Tailoring therapy in endometrial and cervical cancer

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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.

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