Tailoring therapy in endometrial and cervical cancer

Gent, M.D.J.M. van

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

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.