Gynaecological malignancies in Lynch syndrome

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General introduction
LYNCH SYNDROME

Lynch syndrome (LS), previously called hereditary non-polyposis colorectal cancer syndrome, is an autosomal dominant genetic predisposition for cancer, caused by mutations in the mismatch repair (MMR) genes. (1) These MMR genes in LS are MLH1 (on chromosome 3), MSH2 (on chromosome 2), MSH6 (on chromosome 2), PMS2 (on chromosome 7) and the EPCAM gene, which inactivates the MSH2 gene. (2,3)

When mutations in the MMR genes will develop, disruption of the open frame of the genes involved and an accumulation of small repetitive abnormalities of the DNA (micro satellites) occur. This is called microsatellite instability (MSI-high). Cells with this DNA-repair deficient MSI-high phenotype are prone to neoplastic changes and development of cancer. (3,4) LS is associated with early onset of colorectal cancer and several extra colonic malignancies of which endometrial cancer in female LS carriers is the most frequent. (4,5) Other, less common extra colonic malignancies in LS are ovarian, stomach, small intestine, pancreas, kidney, ureter, brain, kerato-acanthoma and biliary tract cancer. (4-6) In patients with LS, mutations in MLH1 and MSH2 genes contribute to 80-90% of all gene mutations, MSH6 contributes to 5-10% and PMS2 and the EPCAM mutation causing the remaining 5%. (2,7-10)

In this introduction the criteria for referral to a clinical geneticist because of a high probability of LS will be described. Patients can be referred to the clinical geneticist when they have a LS associated tumour at a young age or a positive family history for LS associated tumours. All criteria are formulated in the Dutch guideline hereditary colon cancer (11) and are shown in Table 1. LS is highly associated with the occurrence of colon cancer and gynaecological cancers as endometrial and, to a lesser extent, ovarian cancer. The characteristics of these gynaecological cancers in women with LS and the differences with sporadic endometrial and ovarian cancer are further described in this introduction. A woman with LS or a first degree relative with 50% risk of LS, will be advised for annual gynaecological surveillance. The (dis)advantages of gynaecological surveillance in women with LS are discussed in this introduction and are subject of study in part I of this thesis.

Criteria to refer to the clinical geneticist because of high probability of LS

If a patient develops a LS associated tumour or has a family history meeting one of the LS criteria, (see Table 1), there is a suspicion of LS and these patients are eligible for genetic counselling, genetic testing and/or surveillance. (6,11)
For patients without a malignancy, with a positive family history for LS associated tumours, or a known mutation in the family of one of the LS mismatch repair genes, counselling by a clinical geneticist and a DNA test is recommended.

Since the updated guideline in 2015, in patients diagnosed with a LS associated tumour (endometrial cancer < 70 years, colorectal cancer < 50 years), immunohistochemical (IHC) staining for four MMR proteins (MLH1, MSH2, MSH6 and PMS2) is performed. (11) IHC shows the absence of MMR protein expression in women with LS. (12) If loss of MLH1 protein is found, a MLH1 hypermethylation test is added. Hypermethylation of MLH1 results in an inactivated MLH1 protein, which is not associated with LS. When IHC of the tumour shows loss of MSH2, MSH6, PMS2 or MSH1 (without hypermethylation of MLH1) there is a strong suspicion of LS and a DNA test is recommended to test for a germ line mutation. When IHC is inconclusive, a microsatellite instability (MSI) test can be accomplished. MSI testing demonstrates the end-result of a deficiency in the mismatch repair genes with evaluation of the accumulation of mismatches, insertions and deletions in highly repetitive DNA segments. If the tumour displays microsatellite instability, there is also a strong suspicion of LS and a DNA test is recommended to test for a germ line mutation. Also in young patients diagnosed with a LS associated tumour (endometrial or colon cancer < 40 years of age) a DNA test is recommended regardless of the IHC/MSI results or the family history. (6,11)
Endometrial cancer

Endometrial cancer is one of the most common cancers in women in the Western world. In the Netherlands, endometrial cancer is diagnosed in about 1900 women yearly and around 400 women die of this disease each year. (13) Postmenopausal bleeding is an early symptom of the disease and 75% of the patients are diagnosed with early stage endometrial cancer. Risk factors are obesity, older age, late start of the menopause, nulliparity, unopposed exogenous estrogen suppletion, use of tamoxifen or a genetic predisposition. (14) The mean age at diagnosis in the general population is 60-65 years. (13)

<table>
<thead>
<tr>
<th>TABLE 1 Criteria for referral to the clinical geneticist because of suspicion of Lynch syndrome (11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1: Patients without a malignancy and a positive family history for malignancies</strong></td>
</tr>
<tr>
<td>• A first-degree relative with colon cancer &lt; 50 years of age.</td>
</tr>
<tr>
<td>• Or three or more first or second-degree relatives with a Lynch syndrome associated tumour &lt; 70 years of age.</td>
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<tr>
<td>• Or a mutation in one of the LS mismatch repair genes in the family.</td>
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<tr>
<td><strong>2: Patients with colorectal- or endometrial cancer with abnormal immunohistochemical (IHC) findings or microsatelite instability (MSI) in the tumour</strong></td>
</tr>
<tr>
<td>• &lt; 40 years of age, regardless the IHC/MSI results.</td>
</tr>
<tr>
<td>• Or &lt; 70 years of age with abnormal IHC/MSI results (except hypermethylation of the MLH1-promotor-gene).</td>
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<tr>
<td><strong>3: Patients with endometrial cancer</strong></td>
</tr>
<tr>
<td>• Endometrial cancer &lt; 40 years of age, (regardless the results of IHC/MSI)</td>
</tr>
<tr>
<td>• Or endometrial cancer &lt; 70 years of age, with occurrence of MSI/IHC (except hypermethylation of the MLH1-promotor gene).</td>
</tr>
<tr>
<td>• Or endometrial cancer and colorectal cancer, or a LS associated malignancy* in the same patient, &lt; 70 years of age.</td>
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<tr>
<td>• Or endometrial cancer &lt; 70 years of age and a first degree relative with endometrial cancer, (or a LS associated malignancy*): both under &lt; 70 years of age and one &lt; 50 years of age.</td>
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<tr>
<td>• Or endometrial cancer &lt; 70 years of age and two or more first- or second degree) relatives with endometrial cancer or a LS associated malignancy*, all &lt; 70 years of age.</td>
</tr>
<tr>
<td><strong>4: Patients with colorectal- or endometrial cancer without results of IHC/MSI in the tumour</strong></td>
</tr>
<tr>
<td>• &lt; 50 years of age.</td>
</tr>
<tr>
<td>• Or &lt; 70 years of age and a second primary colorectal or Lynch syndrome associated malignancy* &lt; 70 years of age, (at the same patient).</td>
</tr>
<tr>
<td>• Or &lt; 70 years of age and a first degree relative with colorectal cancer &lt; age 70, and one of them under age 50.</td>
</tr>
<tr>
<td>• Or &lt; 70 years of age and two or more (first or second degree) relatives with colorectal cancer or a LS associated malignancy*, all under age 70.</td>
</tr>
<tr>
<td>• Or &lt; 70 years of age and many polyps or unusual polyps:</td>
</tr>
</tbody>
</table>

* Or cancer of the endometrial tissue, stomach, small intestine, pancreas, biliary tract, ureter, urethra, ovary, brain or sebaceous gland adenoma (carcinoma) or kerato acanthoma. (11)
In endometrial cancer several histological types are distinguished. The most frequent type is endometrioid adenocarcinoma, and less common types are mucinous adenocarcinoma, serous adenocarcinoma, clear cell adenocarcinoma, undifferentiated carcinoma and mixed type carcinoma (composed of more than one type, with at least 10% of each component). (15) These carcinomas are grouped in two different subtypes. Type 1 carcinoma; representing 80% of all endometrial carcinomas, occurs around age 60, present at an early stage with symptoms of abnormal uterine bleeding. These carcinomas are linked to unopposed estrogen stimulation, which may result in the development of simple hyperplasia of the endometrial tissue. This may progress to atypical hyperplasia, finally resulting in well-differentiated endometrioid adenocarcinoma. This type of endometrial carcinoma is characterized by good survival rates. Type 2 carcinomas often occur around age 70, representing the other 20% of the endometrial carcinomas. These tumours show non-endometrioid histology like high grade serous and clear cell carcinomas. They are not linked to estrogen stimulation, have a higher risk of lymph vascular invasion and lymphatic and metastatic spread, and behave more clinically aggressive with a decreased survival rate when compared to Type 1. (16-19)

**Endometrial cancer and LS**

The lifetime risk of developing endometrial cancer in LS is 15-55% depending on the type of gene mutation compared with 3% in the general population. (4,9,20-23) The mean age of women who develop endometrial cancer in LS is 50-55 years. (5,20,22,23) This is ten years earlier than in the general population. The most frequently reported symptom is irregular or postmenopausal bleeding and/or increased bleeding during menstrual periods. This can be confusing and misdiagnosed at this age, as many healthy women have this perimenopausal bleeding pattern around age 50. In 75% of the women with LS, endometrial cancer is diagnosed at an early stage, which is the same as in the general population. The five years overall survival of endometrial cancer in women with LS is around 85%, which is also comparable with the survival of endometrial cancer in the general population. (15,24-27)

**Ovarian Cancer**

Ovarian cancer is a less common and more lethal malignancy, with 1300 new cases in the Netherlands each year and around 1000 of these women will die of ovarian cancer. (13) Ovarian cancer is a disease with none, a-specific or late symptoms. Therefore ovarian cancer is most often diagnosed in an advantaged stage with a poor survival. Risk factors are nulliparity, no use of oral contraceptives, or a genetic predisposition.
of which BRCA1/2 or LS mutations are most prevalent. The mean age at diagnosis of ovarian cancer in the general population is 60-65 years. (13) The most frequent histological type of ovarian cancer in the general population is the high grade serous type. (28,29) The fallopian tube is being suggested as the primary site of origin of pelvic high grade serous ovarian cancer and non invasive serous tubal intraepithelial carcinoma’s (STICs) have been identified in prophylactically removed Fallopian tubes in BRCA carriers. (30-32) Most sporadic ovarian cancers and cancers in BRCA 1/2 mutation carriers are diagnosed as FIGO stage III-IV with a five year overall survival rate of 20-40% although a progression free survival above 50% was reported in BRCA 1-2 carriers who used Olaparib additional to standard surgical treatment and platinum based chemotherapy after four years. (13,29,33)

Ovarian cancer and LS
About 10-15% of all ovarian cancers develop in women with a BRCA1/2 or LS mutation. The majority of inherited ovarian cancers are caused by a BRCA1/2 gene mutation and ovarian cancer in LS is not a very common trait. (34-35) The lifetime risk of developing ovarian cancer in LS is 6-12% depending on the type of gene mutation. (36-42) However, in most studies on ovarian cancer, only a small number of women with LS have been included. Therefore the information about the incidence and clinical aspects of ovarian cancer in women with LS is scattered and incomplete. (21-22,36,43) The mean age of a few studies reporting on women with LS who developed ovarian cancer, was at a young age and most patients were diagnosed at an early stage (FIGO stage I/II). (44-46) Due to few studies and limited data on ovarian cancer in LS, the contribution of annual gynaecological surveillance to this early stage disease cannot be established yet.

Gynaecological surveillance and LS
Annual gynaecological surveillance in women with LS consisting of a transvaginal ultrasound and endometrial sampling in case of increased endometrial thickness to detect endometrial abnormalities in an early malignant stage is effective. (5,47-48) However the additional value of standard endometrial sampling to annual transvaginal ultrasound (irrespective of endometrial thickness), in detecting more (pre)malignant endometrial lesions in women with LS is unknown. The value of annual gynecological surveillance for early detection of ovarian cancer in LS has never been studied systematically, due to small numbers and is still under debate. (5,48-49) In general, ovarian cancer surveillance has not been proven effective, in reducing ovarian cancer mortality in the general population (29) and not even among
women with a BRCA 1/2 mutation. (29,50-53) Even during surveillance, most ovarian cancers are found in an advanced stage and interval ovarian cancers develop between two surveillance visits. (50,52-56) As most ovarian cancers in women with LS tend to be detected at an early stage, some ascribe it to annual surveillance in LS. (57) However, there are only a few studies and no solid data to confirm this. Others assume that the good prognosis can be attributed to another biology, as the tumour type of ovarian cancer in LS (more often endometrioid or clear cell) is different from ovarian cancer in sporadic cases and BRCA1/2 mutation carriers (mostly high grade serous).

The current guideline for LS in the Netherlands advises annual endometrial surveillance by transvaginal ultrasound, measurement of the endometrial thickness and performance of a standard endometrial sampling in women from 40-60 years. (11) The choice for endometrial surveillance at this peri-menopausal age (when irregular bleeding is common and often misinterpreted) is not to miss early endometrial cancer. A surveillance advice for ovarian cancer in women with LS could not be given, due to a lack of firm data on surveillance and a certain age-range of appearance. It is advised to evaluate the ovaries while performing the transvaginal ultrasound to check the endometrial thickness for endometrial surveillance, although there is lack of evidence for annual ovarian surveillance alone in women after hysterectomy. (11)

Aim of the thesis:
The aim of this thesis is to study aspects of gynaecological surveillance in women with LS in order to improve counselling and find evidence for continuation or cessation of the various aspects of annual gynaecological surveillance in female LS carriers. In part I we evaluated the additional value of endometrial sampling to transvaginal ultrasound. We also studied the pain scores during this procedure and whether endometrial sampling can be replaced by a less invasive and less painful procedure (vaginal tampons). In part II of the thesis, the clinical and histopathological characteristics of ovarian cancer in women with LS were evaluated and the possible role of surveillance in early detection of these cancers was studied.
OUTLINE OF THE THESIS

Part I: endometrial cancer and LS
In chapter two of this thesis, the additional value of standard endometrial sampling in detecting (pre)malignancies of the endometrial tissue in women with LS or first degree relatives (FDR) was evaluated. In this study, two different surveillance programs were compared. We investigated the results of annual screening in a group of women with LS or FDR who underwent annual transvaginal ultrasound and endometrial sampling in case of symptoms or a thickened endometrial response only (period I), versus women with LS or FDR who underwent transvaginal ultrasound and standard endometrial sampling at every surveillance visit, irrespective of endometrial thickness (period II). The rate of (pre)malignancies of the endometrial tissue detected in both groups was evaluated.

Endometrial sampling during annual surveillance in women with LS is an outpatient procedure, which only takes a few minutes. However, the disadvantage is that it is an invasive procedure during which many women report substantial pain and the annual repetition induces fear for this examination, although the magnitude has never been studied. Chapter three describes the perceived pain on a visual analogue scale (VAS) during repetitive annual endometrial sampling. We also studied pain scores in symptomatic women who underwent a single endometrial sampling procedure. We evaluated if asymptomatic women who underwent annual endometrial sampling reported more pain than the symptomatic group who underwent single endometrial sampling, and if the VAS score aggravated during subsequent annual procedures in women with LS. If women with LS decided for preventive surgery or to quit annual gynaecological surveillance, the reason was examined.

As endometrial sampling at annual surveillance is perceived as a painful procedure by a substantial proportion of the women with LS (median VAS score 5.0) we investigated whether a less invasive procedure would be feasible to collect endometrial cells, which is reported in chapter four. It describes a pilot study in which 25 asymptomatic women with LS or FDR were asked to insert a tampon vaginally 2-4 hours before the annual surveillance visit. At the outpatient clinic, before starting the physical examination, the tampon was removed by the patient, handed to the gynaecologist, swopped in fixation fluid and send to the pathology lab for analysis. Subsequently, the standard annual gynaecological surveillance was performed, including endometrial sampling. The aim of the study was to analyse if endometrial cells can be obtained by using
vaginal tampons and if so, if the cells are of enough good quality to analyse. The level of pain of both procedures was evaluated with VAS scores.

Part II: ovarian cancer and LS
In chapter five of this thesis a literature review is presented about the clinical and pathological characteristics of ovarian cancer in women with LS and we evaluated the role of surveillance in the detection of ovarian cancer in LS.

In the Netherlands, a Dutch Cancer Registry (STOET) has been collecting clinical data of LS mutation carriers since 1987. Clinical data on all LS associated ovarian cancers from this registry and all LS associated ovarian cancers from the University Medical Center Groningen who were not in the STOET database, were studied in chapter six. For these women the following data was collected: data on gynaecological surveillance, age at diagnosis, mutation type, histological type, FIGO stage, treatment and follow-up data. The aim of this study was to describe clinical characteristics of LS associated ovarian cancer and the efficacy of surveillance in the early detection of these ovarian cancers.

In chapter seven, the results of the different studies are discussed and some future perspectives are given. A Dutch summary of all results is given in chapter eight.
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