroxyprogesterone caproate. Am J Obstet Gynecol. 1978;131(5):581-2.

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.

Evans-Metcalf ER, Brooks SE, Reale FR, Baker SP. Profile of women 45 years of age and younger with endometrial cancer. Obstetrics and gynecology. 1998;91(3):349-54.

Fagotti A, Gagliardi ML, Moruzzi C, et al. Excisional cone as fertility-sparing treatment in early-stage cervical cancer. Fertility and sterility. 2011;95(3):1109-12.

Farhi DC, Nosanchuk J, Silverberg SG. Endometrial adenocarcinoma in women under 25 years of age. Obstet Gynecol. 1986;68(6):741-5.

Ferrandina G, Zannoni GF, Gallotta V, Foti E, Mancuso S, Scambia G. Progression of conservatively treated endometrial carcinoma after full term pregnancy: a case report. Gynecol Oncol. 2005;99(1):215-7.

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.

Gallos ID, Yap J, Rajkhowa M, Luesley DM, Coomarasamy A, Gupta JK. Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis. Am J Obstet Gynecol. 2012;207(4):266-12.

Garg K, Broaddus RR, Soslow RA, Urbauer DL, Levine DA, Djordjevic B. Pathologic scoring of PTEN immunohistochemistry in endometrial carcinoma is highly reproducible. Int J Gynecol Pathol. 2012;31(1):48-56.

Gotlieb WH, Beiner ME, Shalmon B, Korach Y, Segal Y, Zmira N, et al. Outcome of fertility-sparing treatment with progestins in young patients with endometrial cancer. Obstet Gynecol. 2003;102(4):718-25.

Greenblatt RB, Gambrell RD, Jr., Stoddard LD. The protective role of progesterone in the prevention of endometrial cancer. Pathology, research and practice. 1982;174(3):297-318.

Gurgan T, Bozdag G, Demirol A, Ayhan A. Preserving fertility before assisted reproduction in women with endometrial carcinoma: case report and literature review. Reproductive biomedicine online. 2007;15(5):561-5.

Hahn HS, Yoon SG, Hong JS, et al. Conservative treatment with progestin and pregnancy outcomes in endometrial cancer. Int J Gynecol Cancer 2009;19:1068.

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.

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.

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.

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.

Hong DG, Lee YS, Park NY, et al. Robotic uterine artery preservation and nerve-sparing radical trachelectomy with bilateral pelvic lymphadenectomy in early-stage cervical cancer. Int J Gynecol Cancer. 2011;21(2):391-6.

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.

Huang SY, Jung SM, Ng KK, Chang YC, Lai CH. Ovarian metastasis in a nulliparous woman with endometrial adenocarcinoma failing conservative hormonal treatment. Gynecol Oncol. 2005;97(2):652-5.

Hug V, Kau S, Hortobagyi GN, Jones L. Adrenal failure in patients with breast carcinoma after long-term treatment of cyclic alternating oestrogen progesterone. Br J Cancer. 1991;63(3):454-6.

Hurst SA, Hartzfeld KM, Del Priore G. Occult myometrial recurrence after progesterone therapy to preserve fertility in a young patient with endometrial cancer. Fertil Steril. 2008;89(3):724 e1-3.

Imai M, Jobo T, Sato R, Kawaguchi M, Kuramoto H. Medroxyprogesterone acetate therapy for patients with adenocarcinoma of the endometrium who wish to preserve the uterus-usefulness and limitations. Eur J Gynaecol Oncol. 2001;22(3):217-20.

Jadoul P, Donnez J. Conservative treatment may be beneficial for young women with atypical endometrial hyperplasia or endometrial adenocarcinoma. Fertil Steril. 2003;80(6):1315-24.

Jobo T, Imai M, Kawaguchi M, Kenmochi M, Kuramoto H. Successful conservative treatment of endometrial carcinoma permitting subsequent pregnancy: report of two cases. Eur J Gynaecol Oncol. 2000;21(2):119-22.

Jones A, Teschendorff AE, Li Q, Hayward JD, Kannan A, Mould T, et al. Role of DNA methylation and epigenetic silencing of HAND2 in endometrial cancer development. PLoS Med. 2013;10(11):e1001551.

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.

Kaku T, Yoshikawa H, Tsuda H, Sakamoto A, Fukunaga M, Kuwabara Y, et al. Conservative therapy for adenocarcinoma and atypical endometrial hyperplasia of the endometrium in young women: central pathologic review and treatment outcome. Cancer Lett. 2001;167(1):39-48.

Kamoi S, Ohaki Y, Mori O, Kurose K, Fukunaga M, Takeshita T. Serial histologic observation of endometrial adenocarcinoma treated with high-dose progestin until complete disappearance of carcinomatous foci--review of more than 25 biopsies from five patients. Int J Gynecol Cancer. 2008;18(6):1305-14.

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.

Kauppila A. Oestrogen and progestin receptors as prognostic indicators in endometrial cancer. A review of the literature. Acta Oncol. 1989;28(4):561-6.

Kempson RL, Pokorny GE. Adenocarcinoma of the endometrium in women aged forty and younger. Cancer. 1968;21(4):650-62.

Kim MK, Seong SJ, Lee TS, Kim JW, Nam BH, Hong SR, et al. Treatment with medroxyprogesterone acetate plus levonorgestrel-releasing intrauterine system for early-stage endometrial cancer in young women: single-arm, prospective multicenter study: Korean gynecologic oncology group study (KGOG2009). Japanese journal of clinical oncology. 2012;42(12):1215-8.

Kim YB, Holschneider CH, Ghosh K, Nieberg RK, Montz FJ. Progestin alone as primary treatment of endometrial carcinoma in premenopausal women. Report of seven cases and review of the literature. Cancer. 1997;79(2):320-7.

Kimmig R, Strowitzki T, Muller-Hocker J, Kurzl R, Korell M, Hepp H. Conservative treatment of endometrial cancer permitting subsequent triplet pregnancy. Gynecol Oncol. 1995;58(2):255-7.

Kinkel K, Kaji Y, Yu KK, Segal MR, Lu Y, Powell CB, et al. Radiologic staging in patients with endometrial cancer: a meta-analysis. Radiology. 1999;212(3):711-8.

Koskas M, Uzan J, Luton D, Rouzier R, Darai E. Prognostic factors of oncologic and reproductive outcomes in fertility-sparing management of endometrial atypical hyperplasia and adenocarcinoma: systematic review and meta-analysis. Fertil Steril. 2014;101(3):785-94.

Kowalczyk CL, Malone J, Jr., Peterson EP, Jacques SM, Leach RE. Well-differentiated endometrial adenocarcinoma in an infertility patient with later conception. A case report. J Reprod Med. 1999;44(1):57-60.

Kung FT, Chen WJ, Chou HH, Ko SF, Chang SY. Conservative management of early endometrial adenocarcinoma with repeat curettage and hormone therapy under assistance of hysteroscopy and laparoscopy. Hum Reprod. 1997;12(8):1649-53.

Kurman RJ, Carcangiu, M.L., Herrington, C.S., Young, R.H. WHO Classification of Tumours of Female Reproductive Organs. Fourth Edition2014 2014.

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.

Lai CH, Hsueh S, Chao AS, Soong YK. Successful pregnancy after tamoxifen and megestrol acetate therapy for endometrial carcinoma. Br J Obstet Gynaecol. 1994;101(6):547-9.

Lanowska M, Morawietz L, Sikora A, et al. Prevalence of lymph nodes in the parametrium of radical vaginal trachelectomy (RVT) specimen. Gynecologic oncology. 2011;121(2):298-302.

Larson DM, Johnson KK, Broste SK, Krawisz BR, Kresl JJ. Comparison of D&C and office endometrial biopsy in predicting final histopathologic grade in endometrial cancer. Obstet Gynecol. 1995;86(1):38-42.

Laurelli G, Falcone F, Gallo MS, Scala F, Losito S, Granata V, et al. Long-Term Oncologic and Reproductive Outcomes in Young Women With Early Endometrial Cancer Conservatively Treated: A Prospective Study and Literature Update. Int J Gynecol Cancer. 2016.

Lee II, Kim JJ. Influence of AKT on Progesterone Action in Endometrial Diseases. Biol Reprod. 2014;91(3):63.

Lee KR, Scully RE. Complex endometrial hyperplasia and carcinoma in adolescents and young women 15 to 20 years of age. A report of 10 cases. Int J Gynecol Pathol. 1989;8(3):201-13.

Lee NK, Cheung MK, Shin JY, Husain A, Teng NN, Berek JS, et al. Prognostic factors for uterine cancer in reproductive-aged women. Obstet Gynecol. 2007;109(3):655-62.

Lee TS, Seong SJ, Kim JW, Ryu HS, Song ES, Nam BH. Management of endometrial hyperplasia with a levonorgestrel-releasing intrauterine system: single arm, prospective multicenter study: Korean gynecologic oncology group study (KGOG2006). Japanese journal of clinical oncology. 2011;41(6):817-9.

Li J, Wang LJ, Zhang BZ, et al. Neoadjuvant chemotherapy with paclitaxel plus platinum for invasive cervical cancer in pregnancy: two case report and literature review. Archives of gynecology and obstetrics. 2011;284(3):779-83.

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.

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.

Lowe MP, Cooper BC, Sood AK, Davis WA, Syrop CH, Sorosky JI. Implementation of assisted reproductive technologies following conservative management of FIGO grade I endometrial adenocarcinoma and/or complex hyperplasia with atypia. Gynecol Oncol. 2003;91(3):569-72.

Maas CP, Kenter GG, Trimbos JB, Deruiter MC. Anatomical basis for nerve-sparing radical hysterectomy: immunohistochemical study of the pelvic autonomic nerves. Acta Obstet Gynecol Scand. 2005;84(9):868-74.

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.

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.

Makino H, Kato H, Furui T, Hayasaki Y, Morishige K, Kanematsu M. Assessment of uterine enhancement rate after abdominal radical trachelectomy using dynamic contrast-enhanced magnetic resonance imaging. Arch Gynecol Obstet. 2016;293(3):625-32.

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.

Maneo A, Sideri M, Scambia G, et al. Simple conization and lymphadenectomy for the conservative treatment of stage IB1 cervical cancer. An Italian experience. Gynecologic oncology.

Martin A, Torrent A. Laparoscopic nerve-sparing radical trachelectomy: surgical technique and outcome. Journal of minimally invasive gynecology. 2010;17(1):37-41.

Mazzon I, Corrado G, Morricone D, Scambia G. Reproductive preservation for treatment of stage IA endometrial cancer in a young woman: hysteroscopic resection. Int J Gynecol Cancer. 2005;15(5):974-8.

McCulloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, et al. No surgical innovation without evaluation: the IDEAL recommendations. Lancet. 2009;374(9695):1105-12.

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.

Minaguchi T, Nakagawa S, Takazawa Y, Nei T, Horie K, Fujiwara T, et al. Combined phospho-Akt and PTEN expressions associated with post-treatment hysterectomy after conservative progestin therapy in complex atypical hyperplasia and stage Ia, G1 adenocarcinoma of the endometrium. Cancer Lett. 2007;248(1):112-22.

Minig L, Franchi D, Boveri S, Casadio C, Bocciolone L, Sideri M. Progestin intrauterine device and GnRH analogue for uterus-sparing treatment of endometrial precancers and well-differentiated early endometrial carcinoma in young women. Ann Oncol. 2011;22(3):643-9.

Mitsushita J, Toki T, Kato K, Fujii S, Konishi I. Endometrial carcinoma remaining after term pregnancy following conservative treatment with medroxyprogesterone acetate. Gynecol Oncol. 2000;79(1):129-32.

Moyer DL, Felix JC. The effects of progesterone and progestins on endometrial proliferation. Contraception. 1998;57(6):399-403.

Muechler EK, Bonfiglio T, Choate J, Huang KE. Pregnancy induced with menotropins in a woman with polycystic ovaries, endometrial hyperplasia, and adenocarcinoma. Fertil Steril. 1986;46(5):973-5.

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.

Mutter GL, Ince TA, Baak JP, Kust GA, Zhou XP, Eng C. Molecular identification of latent precancers in histologically normal endometrium. Cancer Res. 2001;61(11):4311-4.

Mutter GL, Lin MC, Fitzgerald JT, Kum JB, Baak JP, Lees JA, et al. Altered PTEN expression as a diagnostic marker for the earliest endometrial precancers. J Natl Cancer Inst. 2000;92(11):924-30.

Mutter GL, Lin MC, Fitzgerald JT, Kum JB, Eng C. Changes in endometrial PTEN expression throughout the human menstrual cycle. J Clin Endocrinol Metab. 2000;85(6):2334-8.

Nakao Y, Nomiyama M, Kojima K, Matsumoto Y, Yamasaki F, Iwasaka T. Successful pregnancies in 2 infertile patients with endometrial adenocarcinoma. Gynecol Obstet Invest. 2004;58(2):68-71.

Nishio H, Fujii T, Kameyama K, et al. Abdominal radical trachelectomy as a fertility-sparing procedure in women with early-stage cervical cancer in a series of 61 women. Gynecologic oncology. 2009;115(1):51-5.

Niwa K, Tagami K, Lian Z, Onogi K, Mori H, Tamaya T. Outcome of fertility-preserving treatment in young women with endometrial carcinomas. BJOG. 2005;112(3):317-20.

Nout RA, Bosse T, Creutzberg CL, Jurgenliemk-Schulz IM, Jobsen JJ, Lutgens LC, et al. Improved risk assessment of endometrial cancer by combined analysis of MSI, PI3K-AKT, Wnt/beta-catenin and P53 pathway activation. Gynecol Oncol. 2012;126(3):466-73.

Nyholm HC, Nielsen AL, Lyndrup J, Dreisler A, Thorpe SM. Estrogen and progesterone receptors in endometrial carcinoma: comparison of immunohistochemical and biochemical analysis. Int J Gynecol Pathol. 1993;12(3):246-52.

O'Neill RT. Pregnancy following hormonal therapy for adenocarcinoma of the endometrium. Am J Obstet Gynecol. 1970;108(2):318-21.

Ogawa S, Koike T, Shibahara H, Ohwada M, Suzuki M, Araki S, et al. Assisted reproductive technologies in conjunction with conservatively treated endometrial adenocarcinoma. A case report. Gynecol Obstet Invest. 2001;51(3):214-6.

Ota T, Yoshida M, Kimura M, Kinoshita K. Clinicopathologic study of uterine endometrial carcinoma in young women aged 40 years and younger. Int J Gynecol Cancer. 2005;15(4):657-62.

Ozdegirmenci O, Kayikcioglu F, Bozkurt U, Akgul MA, Haberal A. Comparison of the efficacy of three progestins in the treatment of simple endometrial hyperplasia without atypia. Gynecol Obstet Invest. 2011;72(1):10-4.

Pareja R, Rendon GJ, Sanz-Lomana CM, Monzon O, Ramirez PT. Surgical, oncological, and obstetrical outcomes after abdominal radical trachelectomy - a systematic literature review. Gynecol Oncol. 2013;131(1):77-82.

Park JC, Cho CH, Rhee JH. A successful live birth through in vitro fertilization program after conservative treatment of FIGO grade I endometrial cancer. Journal of Korean medical science. 2006;21(3):567-71.

Park JY, Kim DY, Kim JH, Kim YM, Kim KR, Kim YT, et al. Long-term oncologic outcomes after fertility-sparing management using oral progestin for young women with endometrial cancer (KGOG 2002). Eur J Cancer. 2013;49(4):868-74.

Park JY, Lee SH, Seong SJ, Kim DY, Kim TJ, Kim JW, et al. Progestin re-treatment in patients with recurrent endometrial adenocarcinoma after successful fertility-sparing management using progestin. Gynecol Oncol. 2013;129(1):7-11.

Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55(2):74-108.

Paulson RJ, Sauer MV, Lobo RA. Pregnancy after in vitro fertilization in a patient with stage I endometrial carcinoma treated with progestins. Fertil Steril. 1990

Penner KR, Dorigo O, Aoyama C, Ostrzega N, Balzer BL, Rao J, et al. Predictors of resolution of complex atypical hyperplasia or grade 1 endometrial adenocarcinoma in premenopausal women treated with progestin therapy. Gynecol Oncol. 2012;124(3):542-8.

Perri T, Korach J, Gotlieb WH, Beiner M, Meirow D, Friedman E, et al. Prolonged conservative treatment of endometrial cancer patients: more than 1 pregnancy can be achieved. Int J Gynecol Cancer. 2011;21(1):72-8.

Peters WA, 3rd, Liu PY, Barrett RJ, 2nd, Stock RJ, Monk BJ, Berek JS, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2000;18(8):1606-13.

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.

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.

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.

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.

Pinto AB, Gopal M, Herzog TJ, Pfeifer JD, Williams DB. Successful in vitro fertilization pregnancy after conservative management of endometrial cancer. Fertil Steril. 2001;76(4):826-9.

Piver MS, Rutledge F, Smith JP. Five classes of extended hysterectomy for women with cervical cancer. Obstet Gynecol. 1974;44(2):265-72.

Plante M, Gregoire J, Renaud MC, et al. The vaginal radical trachelectomy: an update of a series of 125 cases and 106 pregnancies. Gynecologic oncology. 2011;121(2):290-7.

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

Plante M. Bulky Early-Stage Cervical Cancer (2-4 cm Lesions): Upfront Radical Trachelectomy or Neoadjuvant Chemotherapy Followed by Fertility-Preserving Surgery: Which Is the Best Option? Int J Gynecol Cancer. 2015;25(4):722-8.

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

Porter ME. What is value in health care? The New England journal of medicine. 2010;363(26):2477-81.

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.

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.

Prat J, Ribe A, Gallardo A. Hereditary ovarian cancer. Human pathology. 2005;36(8):861-70.

Querleu D, Morrow CP. Classification of radical hysterectomy. Lancet Oncol. 2008;9:297-303.

Rackow BW, Arici A. Endometrial cancer and fertility. Curr Opin Obstet Gynecol. 2006;18(3):245-52.

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.

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.

Ramirez PT, Frumovitz M, Bodurka DC, Sun CC, Levenback C. Hormonal therapy for the management of grade 1 endometrial adenocarcinoma: a literature review. Gynecol Oncol. 2004;95(1):133-8.

Randall TC, Kurman RJ. Progestin treatment of atypical hyperplasia and well-differentiated carcinoma of the endometrium in women under age 40. Obstetrics and gynecology. 1997;90(3):434-40.

Raspagliesi F, Ditto A, Fontanelli R, et al. Nerve-sparing radical hysterectomy: a surgical technique for preserving the autonomic hypogastric nerve. Gynecologic oncology. 2004;93(2):307-14.

Reid-Nicholson M, Iyengar P, Hummer AJ, Linkov I, Asher M, Soslow RA. Immunophenotypic diversity of endometrial adenocarcinomas: implications for differential diagnosis. Mod Pathol. 2006;19(8):1091-100.

Renehan AG, Soerjomataram I, Leitzmann MF. Interpreting the epidemiological evidence linking obesity and cancer: A framework for population-attributable risk estimations in Europe. Eur J Cancer. 2010;46(14):2581-92.

Rob L, Halaska M, Robova H. Nerve-sparing and individually tailored surgery for cervical cancer. Lancet Oncol. 2010;11(3):292-301.

Rob L, Pluta M, Skapa P, Robova H. Advances in fertility-sparing surgery for cervical cancer. Expert Rev Anticancer Ther. 2010;10(7):1101-14.

Rodolakis A, Biliatis I, Morice P, Reed N, Mangler M, Kesic V, et al. European Society of Gynecological Oncology Task Force for Fertility Preservation: Clinical Recommendations for Fertility-Sparing Management in Young Endometrial Cancer Patients. Int J Gynecol Cancer. 2015;25(7):1258-65.

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.

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.

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.

Rotman M, Sedlis A, Piedmonte MR, Bundy B, Lentz SS, Muderspach LI, et al. A phase III randomized trial of postoperative pelvic irradiation in Stage IB cervical carcinoma with poor prognostic features: follow-up of a gynecologic oncology group study. Int J Radiat Oncol Biol Phys. 2006;65(1):169-76.

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.

Rydzewska L, Tierney J, Vale CL, et al. Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer. Cochrane database of systematic reviews (Online). 2010(1):CD007406.

Saegusa M, Hashimura M, Yoshida T, Okayasu I. beta- Catenin mutations and aberrant nuclear expression during endometrial tumorigenesis. Br J Cancer. 2001;84(2):209-17.

Saegusa M, Okayasu I. Frequent nuclear beta-catenin accumulation and associated mutations in endometrioid-type endometrial and ovarian carcinomas with squamous differentiation. J Pathol. 2001;194(1):59-67.

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.

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.

Salha O, Martin-Hirsch P, Lane G, Sharma V. Endometrial carcinoma in a young patient with polycystic ovarian syndrome: first suspected at time of embryo transfer. Hum Reprod. 1997;12(5):959-62.

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.

Sardi J, Anchezar Henry JP, Paniceres G, Gomez Rueda N, Vighi S. Primary hormonal treatment for early endometrial carcinoma. Eur J Gynaecol Oncol. 1998;19(6):565-8.

Satyaswaroop PG. Development of a preclinical model for hormonal therapy of human endometrial carcinomas. Annals of medicine. 1993;25(2):105-11.

Schain WS. Patients' rights in decision making: the case for personalism versus paternalism in health care. Cancer. 1980;46(4 Suppl):1035-41.

Schammel DP, Mittal KR, Kaplan K, Deligdisch L, Tavassoli FA. Endometrial adenocarcinoma associated with intrauterine pregnancy. A report of five cases and a review of the literature. Int J Gynecol Pathol. 1998;17(4):327-35.

Scholten AN, Creutzberg CL, van den Broek LJ, Noordijk EM, Smit VT. Nuclear beta-catenin is a molecular feature of type I endometrial carcinoma. J Pathol. 2003;201(3):460-5.

Scholten RJPM OM, Assendelft WJJ. Inleiding in Evidence-Based Medicine. Klinisch handelen gebaseerd op bewijsmateriaal. Houten: Bohn, Stafleu, Van Loghum; 2013. 285 p.

Schouten LJ, Goldbohm RA, van den Brandt PA. Anthropometry, physical activity, and endometrial cancer risk: results from the Netherlands cohort study. Int J Gynecol Cancer. 2006;16 Suppl 2:492.

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.

Sedrakyan A, Campbell B, Graves S, Cronenwett JL. Surgical registries for advancing quality and device surveillance. Lancet. 2016;388(10052):1358-60.

Shamshirsaz AA, Withiam-Leitch M, Odunsi K, Baker T, Frederick PJ, Lele S. Young patients with endometrial carcinoma selected for conservative treatment: a need for vigilance for synchronous ovarian carcinomas, case report and literature review. Gynecol Oncol. 2007;104(3):757-60.

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.

Shibahara H, Shigeta M, Toji H, Wakimoto E, Adachi S, Ogasawara T, et al. Successful pregnancy in an infertile patient with conservatively treated endometrial adenocarcinoma after transfer of embryos obtained by intracytoplasmic sperm injection. Hum Reprod. 1999;14(7):1908-11.

Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014;64(1):9-29.

Simpson AN, Feigenberg T, Clarke BA, Gien LT, Ismiil N, Laframboise S, et al. Fertility sparing treatment of complex atypical hyperplasia and low-grade endometrial cancer using oral progestin. Gynecol Oncol. 2014;133(2):229-33.

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.

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.

Sobin L. TNM Classification of malignant tumours. Geneva2002 [updated 2002. UICC Internation Union against Cancer:[155-7].

Soderini A. Is the nerve sparing (NS) a new standard in radical hysterectomy (NSRH) for cervical cancer (CC)? International Gynecological Cancer Society 12th Biennial Meeting, Bangkok, Thailand; 25 October 2008.

Song T, Seong SJ, Bae DS, Suh DH, Kim DY, Lee KH, et al. Synchronous primary cancers of the endometrium and ovary in young women: a Korean Gynecologic Oncology Group Study. Gynecol Oncol. 2013;131(3):624-8.

Sorosky JI. Endometrial cancer. Obstetrics and gynecology. 2008;111(2 Pt 1):436-47.

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.

Spaans VM, Trietsch MD, Crobach S, Stelloo E, Kremer D, Osse EM, et al. Designing a high-throughput somatic mutation profiling panel specifically for gynaecological cancers. PLoS One. 2014;9(3):e93451.

Sparac V, Ujevic B, Ujevic M, Pagon-Belina Z, Marton U. Successful pregnancy after hysteroscopic removal of grade I endometrial carcinoma in a young woman with Lynch syndrome. Int J Gynecol Cancer. 2006;16 Suppl 1:442-5.

Speiser D, Mangler M, Kohler C, et al. Fertility Outcome After Radical Vaginal Trachelectomy: A Prospective Study of 212 Patients. Int J Gynecol Cancer. 2011.

Stein PD, Beemath A, Olson RE. Obesity as a risk factor in venous thromboembolism. Am J Med. 2005;118(9):978-80.

Stelloo E, Bosse T, Nout RA, MacKay HJ, Church DN, Nijman HW, et al. Refining prognosis and identifying targetable pathways for high-risk endometrial cancer; a TransPORTEC initiative. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc. 2015;28(6):836-44.

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.

Takahashi N, Hirashima Y, Harashima S, Takekuma M, Kawaguchi R, Yamada Y, et al. A patient with stage 1a endometrial carcinoma in whom a solitary recurrent lesion was detected in the external iliac lymph node after MPA therapy. Arch Gynecol Obstet. 2008;278(4):365-7.

Tang J, Li J, Wang S, Zhang D, Wu X. On what scale does it benefit the patients if uterine arteries were preserved during ART? Gynecol Oncol. 2014;134(1):154-9.

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

Thigpen JT, Brady MF, Alvarez RD, Adelson MD, Homesley HD, Manetta A, et al. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the **Gynecologic Oncology Group**. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1999;17(6):1736-44.

Thornton JG, Brown LA, Wells M, Scott JS. Primary treatment of endometrial cancer with progestagen alone. Lancet. 1985;2(8448):207-8.

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.

Tran BN, Connell PP, Waggoner S, Rotmensch J, Mundt AJ. Characteristics and outcome of endometrial carcinoma patients age 45 years and younger. American journal of clinical oncology. 2000;23(5):476-80.

Treffers. Obstetrie en gynaecologie. 2e herziene druk ed1995. p. 672.

Trimbos JB, Maas CP, Deruiter MC, Kenter GG. [Nerve sparing radical hysterectomy in the case of cervical cancer]. Ned Tijdschr Geneeskd. 2003;147(28):1344-7.

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.

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.

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.

Twijnstra AR, Blikkendaal MD, van Zwet EW, van Kesteren PJ, de Kroon CD, Jansen FW. Predictors of successful surgical outcome in laparoscopic hysterectomy. Obstetrics and gynecology. 2012;119(4):700-8.

Ulbright TM, Roth LM. Metastatic and independent cancers of the endometrium and ovary: a clinicopathologic study of 34 cases. Human pathology. 1985;16(1):28-34.

Ushijima K, Yahata H, Yoshikawa H, Konishi I, Yasugi T, Saito T, et al. Multicenter phase II study of fertility-sparing treatment with medroxyprogesterone acetate for endometrial carcinoma and atypical hyperplasia in young women. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2007;25(19):2798-803.

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.

van der Zee M, Jia Y, Wang Y, Heijmans-Antonissen C, Ewing PC, Franken P, et al. Alterations in Wnt-beta-catenin and Pten signalling play distinct roles in endometrial cancer initiation and progression. J Pathol. 2013;230(1):48-58.

van Eijk R, Licht J, Schrumpf M, Talebian YM, Ruano D, Forte GI, et al. Rapid KRAS, EGFR, BRAF and PIK3CA mutation analysis of fine needle aspirates from non-small-cell lung cancer using allele-specific qPCR. PLoS One. 2011;6(3):e17791.

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.

van Gent MDJM, Kagie MJ, Trimbos JB. No surgery for Low-Grade Endometrial Cancer in Women with a Desire to Preserve Fertility. Journal of gynecologic Surgery. 2012;28(6):389-98.

van Gent MDJM, Kagie MJ, Trimbos JBMZ. Conservatieve behandeling van endometriumcarcinoom bij patiënten met kinderwens. Nederlands Tijdschrift voor Obstetrie en Gynaecologie. 2009;122:33-6.

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.

Vasen HF, Wijnen JT, Menko FH, et al. Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. Gastroenterology 1996;110:1020.

Vereide AB, Kaino T, Sager G, Orbo A. Bcl-2, BAX, and apoptosis in endometrial hyperplasia after high dose gestagen therapy: a comparison of responses in patients treated with intrauterine levonorgestrel and systemic medroxyprogesterone. Gynecol Oncol. 2005;97(3):740-50.

Vinker S, Shani A, Open M, Fenig E, Dgani R. Conservative treatment of adenocarcinoma of the endometrium in young patients. Is it appropriate? Eur J Obstet Gynecol Reprod Biol. 1999;83(1):63-5.

Wan YL, Beverley-Stevenson R, Carlisle D, Clarke S, Edmondson RJ, Glover S, et al. Working together to shape the endometrial cancer research agenda: The top ten unanswered research questions. Gynecol Oncol. 2016;143(2):287-93.

Wang CB, Wang CJ, Huang HJ, Hsueh S, Chou HH, Soong YK, et al. Fertility-preserving treatment in young patients with endometrial adenocarcinoma. Cancer. 2002;94(8):2192-8.

Wang S, Pudney J, Song J, Mor G, Schwartz PE, Zheng W. Mechanisms involved in the evolution of progestin resistance in human endometrial hyperplasia--precursor of endometrial cancer. Gynecol Oncol. 2003;88(2):108-17

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.

Wang Y, Hanifi-Moghaddam P, Hanekamp EE, Kloosterboer HJ, Franken P, Veldscholte J, et al. Progesterone inhibition of Wnt/beta-catenin signaling in normal endometrium and endometrial cancer. Clin Cancer Res. 2009;15(18):5784-93.

Wang Y, van der Zee M, Fodde R, Blok LJ. Wnt/Beta-catenin and sex hormone signaling in endometrial homeostasis and cancer. Oncotarget. 2010;1(7):674-84.

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.

Wheeler DT, Bristow RE, Kurman RJ. Histologic alterations in endometrial hyperplasia and well-differentiated carcinoma treated with progestins. Am J Surg Pathol. 2007;31(7):988-98.

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.

Wu HM, Lai CH, Huang HY, Wang HS, Soong YK. A successful live twin birth by in vitro fertilization after conservative treatment of recurrent endometrial cancer. Chang Gung medical journal. 2008;31(1):102-6.A229

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.

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.

Yahata T, Fujita K, Aoki Y, Tanaka K. Long-term conservative therapy for endometrial adenocarcinoma in young women. Hum Reprod. 2006;21(4):1070-5.

Yamazawa K, Hirai M, Fujito A, Nishi H, Terauchi F, Ishikura H, et al. Fertility-preserving treatment with progestin, and pathological criteria to predict responses, in young women with endometrial cancer. Human reproduction (Oxford, England). 2007;22(7):1953-8.

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.

Yang YC, Wu CC, Chen CP, Chang CL, Wang KL. Reevaluating the safety of fertility-sparing hormonal therapy for early endometrial cancer. Gynecologic oncology. 2005;99(2):287-93.

Yang S, Thiel KW, Leslie KK. Progesterone: the ultimate endometrial tumor suppressor. Trends Endocrinol Metab. 2011;22(4):145-52.

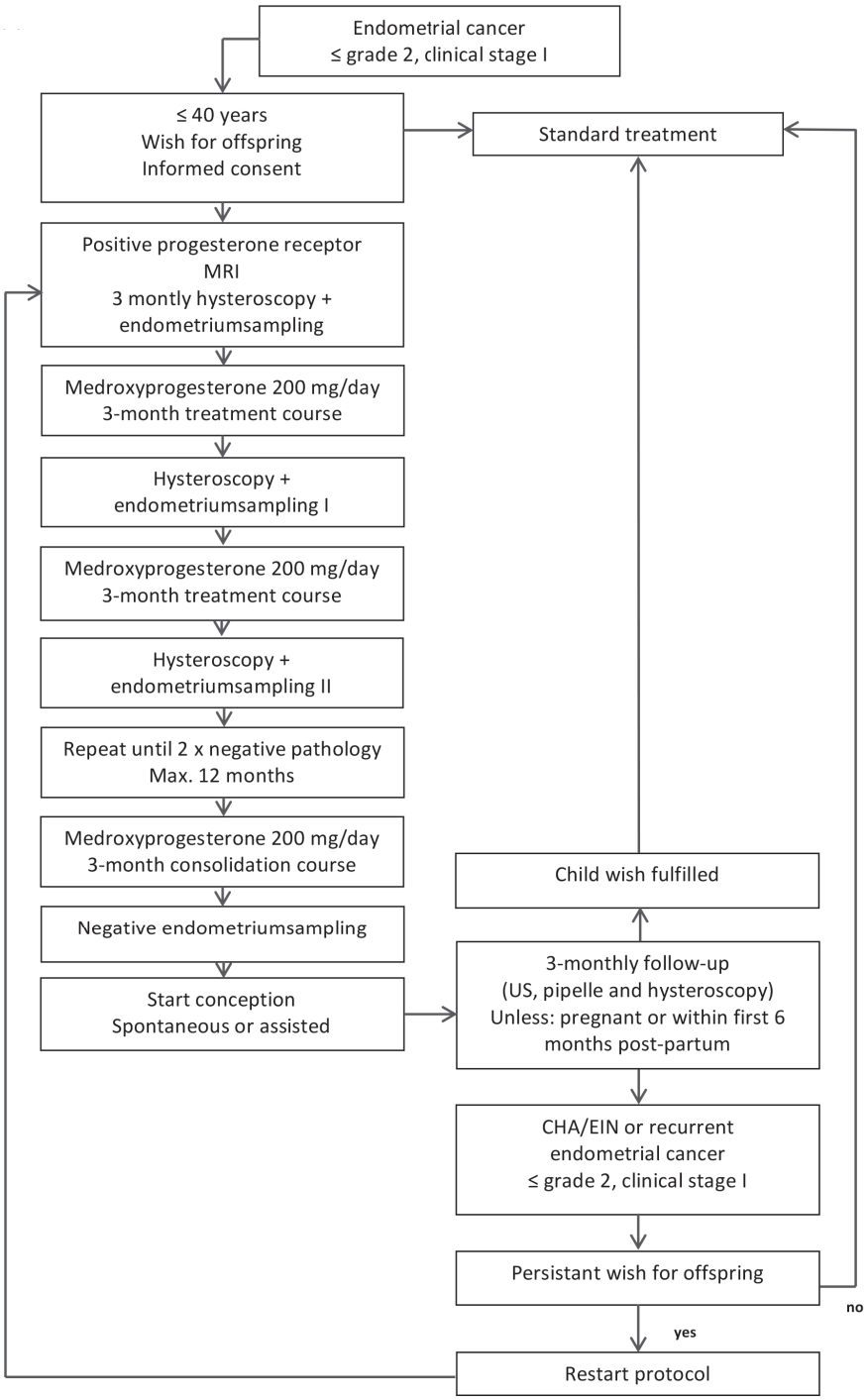
Yao YY, Wang Y, Wang JL, Zhao C, Wei LH. Outcomes of fertility and pregnancy in patients with early-stage cervical cancer after undergoing neoadjuvant chemotherapy. European journal of gynaecological oncology. 2016;37(1):109-12.

Yarali H, Bozdag G, Aksu T, Ayhan A. A successful pregnancy after intracytoplasmic sperm injection and embryo transfer in a patient with endometrial cancer who was treated conservatively. Fertil Steril. 2004;81(1):214-6.

Zanetta G GA, Losa G, Cappellini A, Mangioni C. conservative management of endometrial carcinoma with prolonged preservation of the uterus in a young patient. Int J Gynecol Cancer. 1997;7:332-4.

Zuckerman B LO, Neumann M, et al. Endometrial carcinoma Stage I-Grade II. Conservative treatment followed by a healthy twin pregnancy. Int J Gynecol Cancer. 2002;8(2):172-4.

APPENDIX 1. FLOWCHART



A

APPENDIX 2.

Part 1a. Results of 33 patients with EIN or LG EEC treated with progesterones in order to preserve fertility

Treated according to protocol	Pts (n = 33)	Age at Dx	BMI	Reason for analysis	GxPx pre-Tx	MRI	PA	PR	ER	Tx
NO	**a**	33	28.7	F	G1P0	-	LG EEC	+	+	MPA other
NO	**b**	21	38.8	P	G0	Normal	LG EEC	+	uk	MPA other (12 mo) + LNG-IUD
NO	**c**	33	26.0	F	G0	<50 % MI	LG EEC	+	+	MPA other
NO	**d**	29	28.0	F & P	G.P1	Normal	LG EEC	+	+	MPA 200mg/d + LNG-IUD
NO	**e**	30	38.2	F & P	G0	0 % MI	LG EEC	uk	uk	MPA other
NO	**f**	37	30.0	P	G0	Normal	LG EEC	+	uk	MPA 200mg/d
NO	**g**	36	33.2	F & P	G0	-	LG EEC	uk	uk	MPA other + LNG-IUD
NO	**h**	40	24.0	P	G0	> 50% MI	LG EEC	+	+	MPA 200mg/d
NO	**i**	32	23.7	P	G0	<50 % MI	LG EEC	+	+	MPA 200mg/d
NO	**j**	27	31.1	F	G1P1	Normal	LG EEC	+	+	MPA 200mg/d
NO	**k**	38	23.2	F	G3P0	0 % MI	LG EEC	+	+	Prog. other
NO	**l**	28	32.9	F & P	G.P1	-	EIN	uk	uk	MPA other
YES	**m**	33	-	P	G0	-	EIN	+	+	MPA 200mg/d
YES	**n**	37	28.0	P	G1P0	-	EIN	+	+	Endometrium resection + MPA 200mg/d

Duration Course 1	FR after	CR after	Time to recurrence after end Tx	No of Hx	Fertility after course 1	Duration Course 2	FR after	CR after	Time to recurrence after end Tx	No of Hx
11 mo	5 mo	11 mo	-	9	1 x term, 1 x MC	-	-	-	-	-
24 mo	10 mo	24 mo	-	8	0	-	-	-	-	-
8 mo	4 mo	8 mo	16 mo	3	0 (2 x IVF/ ICSI)	4 mo	1 mo	4 mo	-	6
12 mo +	?	?	-	5 +	1	-	-	-	-	-
10 mo	9 mo	-	21 mo	3	1 x MC	4 mo	3 mo	-	-	2
19 mo	16 mo	19 mo	7 mo	8	0	-	-	-	-	-
17 mo	17 mo	-	5 mo	7	0	-	-	-	-	-
25 mo	17 mo	-	-	6	0	-	-	-	-	-
3 mo	-	-	-	3	0	-	-	-	-	-
12 mo	5 mo	8 mo	3 mo	4	0	22 mo ?	19 mo	22 mo	43 mo	6
10 mo	6 mo	-	-	5	0	-	-	-	-	-
8 mo	5 mo	8 mo	20 mo	6	0	14 mo	5 mo	22 mo	15 mo	7
11 mo	4 mo	7 mo	-	6	1 x AD 25 wk	-	-	-	-	-
8 mo	3 mo	8 mo	-	-	-	-	-	-	-	-

Part 1a. Continued

Treated according to protocol	Pts (n = 33)	Age at Dx	BMI	Reason for analysis	GxPx pre-Tx	MRI	PA	PR	ER	Tx
YES	**o**	35	20.8	F	G0	Normal	LG EEC	+	+	MPA 200mg/d
YES	**p**	37	23.0	F	G0	Normal	LG EEC	+	+	MPA 200mg/d
YES	**q**	39	-	P	G0	Normal	LG EEC	+		MPA 200mg/d + LNG-IUD
YES	**r**	31	20.2	P	G0	0 % MI	LG EEC	+	+	MPA 200mg/d
YES	**s**	36	23.0	F	G0	-	EIN	-	+	MPA 200mg/d
YES	**t**	36	36.9	F	G1P0	-	EIN	+	+	MPA 200mg/d
YES	**u**	29	22.0	F	G0	0 % MI	LG EEC	+	+	MPA other
YES	**v**	34	27.7	P	G0	-	LG EEC	+	+	Prog. other
YES	**w**	37	48.0	uk	G0	-	LG EEC	+	+	MPA 200mg/d
YES	**x**	32	30.1	F & P	G0	Normal	LG EEC	+	+	MPA 200mg/d + LNG-IUD
YES	**y**	37	25.6	P	G0	0 % MI	LG EEC	+	+	MPA 200mg/d
YES	**z**	27	35.0	P	G0	<50 % MI	LG EEC	+	uk	MPA 200mg/d
YES	**aa**	35	20.0	F	G0	0 % MI	LG EEC	+	uk	MPA 200mg/d
YES	**bb**	31	23.9	P	G0	0 % MI	LG EEC	+	+	MPA 200mg/d
YES	**cc**	25	29.0	P	G0	-	LG EEC	+		MPA 200mg/d + LNG-IUD
YES	**dd**	28	23.9	P	G0	Normal	LG EEC	+	+	MPA 200mg/d

Duration Course 1	FR after	CR after	Time to recurrence after end Tx	No of Hx	Fertility after course 1	Duration Course 2	FR after	CR after	Time to recurrence after end Tx	No of Hx
9 mo	6 mo	9 mo	23 mo	6	0	6 mo	3 mo	6 mo	-	3 +
6 mo	3 mo	6 mo	-	9	2 (1 x IUFD AD 16 wk, 1 x term)	-	-	-	-	-
11 mo	7 mo	11 mo	-	5	0	-	-	-	-	-
10 mo	4 mo	7 mo	-	6	-	-	-	-	-	-
7 mo	2 mo	6 mo	-	-	-	-	-	-	-	-
10 mo	7 mo	10 mo	-	-	-	-	-	-	-	-
10 mo	5 mo	8 mo	-	-	1 x term	-	-	-	-	-
11 mo	3 mo	-	-	5	0	-	-	-	-	-
6 mo	3 mo	6 mo	-	3	0	-	-	-	-	-
4 mo	-	-	-	2	0	-	-	-	-	-
11 mo	-	-	-	5	0	-	-	-	-	-
6 mo	3 mo	6 mo	13 mo	6	0	-	-	-	-	-
14 mo	10 mo	14 mo	8 mo	6	0	6 mo	3 mo	6 mo	12 mo	3
11 mo	4 mo	7 mo	11 mo	7	0	-	-	-	-	-
34 mo	5 mo	8 mo	5 mo	7	0	3 mo +	-	-	-	-
6 mo	3 mo	6 mo	6 mo	4	0	12 mo	4 mo	-	-	-

Part 1a. Continued

Treated according to protocol	Pts (n = 33)	Age at Dx	BMI	Reason for analysis	GxPx pre-Tx	MRI	PA	PR	ER	Tx
YES	**ee**	27	27.4	F	G0	Normal	LG EEC	+	+	MPA 200mg/d
YES/no¥	**ff**	38	22.8	F	G0	0 % MI	LG EEC	+	+	MPA other
YES/no¥¥	**gg**	31	22.0	P	G0	0 % MI	LG EEC			MPA 200mg/d

Legend: Dx: diagnosis, Tx: therapy, FR: first response, CR: complete response, Hx: hysteroscopy, FU: follow-up, LNG-IUD: levonogestrel releasing IUD, MPA: medroxyprogesterone, mo: months, F: fertility issues, P: period issues, ER: Estrogen receptor, PR: progesterone receptor, MI: myometrial involvement, MC: miscarriage, LG ECC: low-grade endometrial cancer, EIN: endometrioid intra-epithelial neoplasia, Hyst: hysterectomy, BSO: bilateral salpingo-oophorectomy, USO: unilateral salpingo-oophorectomy, NED: no evidence of disease, IUFD: intra- uterine fetal death, term: term delivery, GTD: Gestational Trophoblastic Disease, LTFU: lost to follow up.

Duration Course 1	FR after	CR after	Time to recurrence after end Tx	No of Hx	Fertility after course 1	Duration Course 2	FR after	CR after	Time to recurrence after end Tx	No of Hx
11 mo	3 mo	6 mo	36 mo	9	1 x term 1 x MC	6 mo	3 mo	6 mo	-	3
9 mo	9 mo	12 mo	-	5	0	-	-	-	-	-
9 mo	4 mo	7 mo	- 3 mo ##	5	1 x MC	-	-	-	-	-

Definitions: Negative pathology result: no abnormalities/hyperplasia without atypia/progesterone effect; Responder: 2 x negative pathology result

* Recurrence in remaining ovary. Laparoscopic resection, no other signs of disease, abdominal fluid negative. Adjuvant pelvic irradiation. Stage 3 EC.

** Advice: hysterectomy since no response after 12 months. Second opinion abroad: continued medication and resulted in response and pregnancy, therefore temporarily LTFU.

*** Temporarily refusal for definitive therapy

**** Progression after first 3 mo. Advice: hysterectomy, temporarily refusal by patient, 4 month delay until surgery.

Last therapy before Hysterectomy was endometrium resection

3 Months before stop progesterone: EIN

¥ Mostly but no because therapy was stopped after only one negative pathology report

¥¥ Mostly but no because therapy was stopped eventhough 3 months before pathology was reported as EIN

Part 1b. Results of 33 patients with EIN or LG EEC treated with progesterones in order to preserve fertility

Treated according to protocol	Pts (n = 33)	Fertility after course 2	Total FU	Status at last FU	Final treatment	PA final
NO	**a**	-	124 mo	NED	FU	-
NO	**b**	-	24 mo	NED	FU	-
NO	**c**	0 (IVF-ICSI attempt)	87 mo	NED	FU	-
NO	**d**	-	34 mo	NED	FU	-
NO	**e**	1 x MC 2 x Term	129 mo	NED	Hysterectomy	no cancer
NO	**f**	-	75 mo	NED	Hysterectomy	LG EEC
NO	**g**	-	33 mo	NED	Hysterectomy + BSO	LG EEC
NO	**h**	-	38 mo	NED	Hysterectomy + BSO	LG EEC
NO	**i**	-	23 mo	NED	Hysterectomy + BSO	LG EEC
NO	**j**	2 x MC	89 mo	NED	Hysterectomy + tubectomy	no cancer
NO	**k**	-	16 mo	LG EEC	Hysterectomy + tubectomy	no cancer #
NO	**l**	0	59 mo	EIN	Ongoing treatment	-
YES	**m**	-	19 mo	Pregnant AD 25	FU	-
YES	**n**	-	15 mo	NED	FU	-

Stage	Reason Hysterectomy	GxPx post-Tx	Fertility tx	Pregnancy outcome	Recurrence after hysterectomy	Other
-	-	G3P1	IVF	1 x term, 1 x MC	-	Temp. LTFU
-	-	G0	-	UK	-	FU elsewhere
-	-	G0	IVF/ICSI	-	-	LTFU gyn, GP: NED
-	-	-	-	Pre-term delivery AD 36.5	-	SO abroad**
-	Completed family	G4P2	IUI	2 x Term 2 x MC	no	2 Extra periods of LNG-IUD
1A	Inadequate response + recurrent disease	G0	IVF	-	no	-
1A	Recurrence	G0	none	-	-	After 10 mo + LNG-IUD
1A	Persistant disease	G0	-	-	no	Patient delay ***
3	Progressive disease	G0	-	-	no	Patient delay ****
-	doubt on IVF chances	G3P1	IVF	2 x MC	no	Course 3: CR after 6 months, 7 hysteroscopies
-	no response	G3P0	-	-	no	
-	-	-	-	-	-	-
-	-	G1 AD 25 wk	none	AD 25 wk	-	-
-	-	-	-	-	-	-

Part 1b. Continued

Treated according to protocol	Pts (n = 33)	Fertility after course 2	Total FU	Status at last FU	Final treatment	PA final
YES	**o**	-	89 mo	NED	FU	-
YES	**p**	-	49 mo	NED	FU	-
YES	**q**	-	26 mo	NED	FU	-
YES	**r**	-	14 mo	NED	FU	-
YES	**s**	-	9 mo	NED	FU	-
YES	**t**	-	10 mo	NED	FU	-
YES	**u**	-	21 mo	post partum	FU	-
YES	**v**	-	46 mo	NED	Hysterectomy	no cancer
YES	**w**	-	33 mo	NED	Hysterectomy	LG EEC
YES	**x**	-	23 mo	NED	Hysterectomy + BSO	LG EEC
YES	**y**	-	23 mo	NED	Hysterectomy + BSO	LG EEC
YES	**z**	-	20 mo	NED	Hysterectomy + tubectomy	LG EEC
YES	**aa**	0	75 mo	NED	Hysterectomy + tubectomy	no cancer
YES	**bb**	-	62 mo	NED	Hysterectomy + USO	LG EEC
YES	**cc**	-	40 mo	EIN	Ongoing treatment	-
YES	**dd**	-	25 mo	NED	Ongoing treatment	-
YES	**ee**	1 x AD 32	67 mo	Pregnant AD 32	-	-

Stage	Reason Hysterectomy	GxPx post-Tx	Fertility tx	Pregnancy outcome	Recurrence after hysterectomy	Other
-	-	G0	IUI	-	-	-
-	-	G2P2-1	IVF	1 x IUFD 1 x term	-	-
-	-	-	-	-	-	-
-	-	-	-	-	-	-
-	-	-	IUI	-	-	-
-	-	-	-	-	-	-
-	-	G1 P1	IVF	1 x term	-	-
	no response	0	-	-	no	-
1A	no more wish to preserve fertility	0	-	-	no	-
1A	no more wish to preserve fertility	G0	-	-	no	-
1A	no response	G0	-	-	no	-
1A	recurrence	G0	clomid	-	no	-
-	recurrence	G0	none	-	no	Extra periods of LNG -IUD
1A	recurrence	G0	none	0	yes *	-
-	-	-	-	-	-	Repeated dislocation LNG-IUD
-	-	-	-	-	‘-	-
-	-	G3P1	IUI	1 x term, 1 x MC, 1 x AD 32 wkn	-	-

Part 1b. Continued

Treated according to protocol	Pts (n = 33)	Fertility after course 2	Total FU	Status at last FU	Final treatment	PA final
YES/no[¥]	**ff**	-	53 mo	NED	Hysterectomy	LG EEC
YES/no[¥¥]	**gg**	-	16 mo	GTD	-	-

Legend: Dx: diagnosis, Tx: therapy, FR: first response, CR: complete response, Hx: hysteroscopy, FU: follow-up, LNG-IUD: levonogestrel releasing IUD, MPA: medroxyprogesterone, mo: months, F: fertility issues, P: period issues, ER: Estrogen receptor, PR: progesterone receptor, MI: myometrial involvement, MC: miscarriage, LG ECC: low-grade endometrial cancer, EIN: endometrioid intra-epithelial neoplasia, Hyst: hysterectomy, BSO: bilateral salpingo-oophorectomy, USO: unilateral salpingo-oophorectomy, NED: no evidence of disease, IUFD: intra- uterine fetal death, term: term delivery, GTD: Gestational Trophoblastic Disease, LTFU: lost to follow up.

Stage	Reason Hysterectomy	GxPx post-Tx	Fertility tx	Pregnancy outcome	Recurrence after hysterectomy	Other
1A	Hyperplasia, no atypia, worries with doctor/pt	G0	none	-	no	-
-	-	1	-	1 x MC	-	

Definitions: Negative pathology result: no abnormalities/hyperplasia without atypia/progesterone effect; Responder: 2 x negative pathology result

* Recurrence in remaining ovary. Laparoscopic resection, no other signs of disease, abdominal fluid negative. Adjuvant pelvic irradiation. Stage 3 EC.

** Advice: hysterectomy since no response after 12 months. Second opinion abroad: continued medication and resulted in response and pregnancy, therefore temporarily LTFU.

*** Temporarily refusal for definitive therapy

**** Progression after first 3 mo. Advice: hysterectomy, temporarily refusal by patient, 4 month delay until surgery.

Last therapy before Hysterectomy was endometrium resection

3 Months before stop progesterone: EIN

¥ Mostly but no because therapy was stopped after only one negative pathology report

¥¥ Mostly but no because therapy was stopped eventhough 3 months before pathology was reported as EIN

Part 2. Results of 33 patients with EIN or LG EEC treated with progesterones in order to preserve fertility

Age	mean/median	33
BMI	mean	28
	median	27.4
Follow-up (months)	mean	44.4
	median	33
CR course 1 (n)		61% (20/33)
Time to CR course 1 (months)	mean	8
	median	7.5
Recurrence after CR course 1 (n)		65% (13/20)
Time to recurrence after stop Tx course 1 (months)	mean	13.4
	median	11
CR course 2 after recurrence (9 attempts)		67% (6/9)
Time to CR course 2 (months)	mean	11
	median	6
Recurrence after CR course 2 (n)		50% (3/6)
Time to recurrence after stop Tx course 2 (months)	mean	23.3
	median	15
Pregnancies		**17**
Term delivery		6
Pre-term delivery (AD 36.5 wk)		1
Pregnant (AD 25 + 32 wk)		2
IUFD (16 wks)		1
Miscarriage		7
Hysterectomies		**15**
No malignancy		5
Grade 1		**10**
	Stage 1A	9
	Stage 3	1
Recurrence after hysterectomy + USO	Ovarian met.	1

A

CURRICULUM VITAE

The author of this thesis was born in Veghel, the Netherlands, on September 14, 1980. She attended the public elementary school "De Uilenbrink" in Veghel and went subsequently to the pre-university school "Gymnasium Bernrode".
She started medical school at the University of Leiden in September 1998 and obtained her bachelor's degree in 1999. From 1999 until 2005 she studied medicine. During this time, she spent a month in Messina, Sicily, learning under Professor Maggazu' (paediatrics). After receiving a grant from the Dutch and the American Heart association, she worked during half a year, under Associate Professor Mary Etta King (paediatrics), as a researcher on extra corporeal membrane oxygenation (ECMO) at the department of paediatric cardiology of Harvard affiliated Massachusetts General Hospital, Boston, USA. Directly after finishing medical school she started working as a junior obstetrics and gynaecology resident at Haaglanden Medical Center (HMC), The Hague, previously known as Medical Center Haaglanden (MCH). She continued working there as a registrar from 2008 onwards (Prof. Dr. P.J. Dörr †, Dr. M.J. Kagie). The academic part of the training was performed at the Leiden University Medical Center (Prof. Dr. H.H.H. Kanhai, later Prof. Dr. J.M.M. van Lith), Leiden. She went to Perth, Australia to do her fourth year of training at the King Edward Memorial Hospital (Dr. Anne Karczub).
During her junior residency, she started the research on conservative management of endometrial cancer for women with the desire to preserve fertility. This developed into a PhD project including fertility-sparing and nerve-sparing surgery for cervical cancer. In 2014 she finished her training and became a consultant gynaecologist. She started her career as a gynaecologist at the HMC. In order to realize her future goal of becoming a gynaecologic oncologist, she started at the Antoni van Leeuwenhoek Hospital – Netherlands Cancer Institute in Amsterdam as a consultant. In 2016, she started her fellowship gynaecologic oncology at the Center of Gynaecologic Oncology Amsterdam.
Mignon is married to Sjoerd Meijer and they have 3 sons: Mats (2011), Joep (2013) and Wiebe (2014).

A

ACKNOWLEDGEMENTS/DANKWOORD

Dankzij de steun van velen is dit proefschrift tot stand gekomen. Het is onmogelijk iedereen te noemen maar ik wil een aantal in het bijzonder bedanken.

De patiënten - Gynaecologen die patiënten hebben aangeleverd voor het onderzoek -Secretariaten gynaecologie van het HMC, LUMC en AVL - Landsteiner Instituut/ wetenschapscommissie (HMC) - Maatschap gynaecologie HMC - Mijn oud-opleiders Joep Dörr †, Marjolein Kagie, Cas Holleboom, Humphrey Kanhai, Anne Karczub en Jan van Lith - Afdelingen pathologie en medische statistiek en ethiek (LUMC) - Mijn opleidingsgenoten en in het bijzonder Muriel, Jessica, Heleen en Wietske - Jan Schoones (Walaeus bibliotheek), Thomas Vissers (bibliotheek HMC) - Ellen, Inge (x2), Mandy, Dacia, Evelien, Loes en Karin en Linda; jullie kennis, loyaliteit en doorzettingsvermogen zijn van grote waarde - Mijn collega's uit het AVL: Marc, Hans, Willemien, Christianne, Henry, Nienke, Frédéric, Lotte, Samantha, Regillio en de rest van het CGOA. Frédéric, het eerste kopje koffie op de stoep voor onze introductiecursus bleek goud waard - Marijke, dank voor je snelle acties op mijn duizenden verzoeken (en je koffie en zelfgemaakte taart) - Mijn vrienden - Mijn co-autheurs - Mijn (schoon) familie - aanhang - Saskia Sedney, zonder jou waren we nergens – Lobke, Kaak en Moniek, old friends en natuurlijk mijn paranimfen Wietske, Naomi en Eveliene.

-

Baptist, ik heb veel respect voor jouw chirurgische kunsten en ben vereerd nog "in het staartje" je promovendus te mogen zijn.

-

Cor, dank voor je positieve energie en je flexibiliteit, wat was het een project! Heel fijn hoe je me altijd weer wist te motiveren om door te gaan.

-

Marjolein, vanaf dag één dat ik in het Westeinde binnenstapte was het goed en heb je me gestimuleerd onderzoek te doen en werk te maken van mijn carrière. Je hebt meermaals een cruciale rol gespeeld in deze, ik kan je daar niet genoeg voor bedanken.

-

Gemma "G", jij hebt het stokje van Marjolein overgenomen. De sandwich op de IGCS was hilarisch, gelukkig hadden we publiek.

-

Ko, dank voor je eis dat mijn proefschrift af moest zijn voor de start van mijn fellowship. Dat gaf de boost om er een flinke slinger aan te geven. In ieder geval is het af voordat ik naar het AMC kom.

-

Lieve Naomi en Eveliene, jullie zijn vanaf de eerste studiedag van geneeskunde mijn dikke vriendinnen en daar is nooit verandering in gekomen. We hebben zo veel life events met elkaar doorgemaakt en elkaar zien groeien in het vak en in het leven. Dit zetten we voort tot we 134 zijn. Lieve Caro, jij vlocht hier mooi bij in, en dank voor het prachtige kunstwerk op de kaft.

-

Lieve Wiets, we hebben ieder duidelijk een andere weg gekozen maar blijven ongelofelijk veel overeenkomsten creëren. Ik vind dat mooi.

-

Lieve opa en oma van Gent, dank voor alles, u mag weer naar het academiegebouw!

-

Lieve opa en oma van Well, vreselijk zonde dat ik dit proefschrift niet meer aan u kan sturen, maar ik voel me nog altijd door jullie gesteund.

-

Lieve ouders, dank voor jullie onvoorwaardelijke steun vanaf het moment dat ik dokter wilde worden op de basisschool. Jullie hebben nooit getwijfeld aan mijn kunnen en hebben altijd overal kansen in gezien. Jullie hebben mij geleerd dat doelen bereikbaar zijn.

-

Lieve broertjes en zusje (Harry, Sébastiaan en Nathalie), ik ben trots op alles wat jullie doen, trots op jullie als persoon en trots dat ik jullie zus ben.

-

Lieve mannen, Sjoerd, Mats, Joep en Wiebe, jullie zijn mijn liefsten. Doordat jullie zo onvermoeibaar, energiek, positief, ondersteunend, komisch, fysiek, puur, onvoorwaardelijk en lief zijn, kan ik de wereld aan.