RISK-STRATIFICATION OF ENDOMETRIAL CARCINOMA

PREDICTION OF AN ADVANCED DISEASE AND HIGH-RISK FEATURES OF THE PRIMARY TUMOR

Anna Luomaranta

ACADEMIC DISSERTATION

To be presented by permission of the Medical Faculty of the University of Helsinki for public discussion in the Seth Wichmann Auditorium of the Department of Obstetrics and Gynecology; Helsinki University Hospital, Haartmaninkatu 2, Helsinki, on 20th November, at noon.

HELSINKI 2015
To my beloved ones
## CONTENTS

**ABSTRACT** ...................................................................................................................... 7

**LIST OF ORIGINAL PUBLICATIONS** .................................................................................. 9

**ABBREVIATIONS** ............................................................................................................... 10

**INTRODUCTION** .............................................................................................................. 11

**REVIEW OF THE LITERATURE** ..................................................................................... 12

  - Epidemiology .................................................................................................................. 12
  - Risk factors .................................................................................................................... 12
  - Classification .................................................................................................................. 13
    - Histology .................................................................................................................... 13
    - Clinicopathology ........................................................................................................ 13
    - Genomic classification ................................................................................................. 14
  - Pathogenesis .................................................................................................................. 14
    - Endometrial hyperplasia as a precursor lesion for carcinoma ....................................... 14
    - Genetic alterations in endometrioid carcinoma .............................................................. 15
    - Genetic alterations in serous and clear cell carcinoma .................................................. 16
  - Diagnosis ...................................................................................................................... 16
  - Staging ........................................................................................................................... 17
  - Spread patterns .............................................................................................................. 18
  - Risk-stratification .......................................................................................................... 18
    - Rationale ..................................................................................................................... 18
    - Factors determining disease spread and outcome ......................................................... 19
      - Uterine risk factors ................................................................................................... 19
      - Tissue biomarkers ..................................................................................................... 20
      - Demographics .......................................................................................................... 21
      - Hematological parameters ......................................................................................... 21
    - Clinically applicable methods for risk-stratification .................................................... 21
      - Preoperative histology .............................................................................................. 21
      - Imaging ..................................................................................................................... 21
      - Serum markers ......................................................................................................... 22

---

### ABSTRACT

7

### LIST OF ORIGINAL PUBLICATIONS

9

### ABBREVIATIONS

10

### INTRODUCTION

11

### REVIEW OF THE LITERATURE

12

#### Epidemiology

12

#### Risk factors

12

#### Classification

13

- **Histology**

13

- **Clinicopathology**

13

- **Genomic classification**

14

#### Pathogenesis

14

- *Endometrial hyperplasia as a precursor lesion for carcinoma* ........................................... 14

- *Genetic alterations in endometrioid carcinoma* .............................................................. 15

- *Genetic alterations in serous and clear cell carcinoma* .................................................. 16

#### Diagnosis

16

#### Staging

17

#### Spread patterns

18

#### Risk-stratification

18

- **Rationale**

18

- *Factors determining disease spread and outcome* ......................................................... 19

- **Uterine risk factors**

19

- **Tissue biomarkers**

20

- **Demographics**

21

- **Hematological parameters**

21

- *Clinically applicable methods for risk-stratification* ................................................... 21

- **Preoperative histology**

21

- **Imaging**

21

- **Serum markers**

22
Intraoperative assessment ........................................................................................................ 22
Combined methods and nomograms .................................................................................. 24
Sentinel lymph node biopsy ............................................................................................... 24
TREATMENT .......................................................................................................................... 26
  Surgery ............................................................................................................................... 26
  Adjuvant therapy ............................................................................................................... 27
  Treatment of endometrial hyperplasias ............................................................................. 27
  Fertility-sparing treatment ............................................................................................... 27
  Treatment of relapsed endometrial carcinoma ................................................................... 28
FOLLOW-UP AFTER TREATMENT ...................................................................................... 29
PROGNOSIS .......................................................................................................................... 30
AIMS OF THE STUDY .......................................................................................................... 31
MATERIAL AND METHODS ............................................................................................... 32
  SUBJECTS .......................................................................................................................... 32
  SURGERY ............................................................................................................................ 32
  LABORATORY ANALYSES ................................................................................................. 33
  PREOPERATIVE HISTOLOGY ............................................................................................ 34
  IMAGING ............................................................................................................................. 34
  STATISTICAL ANALYSES .................................................................................................. 34
  META-ANALYSIS ................................................................................................................ 35
RESULTS .............................................................................................................................. 37
  RISK-SCORING MODEL ...................................................................................................... 37
  PREDICTION OF PARA-AORTIC LYMPH NODE METASTASIS ......................................... 38
  RISK-STRATIFICATION BY PREOPERATIVE HISTOLOGY AND MAGNETIC RESONANCE IMAGING ................................................................................................. 39
  META-ANALYSIS ON MAGNETIC RESONANCE IMAGING ................................................ 40
DISCUSSION .......................................................................................................................... 42
  IMPORTANCE OF THE STUDY .......................................................................................... 42
  PREOPERATIVE PREDICTION OF AN ADVANCED DISEASE AND HIGH-RISK TUMOR FEATURES ........................................................................................................... 42
    Risk-scoring model .......................................................................................................... 42
    Magnetic resonance imaging ........................................................................................... 43
    Combination of preoperative histology and magnetic resonance imaging ...................... 45
ABSTRACT

Risk-stratification is an essential step in planning of the treatment of patients with endometrial carcinoma, as it allows the omission of lymphadenectomy and/or adjuvant treatments in patients who are at low risk for extrauterine spread and have a good prognosis. This thesis consists of three cohort studies and one meta-analysis that were conducted to evaluate the reliability of methods that are currently available for the risk-stratification of endometrial carcinoma, and to develop new methods that might be clinically applicable. Cohort studies were based on a sample of 1166 women who were surgically treated for endometrial carcinoma at the Department of Obstetrics and Gynecology, Helsinki University Hospital, between January 2007 and December 2013. The number of women varied for each study because new patients were included in the database both retrospectively and prospectively.

In the first study, including 774 women, previously recognized risk factors for an advanced stage and poor outcome were used to create a calculatory score to predict lymph node and distant metastasis in endometrial carcinoma. The association of an advanced disease with demographic factors (age, body mass index), biochemical factors (complete blood count, serum CA125), and preoperative tumor characteristics was examined in unadjusted analyses. Logistic regression analysis was used for the identification of variables that independently predict an advanced disease. Statistically significant odds ratios in the regression model were rounded to the nearest whole number. These rounded values were the estimated weights for each factor that were summed to generate a score that might predict the probability of lymph node and distant metastasis. The score combining weighted risk factors was: (2 x leukocytosis) + (3 x thrombocytosis) + (7 x elevated CA125) + (4 x preoperative high-risk histology, defined as grade 3 endometrioid or nonendometrioid carcinoma). Depending on the number of risk factors of an individual patient, the score ranged from 0 to 16 points. Using six as the cut-point for positive and negative test results, the area under curve for this total score was 0.823, with 71.6% sensitivity, 75.2% specificity, 25.9% positive predictive value, and 95.7% negative predictive value.

In the second study, including 854 women, the reliability of macroscopic pelvic lymph node findings at surgery in predicting para-aortic metastasis was evaluated. Lymph nodes were considered grossly positive based on size and morphology. In patients who underwent comprehensive lymphadenectomy (n = 117), grossly positive pelvic nodes predicted para-aortic metastasis with a sensitivity of 52.4% and specificity of 93.8%. The positive and negative likelihood ratios were 8.4 and 0.51, respectively. The whole sample of 854 patients was employed for Bayesian calculations. Grossly positive pelvic nodes at surgery predicted para-aortic metastasis with a negative predictive value of 99.7% in patients with superficial grade 1-2 endometrioid carcinomas and 98.0% in patients with deeply invasive grade 1-2 endometrioid carcinomas. For patients with grade 3 endometrioid and nonendometrioid carcinomas, negative predictive values were 97.3% and 92.2%, respectively. The value was 98.4% for all 854 patients.
The third study, based on 1166 women, compared two surgical treatment strategies: 1) routine pelvic lymphadenectomy, and 2) selective pelvic lymphadenectomy for women with high-risk carcinomas according to preoperative histology and magnetic resonance imaging. High-risk carcinomas included grade 1-2 endometrioid carcinomas with deep myometrial invasion, grade 3 endometrioid carcinomas, and nonendometrioid carcinomas. Others were considered low-risk carcinomas. Uterine biopsy/curettage was obtained in 1140 patients, of whom 229 also had magnetic resonance imaging. The combination of preoperative histology and magnetic resonance imaging detected high-risk carcinomas with a sensitivity of 85.7%, specificity of 75.0%, positive predictive value of 74.4%, and negative predictive value of 86.1%. The area under curve was 0.804. In the routine lymphadenectomy algorithm, 54.1% of lymphadenectomies were performed in patients with low-risk carcinoma. In the selective lymphadenectomy algorithm, 14.3% of patients with high-risk carcinoma did not receive lymphadenectomy. Missed positive pelvic nodes were estimated to occur in 2.1% of patients in the selective lymphadenectomy strategy. Similarly, the estimated risk for isolated para-aortic metastasis was 2.1%, regardless of treatment strategy.

Finally, a meta-analysis was conducted to review the available literature on the reliability of contemporary magnetic resonance imaging techniques in the assessment of deep myometrial invasion, cervical stromal involvement, and lymph node metastasis in endometrial carcinoma. The PubMed and Scopus databases were searched for studies published before March 2014. Studies on plain magnetic resonance imaging were excluded. Fifty-two eligible studies were identified. For the assessment of deep myometrial invasion (50 studies, 3,720 patients), the pooled sensitivity, specificity, and positive and negative predictive values were 80.7%, 88.5%, 77.6% and 89.5%, respectively, by random-effects analysis. For predicting cervical stromal involvement (12 studies, 1,153 patients), the pooled values were 57.0%, 94.8%, 68.7% and 90.5%. For lymph node metastasis on a per patient basis (10 studies, 862 patients), they were 43.5%, 95.9%, 66.3% and 92.2%. According to a meta-regression analysis, dynamic and diffusion-weighted imaging may be more reliable in the radiological staging of endometrial carcinoma than contrast-enhanced imaging.

In conclusion, the risk-scoring model that was developed may provide a cost-effective approach to the risk-stratification of endometrial carcinoma, as it allows prediction of high-risk cases prior to surgery without advanced technology. Selective para-aortic lymphadenectomy, based on gross findings of pelvic nodes, is feasible for patients with grade 1-2 endometrioid carcinomas, regardless of the depth of myometrial invasion. Similarly, gross findings of pelvic nodes can be used to evaluate the need for para-aortic lymphadenectomy in the strategy of routine pelvic lymphadenectomy. The combination of preoperative histology and magnetic resonance imaging is moderately sensitive and specific in detecting high-risk endometrial carcinomas. However, the clinical utility of the method is hampered by the relatively high proportion of high-risk cases that remain unrecognized preoperatively. Considering the poor-to-moderate sensitivity of magnetic resonance imaging in detecting high-risk features of endometrial carcinoma, patients with negative findings may not safely forego lymphadenectomy unless the findings are confirmed by a backup method. The high specificities allow targeting of staging procedures by magnetic resonance imaging alone in patients with positive findings.
LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals:


The original publications are reproduced with permission of the copyright holders.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>Area under curve</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CA125</td>
<td>Cancer antigen 125</td>
</tr>
<tr>
<td>CE</td>
<td>Contrast-enhanced</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CSI</td>
<td>Cervical stromal involvement</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>DW</td>
<td>Diffusion-weighted</td>
</tr>
<tr>
<td>EC</td>
<td>Endometrial carcinoma</td>
</tr>
<tr>
<td>EH</td>
<td>Endometrial hyperplasia</td>
</tr>
<tr>
<td>FDG PET/CT</td>
<td>Integrated fluorodeoxyglucose positron emission tomography and computed tomography</td>
</tr>
<tr>
<td>FIGO</td>
<td>International Federation of Gynecology and Obstetrics</td>
</tr>
<tr>
<td>HE4</td>
<td>Human epididymis protein 4</td>
</tr>
<tr>
<td>L1CAM</td>
<td>L1 cell adhesion molecule</td>
</tr>
<tr>
<td>LNM</td>
<td>Lymph node metastasis</td>
</tr>
<tr>
<td>LVSI</td>
<td>Lymphovascular space involvement</td>
</tr>
<tr>
<td>MI</td>
<td>Myometrial invasion</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NLR</td>
<td>Negative likelihood ratio</td>
</tr>
<tr>
<td>NPV</td>
<td>Negative predictive value</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PLR</td>
<td>Positive likelihood ratio</td>
</tr>
<tr>
<td>POLE</td>
<td>Exonuclease domain of DNA polymerase epsilon</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td>PTEN</td>
<td>Phophatase and tensin homolog</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver-operator characteristic</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SLN</td>
<td>Sentinel lymph node</td>
</tr>
<tr>
<td>TVUS</td>
<td>Transvaginal ultrasound</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>WPRT</td>
<td>Whole pelvic radiotherapy</td>
</tr>
</tbody>
</table>
INTRODUCTION

Endometrial carcinoma (EC) is a cancer that arises from the inner lining of the uterine corpus. It is the most common gynecologic malignancy in Western Europe and North America. The usual presenting symptom is abnormal uterine bleeding.

At diagnosis, EC is confined to the uterine corpus in more than two thirds of patients. Local tumors have generally a favorable outcome. The presence of extrauterine disease, particularly pelvic and para-aortic lymph node metastasis (LNM), significantly deteriorates outcome. The five-year survival rate is 80 to 90% in patients with a local disease but less than 60% in those with LNM (Lewin et al. 2010). The mainstay of the initial treatment for EC is surgery with total hysterectomy and bilateral salpingo-oophorectomy. Due to the propensity of the disease to disseminate to retroperitoneal lymph nodes, pelvic and para-aortic lymphadenectomy or adjuvant radiotherapy has traditionally been included in the treatment of patients with EC.

According to two prospective randomized trials, lymphadenectomy does not improve survival of patients with a preoperative early stage carcinoma (Benedetti Panici et al. 2008, ASTEC study group 2009). These findings have encouraged many practitioners to omit surgical staging in patients with low risk for metastasis. For other patients, lymphadenectomy remains the standard of care. The rationale of lymph node dissection lies in prognostication, proper triage of patients for adjuvant therapy and, as suggested by cohort and registry-based studies, improved survival of patients at high risk for extrauterine disease (Chan et al. 2006, Todo et al. 2010, Mahdi et al. 2013).

The risk for LNM in EC can be estimated from the pathologic findings of the primary tumor. Because final pathologic findings after hysterectomy are difficult to reproduce by any preoperative or intraoperative method, it has not been possible to establish definitive guidelines for the assessment of the risk for lymphatic dissemination. This study was conducted to evaluate the reliability of currently available risk-stratification methods and to develop new, clinically applicable methods to allow evidence-based decisions regarding the surgical treatment of patients with EC.
REVIEW OF THE LITERATURE

EPIDEMIOLOGY

EC is the most common cancer of the female genital tract in developed countries (Jemal et al. 2011). In Finland, for example, the age-standardized rate was 14.0 per 100,000 women in 2007 to 2011, with more than 800 new cases diagnosed annually (Engholm et al. 2014). The number of women living with the diagnosis was 413 per 100,000 at the end of 2011. The estimated median age at diagnosis is 62 years, and less than 10% of new cases are found in women under 45 years of age (Howlader et al. 2014).

RISK FACTORS

Endometrial hyperplasia (EH) and cancer can result from excess amounts of estrogen. Thus, the risk is increased by postmenopausal estrogen therapy without sufficient progestin opposition and chronic anovulation from polycystic ovary syndrome (Weiderpass et al. 1999, Archer 2001, Barry, Azizia & Hardiman 2014). An uncommon cause of unopposed estrogen and increased risk of EC is estrogen-secreting tumors, such as granulosa cell tumor of the ovary. Factors that increase the number of lifetime menstrual cycles, such as late menarche, nulligravidity and late menopause, increase the life-long estrogen burden and risk of disease (McPherson et al. 1996). Tamoxifen, a selective estrogen receptor modulator, acts as an estrogen receptor agonist in endometrial tissue, and predisposes to the development of EH and EC (Fisher et al. 1994). In women with breast cancer using tamoxifen, the relative risk of EC is 2.0 after two to five years and 6.9 after five or more years compared with non-users (Bergman et al. 2000).

A growth in the incidence of EC has been observed (Wartko et al. 2013). This can be largely explained by the obesity epidemic, as excessive adipose tissue aromatizes higher amounts of androgens to estrogen. In a meta-analysis of more than three million women, a 1.59-fold increase in the risk was attributed to each 5 kg/m2 increase in body mass index (BMI) (Schouten, Goldbohm & van den Brandt 2004, Renehan et al. 2008, Wartko et al. 2013).

Along with obesity, diabetes mellitus is highly prevalent in women with EC (Ko et al. 2014). The relationship between diabetes and EC may not be explained solely by concurrent obesity, as recent studies have shown that diabetes is an independent risk factor for the disease (Friberg, Mantzoros & Wolk 2007, Friberg et al. 2007, Zhang et al. 2013).
Lynch syndrome, or hereditary nonpolyposis colon cancer, is an autosomal dominant genetic condition that is characterized by germline mutations in one of the DNA mismatch repair genes. Such mutations increase the risk of colorectal cancer as well as several other cancers, particularly cancers of the stomach, ovary, and endometrium. Women with Lynch syndrome have up to a 40 to 60% lifetime risk of both colorectal and endometrial cancer (Lancaster et al. 2007).

CLASSIFICATION

Histology

The histologic classification of EC follows the guidelines of the World Health Organization (WHO) (International classification of diseases, 10th revision) (Table 1). Up to 90% of ECs are of the endometrioid subtype that are graded as well (grade 1), moderately (grade 2), and poorly (grade 3) differentiated carcinomas. Poor differentiation is least common, comprising 15 to 20% of all endometrioid carcinomas. Serous carcinoma and clear cell carcinoma are the most common nonendometrioid carcinomas. They are histologically similar to those found in the ovary and fallopian tube, and harbor a poorer prognosis than endometrioid carcinomas (Boruta et al. 2004).

Table 1. Histologic classification of ECs and estimated proportions for each type (modified from the WHO classification).

<table>
<thead>
<tr>
<th>Histologic type</th>
<th>Estimated proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrioid</td>
<td>Up to 90%</td>
</tr>
<tr>
<td>Serous</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Clear cell</td>
<td>~4%</td>
</tr>
<tr>
<td>Mucinous</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Squamous cell</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Clinicopathology

ECs have traditionally been divided into two subtypes, type I and type II, based on clinicopathologic findings (Bokhman 1983). Type I carcinomas, representing about 80% of all ECs, are estrogen related carcinomas that are typically diagnosed at early stages in younger, obese women. The usual histologic subtype is a well-differentiated endometrioid carcinoma. Type II carcinomas are mostly poorly differentiated endometrioid carcinomas, serous, and clear cell carcinomas. They are estrogen-independent, tend to occur in older women, and have poorer prognoses. Although obesity occurs in a larger proportion of women with type I carcinomas, it is
also associated with type II carcinomas. The prevalence of diabetes is similar in both subtypes (Setiawan et al. 2013, Ko et al. 2014).

**Genomic classification**

An integrated genomic and proteomic analysis allowed a classification of ECs into four novel categories, each with a distinct clinical behavior: exonuclease domain of DNA polymerase epsilon (POLE) ultramutated, microsatellite instability hypermutated, copy-number low, and copy-number high (Cancer Genome Atlas Research Network 2013). Interestingly, 15% of high grade endometrioid carcinomas are identified with POLE ultramutations, associated with a good clinical outcome (Meng et al. 2014). On the other hand, about 25% of grade 3 endometrioid carcinomas have a molecular phenotype similar to serous carcinomas. These findings suggest that the treatment of patients with EC will be optimized in the future by genomic classification.

**PATHOGENESIS**

The molecular pathogenesis of ECs of endometrioid and other histologic subtypes differ from one another. Endometrioid carcinomas seem to be an outcome of a combination of hormonal factors and mutational events. They develop through a precursor lesion, EH. In endometrioid carcinomas, estrogen and progesterone receptors are commonly present, and serum estradiol level is high. By contrast, serous and clear cell carcinomas appear to develop independently of estrogen-related risk factors. Serous carcinomas are suggested to develop from “endometrial intraepithelial carcinoma”, a precursor lesion on the atrophic endometrium representing a malignant transformation of the endometrial surface epithelium (Sherman 2000).

**Endometrial hyperplasia as a precursor lesion for carcinoma**

Of the women presenting with abnormal uterine bleeding, about 15% are diagnosed with EC, 15% with EH, and the rest with a benign condition. EHs include a wide spectrum of lesions, ranging from mild and reversible to direct precursors of EC (Lacey & Chia 2009). WHO classifies EHs into four subgroups based on the glandular/stromal structure of the endometrium (simple or complex) and the presence or absence of nuclear atypia (Scully et al. 1994). Research on the natural behavior of EH regarding the risk of progressing to a carcinoma lacks high-quality data. The subject was studied in a retrospective study of 170 women with an endometrial biopsy sample with EHs of various subtypes (Kurman, Kaminski & Norris 1985). Hysterectomy was not the initial treatment; however, the women were followed up or treated with various progesterone regimens, and hysterectomy was ultimately performed after an average of 13.4 years (range 1-27). Outcomes of the patients in this study are presented in Table 2. In a prospective study of 306 women with atypical EH in endometrial biopsy or curettage, 42.6% had a coexisting carcinoma in the hysterectomy specimen (Trimble et al. 2006).
Table 2. Disease outcome of patients with different subtypes of EH (n = 170) (Kurman, Kaminski & Norris 1985).

<table>
<thead>
<tr>
<th>Subtype of EH</th>
<th>n</th>
<th>Regressed (%)</th>
<th>Persisted (%)</th>
<th>Progressed to cancer (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple hyperplasia</td>
<td>93</td>
<td>74 (80)</td>
<td>18 (19)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Complex hyperplasia</td>
<td>29</td>
<td>23 (80)</td>
<td>5 (17)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Simple with atypia</td>
<td>13</td>
<td>9 (69)</td>
<td>3 (23)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Complex with atypia</td>
<td>35</td>
<td>20 (57)</td>
<td>5 (14)</td>
<td>10 (29)</td>
</tr>
</tbody>
</table>

Genetic alterations in endometrioid carcinoma

Endometrioid ECs typically have a high load of mutations in signaling pathways that regulate cell growth and survival or gene transcription and development (PI3K/AKT/mTOR and Wnt/β-catenin pathways, respectively) (Murali, Soslow & Weigelt 2014). Hormone-driven changes in the expression of phosphatase and tensin homolog (PTEN), an endometrial tumor suppressor gene, in normal non-cancerous endometrium have been observed. The findings suggest that progesterone increases PTEN levels in endometrium and promotes the involution of PTEN-mutated endometrial cells. Thus, abnormal hormonal conditions, such as hyperestrogenism in obesity or unopposed estrogen therapy, might lead to disruptions in the normal PTEN expression in the endometrium (Mutter et al. 2000a). PTEN appears to be mutated in up to 83% of endometrioid ECs and in 55% of complex and atypical EHs (Mutter et al. 2000b). PTEN mutation seems to be an early feature of endometrial carcinogenesis. Other frequently encountered mutations in endometrioid tumors include microsatellite instability, K-ras mutation, and alterations in DNA mismatch repair genes. Tumor protein p53 is infrequently mutated in endometrioid carcinomas (Murali, Soslow & Weigelt 2014).

It has recently been suggested that epigenetic changes may be actively involved in carcinogenesis. These epigenetic changes (such as methylation of a set of genes called stem cell polycomb target genes) can be triggered for instance by age or environmental factors. The methylation of polycomb target genes leads to the accumulation of cells that are susceptible to cancer development. In EC, the hypermethylation of a progesterone-regulated polycomb target gene HAND2 was present in more than 90% of all endometrioid cancers. It has been hypothesized that the epigenetic alteration of HAND2 could be a key step in endometrial carcinogenesis. HAND2 hypermethylation has also been demonstrated in premalignant endometrial lesions (Jones et al. 2013).
Genetic alterations in serous and clear cell carcinoma

Serous carcinomas are commonly associated with tumor protein p53 mutations (Lax 2004). DNA aneuploidy and mutations of ERBB-2 (HER2/neu) are also often encountered (Amant et al. 2005). Clear cell carcinomas have a distinctive profile of genetic alterations, and they are generally negative to tumor protein p53 mutations (Zorn et al. 2005).

DIAGNOSIS

The most common presenting symptom of EC is abnormal uterine bleeding in a postmenopausal woman. The diagnosis is based on the pathologic evaluation of an endometrial sample. The diagnostic accuracy of office endometrial biopsy is comparable to that of formal uterine curettage (Fothergill, Brown & Hill 1992). Office endometrial biopsy can be successfully obtained in about 90% of attempted cases (Dijkhuizen et al. 2000). It is a more cost-effective initial strategy to evaluate postmenopausal bleeding than uterine curettage or hysterectomy (Feldman, Berkowitz & Tosteson 1993).

The detection rate of EC by office biopsy is lower in premenopausal women compared with postmenopausal women (Dijkhuizen et al. 2000). The detection rate by the Pipelle device, for example, is 91% for premenopausal women and 99.6% for postmenopausal women. Biopsy under hysteroscopic guidance should be considered in women with persistent symptoms despite a normal finding in an endometrial sample (Lee, Jung & Kim 2011).

Transvaginal ultrasound (TVUS) can be used as a supplementary diagnostic tool in symptomatic women. Malignant growth in the uterine cavity usually manifests in the ultrasound scan as thickened endometrium or a heterogeneous or polypoid mass. At an endometrial thickness cut-off of 5 mm, TVUS detects EC in postmenopausal women with uterine bleeding with 96% sensitivity and 61% specificity (Smith-Bindman et al. 1998).

Occasionally, diagnostic workup is initiated due to a Pap test abnormality in an asymptomatic woman. Atypical glandular cell cytology confers a 38% risk of either preinvasive disease or carcinoma, most commonly in the cervix or endometrium (DeSimone et al. 2006).
Cancer staging is essential in planning of the treatment, determination of prognosis, and evaluation of the effect of therapy. The International Federation of Gynecology and Obstetrics (FIGO) introduced its classification and staging system for EC and other female genital cancers in 1958 (Odicino et al. 2008). The staging of EC was altered from clinical to surgical-pathological in 1988 (Shepherd 1989). A revised version was introduced in 2009 (Table 3), with a rationale to further improve the prognostic performance of surgical staging (Pecorelli 2009).

From the clinical point of view, the most notable change of the FIGO 2009 staging system was to subdivide tumors with LNM to stages IIIC1 (indicating positive pelvic nodes) and IIIC2 (indicating positive para-aortic nodes with or without positive pelvic nodes). This decision was justified by the poorer outcome of patients in the latter category. The renewal emphasizes the importance of comprehensive lymphadenectomy in patients with EC.

### Table 3. FIGO staging of EC (Pecorelli 2009)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumor confined to the corpus uteri</td>
</tr>
<tr>
<td>IA</td>
<td>No or less than half myometrial invasion</td>
</tr>
<tr>
<td>IB</td>
<td>Invasion equal to or more than half of the myometrium</td>
</tr>
<tr>
<td>II</td>
<td>Tumor invades cervical stroma, but does not extend beyond the uterus</td>
</tr>
<tr>
<td>III</td>
<td>Local and/or regional spread of the tumor</td>
</tr>
<tr>
<td>IIIA</td>
<td>Tumor invades the serosa of the corpus uteri and/or adnexae</td>
</tr>
<tr>
<td>IIIB</td>
<td>Vaginal and/or parametrial involvement</td>
</tr>
<tr>
<td>IIIC</td>
<td>Metastases to pelvic and/or para-aortic lymph nodes</td>
</tr>
<tr>
<td>IIIC1</td>
<td>Positive pelvic lymph nodes</td>
</tr>
<tr>
<td>IIIC2</td>
<td>Positive para-aortic lymph nodes with or without positive pelvic nodes</td>
</tr>
<tr>
<td>IV</td>
<td>Tumor invades bladder and/or bowel mucosa, and/or distant metastases</td>
</tr>
<tr>
<td>IVA</td>
<td>Tumor invasion of bladder and/or bowel mucosa</td>
</tr>
<tr>
<td>IVB</td>
<td>Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes</td>
</tr>
</tbody>
</table>

* Positive cytology has to be reported separately without changing the stage.
**SPREAD PATTERNS**

EC has four potential routes of spread: hematogeneous, lymphatic, contiguous, and exfoliation followed by intraperitoneal dissemination. The primary route of extension to the parametrium, found in less than 10% of patients, is through lymphatic and blood vessel invasion (Watanabe et al. 2010). Like their counterparts in the ovary, serous and clear cell carcinoma have a propensity for early spread and peritoneal dissemination. LNM is not an uncommon finding in endometrioid carcinomas when the tumor is poorly differentiated or has other high-risk features.

**RISK-STRATIFICATION**

**Rationale**

Risk-stratification permits personalized treatment approaches for patients. Two prospective randomized trials compared the therapeutic efficacy of pelvic lymphadenectomy to no lymphadenectomy in patients with early stage EC (Benedetti Panici et al. 2008, ASTEC study group 2009). Both trials demonstrated that lymphadenectomy improves surgical staging but does not improve survival. Neither of the studies was powered to resolve whether patients at high risk for nodal metastasis benefit from lymphadenectomy. Despite this and many other criticisms against both studies, they inspired a paradigm shift that has occurred in the surgical treatment of EC. Nowadays, most practitioners agree that lymphadenectomy can safely be omitted in truly low-risk cases. Lymphadenectomy is generally recommended for patients at high risk for positive nodes because it improves prognostication and selection of patients for adjuvant therapy. Further, according to cohort and registry-based studies, lymphadenectomy may improve survival of patients with high-risk carcinoma (Chan et al. 2006, Todo et al. 2010, Mahdi et al. 2013).

The benefits of selective lymphadenectomy include diminished risk of complications, such as vessel and nerve damage, lymphocysts, and lower-extremity lymphedema. Another obvious goal of selective lymphadenectomy is to provide cost-effective care for patients and communities. Disappointingly to proponents of the selective lymphadenectomy strategy, routine lymphadenectomy was found to be more cost-effective than hysterectomy without surgical staging or selective lymphadenectomy based on frozen section (Cohn et al. 2007, Clements et al. 2013). By contrast, selective lymphadenectomy based on a preoperative risk-stratification method developed by the Korean Gynecologic Oncology Group, combining magnetic resonance imaging (MRI) and serum cancer antigen 125 (CA125), was shown to be more cost-effective than routine lymphadenectomy (Lee et al. 2014).

Personalized risk-assessment can be extended to decisions regarding adjuvant therapy. Chemotherapy and radiotherapy are usually reserved for patients with an advanced disease or local carcinoma with high risk for recurrence.
Factors determining disease spread and outcome

Uterine risk factors

Prediction of LNM using characteristics of the primary tumor in clinical stage I ECs was first studied in the 1980s (Boronow et al. 1984, Creasman et al. 1987). Poor differentiation, deep myometrial invasion (MI), and involvement of the uterine isthmus or cervix were found to predict nodal disease. The incidence of pelvic LNM was up to 27% and that of para-aortic LNM up to 19% with one uterine risk factor present, and even higher with multiple risk factors (Creasman et al. 1987). Subsequently, a large tumor size was recognized as an additional risk factor for lymph node involvement; a risk of 4% for nodal involvement was observed for tumors \( \leq 2 \) cm, compared with a risk of 15% for tumors >2 cm (Schink et al. 1991). Lymphovascular space involvement (LVSI) has been found to be an independent predictor of nodal disease and decreased survival; distinction by LVSI may be even more relevant than distinction by the depth of MI (Guntupalli et al. 2012, Aristizabal et al. 2014).

High grade, deep MI and cervical stromal involvement (CSI) determine survival both in the presence and absence of nodal metastasis (Kwon et al. 2009, Barrena Medel et al. 2011). Thus, uterine risk factors may not only determine the risk for LNM, but also the outcome of patients with EC per se.

Uterine risk factors are commonly used in clinical practice to stratify ECs into different prognostic groups. Although uniform definitions of low- and high-risk carcinomas are lacking, Mayo criteria are among the most widely used to define low-risk carcinomas. These include tumors with grade 1-2 endometrioid histology, MI \( \leq 50\% \), and diameter \( \leq 2 \) cm according to frozen section analysis (Mariani et al. 2000). The Mayo algorithm identifies patients with LNM with a negative predictive value (NPV) of 98.2%, given the prerequisite that the preoperative diagnosis is grade 1-2 carcinoma (Convery et al. 2011). The algorithm identifies 27% of cases as low-risk carcinomas (Mariani et al. 2008).

In an update of the Mayo algorithm, patients were stratified into one of three subgroups: high risk, intermediate risk, and low risk (AlHilli et al. 2013a). Patients with preoperative histologic findings consistent with grade 3 endometrioid or nonendometrioid carcinoma were classified as high risk. Patients with preoperative grade 1-2 endometrioid histology or complex and/or atypical hyperplasia were further stratified on the basis of intraoperative findings. Patients with macroscopic extrauterine disease were classified as high risk, patients with a disease confined to the uterus and a tumor diameter >2 cm were classified as intermediate risk, and patients with a disease confined to the uterus and a tumor diameter \( \leq 2 \) cm were classified as low risk.
Tissue biomarkers

Although the knowledge on molecular biomarkers is growing in oncology practices, their utilization in the risk-stratification of EC is not yet common. L1 cell adhesion molecule (L1CAM) is one of the most promising prognostic biomarkers in EC. Its staining on tumor cells segregates a subdivision of aggressive ECs with poor clinical outcome (Fogel et al. 2003, Huszar et al. 2010).

In a study of 865 patients with uterine-confined EC, L1CAM positivity was a strong independent predictor of distant relapses and worse overall survival (Bosse et al. 2014). A positive test result was considered to be a degree of L1CAM staining of >10%. Given this condition, the rate of positives was 7% among the study population. In the study by Zeimet et al. (2013), 17.7% of stage I type I ECs were found to be L1CAM positive. Of the positive cases, 51.4% recurred during follow-up (compared with 2.9% of the negative cases). In the L1CAM negative ECs, the prediction of disease-free survival and overall survival were not related to the stage I subdivision, grading, or risk assessment. Instead, the prognostic relevance of these variables was strictly related to L1CAM positivity. It has been suggested that L1CAM is superior to the standard multifactor risk assessment in the prognostication of EC and that L1CAM positivity in type I EC indicates a need for adjuvant treatment (Zeimet et al. 2013).

In addition to L1CAM, several other in situ biomarkers appear to be prognostically significant in EC. Of these, hormone receptor status is probably most thoroughly validated by research. Loss of estrogen and progesterone receptors in EC has been found to be associated with a higher tumor stage and grade (Kauppila et al. 1986, Singh et al. 2007). Further, lack of progesterone receptor expression is a strong independent risk factor for disease recurrence in patients with stage I-II endometrioid EC (Huvila et al. 2013), and double negative receptor status (loss of both estrogen and progesterone receptors) in a curettage specimen independently predicts LNM and poor prognosis (Trovik et al. 2013).

Overexpression of the oncogene ERBB-2 in curettage and hysterectomy specimens is associated with ECs of aggressive subtype and poor survival (Engelsen et al. 2008). Strong expression of the oncoprotein stathmin appears to be associated with LNM and poor survival (Trovik et al. 2011). Pathologic expression of tumor proteins p16 and p53 has been demonstrated to identify high-risk ECs (Engelsen et al. 2006).

Different subtypes of EC are typically characterized by distinct biomarker profiles, so that estrogen and progesterone receptor positivity is often present in endometrioid carcinomas, whereas overexpression of tumor protein p53 is more common in nonendometrioid carcinomas. Therefore, prognostic effects should be investigated individually for each tumor subtype (Werner & Salvesen 2014). Further studies are needed to establish the true benefit of tissue biomarkers in tailoring the treatment of patients with EC.
**Demographics**

Risk-stratification of EC can be further elaborated by including demographic factors in the analyses. Although age is not associated with the risk for pelvic-nodal disease (Kwon et al. 2009), an age of higher than 65 years was found to be an independent poor prognostic factor in clinical early stage EC, worsening the survival expectation of older women by about 10% when compared with younger patients (Benedetti Panici et al. 2014). A retrospective analysis showed that, after adjusting for confounders, diabetes is associated with worse recurrence-free survival and overall survival in endometrioid carcinomas but not in serous or clear cell carcinomas (Ko et al. 2014).

Although not a uniform finding (von Gruenigen et al. 2006, Akbayir et al. 2012, Crosbie et al. 2012), obesity has been reported to be associated with a decrease in risk of dying of EC (Temkin et al. 2007, Ko et al. 2014) such that a decrease of 3% was observed for each one point increase in BMI. After adjusting for confounders, African-American women with EC appear to have similar overall survival but worse disease-specific survival compared with Caucasian women (Ko et al. 2014, Ruterbusch et al. 2014).

**Hematological parameters**

Anemia, leukocytosis and thrombocytosis are frequently found in advanced cancers as a manifestation of paraneoplastic syndrome, tumor bleeding, or disturbed hematopoiesis through tumor infiltration of the bone marrow (Weiss & Goodnough 2005, Pelosof & Gerber 2010). Similar preoperative disturbances in hematological parameters predict advanced disease and poor disease-specific survival in patients with EC (Njølstad et al. 2013).

**Clinically applicable methods for risk-stratification**

**Preoperative histology**

A higher final grade will be diagnosed in 15 to 25% of patients with a preoperative grade 1 endometrioid carcinoma (Obermair et al. 1999, Leitao et al. 2009, Neubauer et al. 2009). However, upgrading in the final histology is seldom clinically meaningful because only 2 to 3% will be upgraded to grade 3 or diagnosed as a serous or clear cell carcinoma.

**Imaging**

Computed tomography (CT) is the imaging technique of choice for detecting distant metastasis in patients with EC, whereas TVUS and MRI play a more important role in the local staging of the disease. Integrated fluorodeoxyglucose positron emission tomography and computed tomography (FDG PET/CT) may serve as a reliable nonsurgical method for detecting LNM in many cancers, including EC.
The diagnostic accuracy of TVUS and MRI in the radiological staging of EC has been evaluated in numerous single-institution studies that showed variable sensitivity and specificity rates for detecting deep MI, CSI, and LNM. One prospective multicenter study evaluated and compared the diagnostic accuracy of TVUS, MRI and FDG PET/CT in the preoperative assessment of EC (Antonsen et al. 2013). The techniques were found to perform equally in predicting deep MI. For CSI and LNM, FDG PET/CT was the best. Diagnostic indices for the different techniques found in the Antonsen study are summarized in Table 4.

**Serum markers**

Results of a population based study showed that serum levels of CA125 and human epididymis protein 4 (HE4) are higher in stage III and IV ECs and in tumors with >50% MI (Brennan et al. 2014). HE4 was a better predictor of deep MI than CA125, even when the analysis was limited to grade 1-2 endometrioid carcinomas.

In another study, neither of the markers was clearly superior in predicting carcinoma stages ≥IIIA or MI ≥50% (Saarelainen et al. 2013). However, the combination of CA125 and HE4 analysis with a risk score algorithm seemed to improve the diagnostic value of the markers compared with separate analyses.

**Intraoperative assessment**

Reports on the reliability of frozen section analysis in EC are conflicting. According to some authors, findings on frozen section correlate poorly with the final pathology, such that clinically relevant upstaging from frozen to final occurs in 18% of patients (Frumovitz et al. 2004, Case et al. 2006). Others, however, have found that frozen section provides reliable data to guide intraoperative treatment decisions (Kumar et al. 2012, Stephan et al. 2014). In the study by Stephan et al. (2014), the correlation between frozen section and paraffin section for histology, grade, and depth of MI were 97.5%, 88.0%, and 98.2%, respectively. Kumar et al. (2012) used tumor size as an additional variable in their frozen section analysis, and suggested that use of multiple variables to determine when the disease should be surgically staged reduces the clinical impact of inaccurate findings of any single variable. Clinically significant discordance between frozen and paraffin sections occurred in 1.3% of their cases.

According to a meta-analysis of 16 studies and 2567 patients, intraoperative gross examination predicts ≥50% MI in EC with a sensitivity of 75%, specificity of 92%, positive predictive value (PPV) of 80%, and NPV of 89% (Mavromatis et al. 2012). These values are fairly comparable to those of TVUS, MRI, and FDG PET/CT (Table 4).
Table 4. Performance of TVUS, MRI and FDG PET/CT in the radiological staging of EC (Antonsen et al. 2013).

<table>
<thead>
<tr>
<th></th>
<th>MI $\geq 50%$</th>
<th></th>
<th></th>
<th></th>
<th>CSI</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>LNM</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity (%)</td>
<td>Specificity (%)</td>
<td>PPV (%)</td>
<td>NPV (%)</td>
<td></td>
<td>Sensitivity (%)</td>
<td>Specificity (%)</td>
<td>PPV (%)</td>
<td>NPV (%)</td>
<td></td>
<td>Sensitivity (%)</td>
<td>Specificity (%)</td>
</tr>
<tr>
<td>TVUS</td>
<td>71.4</td>
<td>71.7</td>
<td>50.6</td>
<td>86.1</td>
<td>28.6</td>
<td>91.5</td>
<td>48.0</td>
<td>82.4</td>
<td>–</td>
<td>–</td>
<td>58.8</td>
<td>92.8</td>
</tr>
<tr>
<td>MRI</td>
<td>87.3</td>
<td>57.3</td>
<td>44.0</td>
<td>92.2</td>
<td>33.3</td>
<td>94.5</td>
<td>60.0</td>
<td>85.1</td>
<td>58.8</td>
<td>92.8</td>
<td>40.0</td>
<td>96.5</td>
</tr>
<tr>
<td>FDG PET/CT</td>
<td>92.6</td>
<td>48.6</td>
<td>40.6</td>
<td>94.6</td>
<td>42.9</td>
<td>94.3</td>
<td>68.6</td>
<td>85.0</td>
<td>74.2</td>
<td>92.8</td>
<td>59.0</td>
<td>96.2</td>
</tr>
</tbody>
</table>
Combined methods and nomograms

Various risk-stratification methods can be combined to optimize risk-assessment. Examples are shown in Table 5. Risk nomograms denote graphical tools that illustrate the probability of lymphatic dissemination based on multiple prognostic factors. Currently available nomograms utilize factors that need postoperative evaluation, such as LVSI and MI depth as a percentage of myometrial thickness (Bendifallah et al. 2012, Kondalsamy-Chennakesavan et al. 2012, AlHilli et al. 2013a). Although not helpful in planning primary surgical treatment, nomograms may facilitate decisions involving secondary lymphadenectomy or adjuvant therapy in patients who will not undergo surgical staging.

Sentinel lymph node biopsy

Sentinel lymph node (SLN) biopsy, usually with a cervical injection of radiolabeled tracer and/or blue or fluorescent dye, is intended for normal-appearing lymph nodes and patients with clinical stage I carcinoma of low or intermediate risk. A prospective multicenter trial (SENTI-ENDO) showed a detection rate of 89% per patient (Ballester et al. 2011). Node positivity per patient was identified with a sensitivity of 84% and NPV of 97%. In the SENTI-ENDO trial, the recurrence-free survival was similar in patients with and without detected SLN. Among patients with detected SLN, no difference in recurrence-free survival was observed between those with and without positive SLN (Daraï et al. 2015).

Pathologic ultrastaging of sentinel nodes improves the detection of low-volume metastases (micrometastases and isolated cancer cells) that may go undetected with traditional pathologic assessment of lymph nodes. The improved additional detection rate is 0.8 to 8.0%, depending on tumor grade and depth of MI (Kim et al. 2013). The oncologic significance of low-volume metastases in EC has yet to be determined.
Table 5. Examples of combined methods for the risk-stratification of EC.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cohort size</th>
<th>Low-risk criteria</th>
<th>Methods</th>
<th>Proportion of low-risk patients</th>
<th>Risk for LNM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al. (2010)</td>
<td>110</td>
<td>3 or 4 of the following: 1. Grade 1 endometrioid carcinoma 2. Serum CA125 ≤70 U/ml</td>
<td>1. Preoperative histology 2. Preoperative concentration 3. MRI 4. MRI</td>
<td>57%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Absence of MI 4. No extension beyond uterine corpus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AlHilli et al. (2013b)</td>
<td>704</td>
<td>All of the following: 1. Grade 1-2 endometrioid carcinoma 2. Tumor size ≤2 cm 3. No tumor outside the uterus</td>
<td>1. Endometrial biopsy 2. Macroscopic evaluation (frozen section when indicated) 3. Macroscopic intraoperative evaluation</td>
<td>23%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Kang et al. (2013)</td>
<td>319</td>
<td>All of the following: 1. Endometrioid carcinoma 2. Serum CA125 &lt;35 U/ml 3. MI &lt;50%, no enlarged nodes (&lt;1 cm in short axis), no tumor beyond the uterine corpus</td>
<td>1. Endometrial biopsy 2. Preoperative concentration 3. MRI</td>
<td>51%</td>
<td>1.4%</td>
</tr>
</tbody>
</table>
TREATMENT

Surgery

The standard surgical care for EC includes total hysterectomy, bilateral salpingo-oophorectomy, and peritoneal washing. The surgical treatment of serous and clear cell carcinomas, with comprehensive lymphadenectomy and omentectomy, is similar to that of epithelial ovarian cancer.

In the absence of an ideal risk-stratification method, some practitioners favor routine lymphadenectomy for all patients with EC. In the selective lymphadenectomy strategy, principles of lymphadenectomy are similar for high- and intermediate-risk carcinomas, whereas the procedure is omitted in low-risk cases. Pelvic nodes should be removed from the level of the caudal half of the common iliac arteries, the anterior and medial aspect of the cranial half of the external iliac artery and vein, and the caudal half of the obturator fat pad anterior to the obturator nerve. The number of nodal stations sampled, i.e., the anatomical radicality of the procedure, predicts risk for LNM more accurately than lymph node count (Huang et al. 2010).

Station-specific prevalence of LNM was examined in 457 high-risk patients identified by the Mayo algorithm (Kumar et al. 2014). All patients underwent lymphadenectomy; pelvic-aortic lymphadenectomy was performed in 93%. The prevalence of pelvic and para-aortic LNM was 17% and 12%, respectively. In the presence of positive pelvic nodes, 51% had positive para-aortic nodes. The prevalence of isolated para-aortic LNM was 3%, of which 67% were exclusively in high para-aortic area. Among patients with para-aortic LNM, 88% had high para-aortic metastasis and 35% had only high para-aortic metastasis. Based on their findings, the authors proposed that para-aortic lymphadenectomy should ideally be carried out up to the renal vessels. On the other hand, because of the incidence of only 1% of isolated para-aortic LNM in other studies (Abu-Rustum et al. 2009, Chiang et al. 2011), it could be argued that removal of nodal tissue up to the inferior mesenteric artery is sufficient for para-aortic staging.

Results of a randomized trial comparing laparoscopy to laparotomy in patients with EC indicate that laparoscopy should be preferred in the surgical treatment of the disease. Laparoscopy did not compromise surgical staging, and it was associated with short-term advantages, such as shorter hospital stays, fewer perioperative complications, and reduced blood loss (Walker et al. 2009). Long-term oncologic outcomes were also reassuring. The estimated five-year overall survival was identical for both arms at 89.8%, and the potential for increased risk of cancer recurrence with laparoscopy was found to be small. Compared with laparoscopic hysterectomy, robotic hysterectomy is associated with similar perioperative morbidity and oncologic outcomes, but higher direct hospital costs (Wright et al. 2012, Cardenas-Goicoechea et al. 2014).
Adjuvant therapy

Adjuvant therapy is not indicated for patients with small risk of cancer recurrence. Whole pelvic radiotherapy (WPRT) decreases pelvic and vaginal recurrences in stage I and II endometrioid carcinomas, but should be limited to patients whose risk factors fit a high-intermediate risk definition according to age and tumor histopathology (Keys et al. 2004). The treatment does not improve survival because patients who have previously not been irradiated are likely to be salvaged if a recurrence develops. Vaginal brachytherapy effectively ensures vaginal control in stage I endometrioid carcinomas with features of high-intermediate risk, with fewer gastrointestinal toxic effects than WPRT (Nout et al. 2010).

For advanced carcinomas, chemotherapy with doxorubicin and cisplatin is the adjuvant treatment of choice, combined with WPRT in selected cases (Randall et al. 2006). Due to a more favorable toxicity profile, many practitioners use paclitaxel and carboplatin instead of doxorubicin and cisplatin, although randomized trials that would support this practice have not been published. Chemotherapy is initiated to most women with serous or clear cell carcinoma, regardless of their surgical stage.

Treatment of endometrial hyperplasias

Because of the possibility of a concomitant carcinoma and poor efficacy of conservative treatment, hysterectomy should be offered to patients who have EH with atypia. In cases of EH without atypia, progestins are the treatment of choice. Commonly, either medroxyprogesterone acetate or megestrone acetate is administered in either a cyclic or a continuous manner (Masciullo et al. 2010). According to a meta-analysis, a levonorgestrel intrauterine device may produce similar or higher regression rates of EH than orally administered progestins (Gallos et al. 2010). Treatment with progestins should also be considered for women with atypical EH who desire to spare fertility, and for women with comorbidities precluding surgery (Sorosky 2012).

Fertility-sparing treatment

In Finland, the mean age at first labor has risen by one year over the last decade, reaching 28.5 years in 2013. At the same time, more than 20% of delivering women were over 35 years old. Among them, 41% were overweight (BMI ≥25 kg/m2), and 15% were obese (BMI ≥30 kg/m2) (National Institute for Health and Welfare 2014). A similar trend has been observed in other developed countries, implying that an increasing number of women will need fertility-sparing treatment for EH or early EC. The most common fertility-sparing treatment is progestin medication. The goal of this treatment is to achieve a disease-free period during which pregnancy is attempted with assisted reproductive technologies.
Data on fertility-sparing treatments are still quite scarce. In a recent study by Kudesia et al. (2014), 23 women (13 with complex EH and atypia, 10 with grade 1 endometrioid EC) were treated with oral progestins and/or levonorgestrel intrauterine device. Twelve patients underwent in vitro fertilization resulting in six live births. Of the 23 patients, nine had a persistent or progressive disease during a median follow-up time of 13 months. In women who were initially treated conservatively, hysterectomy should be considered after childbearing is completed.

**Treatment of relapsed endometrial carcinoma**

Most EC patients have a low risk of relapse; the total relapse rate is estimated to be 13%. More than two thirds of relapses will appear within three years of the initial diagnosis, and more than 50% are symptomatic. The most common symptoms are pain, vaginal bleeding, malaise, intestinal symptoms, and weight loss (Sartori et al. 2010, Zhang, Wang 2010, Salani et al. 2011). Except in the case of an isolated local recurrence, patients with a recurred disease have poor prognosis, regardless of the treatment. In a retrospective study of 1203 women receiving first-line chemotherapy for either a relapsed or primarily metastasized disease, the overall response rate was 42%. Unlike in newly diagnosed diseases, histology does not appear to predict treatment response in relapsed cases (McMeekin et al. 2007).

Most isolated vaginal vault relapses and some isolated pelvic relapses can be curatively treated by radiation (if no previous radiation has been administered) or surgery (when complete resection can be achieved). In the study by Creutzberg et al. (2003), during eight years of follow-up, the incidence of vaginal vault relapse was higher if the initial treatment of EC did not include adjuvant radiation after surgery, compared with the radiation approach (8% versus 2%). Most of the relapses were treated with WPRT or brachytherapy, and some with surgery. Complete remission after the treatment was achieved in 89% of patients. Despite the difference in the relapse rate between the initial treatment arms, the overall survival was similar in both groups. The three-year survival after vaginal vault relapse was 73%, compared with 8% after pelvic and 14% after distant relapse (Creutzberg et al. 2003).

When a patient has been previously irradiated and is not a surgical candidate, the treatment of pelvic and vaginal relapse should be individually assessed. For example, medical treatment with chemotherapy or high-dose progestins may be offered. Medical treatment is the treatment of choice also in patients with a relapse in distant or multiple sites.
FOLLOW-UP AFTER TREATMENT

To date, there are no prospective studies evaluating the benefit of routine surveillance after the treatment of EC. According to a review by Sartori et al. (2010), only physical examination, including speculum and pelvic-rectal examination, has some utility in detecting a recurrent disease. There is no evidence that cytologic evaluations or chest radiographs of an asymptomatic patient are beneficial or cost-effective. In case of a suspected recurrence, a targeted assessment of the extent of the disease is required (Salani et al. 2011). Most institutions adhere to follow-up protocols despite their uncertain diagnostic utility. The objectives of such protocols are not only to diagnose disease recurrences, but also to recognize treatment-related adverse effects and to provide psychological support.

Following the treatment with paclitaxel, up to 30% of patients may develop grade 3 or 4 neuropathy (Lee & Swain 2006). In a randomized trial of 231 patients, treatment of painful neuropathy with duloxetine proved to be effective (Smith et al. 2013). Tricyclic antidepressants, gabapentin, pregabalin, or topical gels containing baclofen, amitriptyline or ketamine can be offered to patients with painful neuropathy (Hershman et al. 2014). If pharmacological treatments fail, cutaneous electrostimulation may be of benefit (Smith et al. 2010).

Sexual dysfunction and menopausal symptoms are frequently reported after the treatment of EC. During a follow-up period of one to five years, 89% of women reported sexual dysfunction (Onujiogu et al. 2011). The incidence of sexual dysfunction was similar in women who received WPRT and those who did not. Likewise, the rate of sexual dysfunction did not differ between women who received vaginal brachytherapy and those who received WPRT (Nout et al. 2009, Nout et al. 2011).

For the treatment of menopausal symptoms, oral micronized progesterone, selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, gabapentin, and pregabalin have some proven effect in treating hot flashes (Hunter et al. 2004, Nelson et al. 2006, Hitchcock & Prior 2012). For younger women (≤40 years old), estrogen therapy should be administered after the treatment of low-risk EC to prevent long-term health effects of estrogen deficiency. There is no evidence that treatment with estrogens increases the risk of recurrence after the treatment of early-stage EC (Chapman et al. 1996, Barakat et al. 2006).

Lower-leg lymphedema is a common and probably under-reported problem resulting from the treatment of EC. In a retrospective study of more than 1200 women, the rate of lower-leg lymphedema was 3.4%. The adverse effect seemed to be restricted to patients with more than 10 regional lymph nodes removed (Abu-Rustum et al. 2006). Nevertheless, in a questionnaire study of 1048 surgically treated EC patients, 47% of responders reported lower-leg lymphedema, of which 23% was attributable to lymphadenectomy (Yost et al. 2014). Decongestive lymphatic therapy has shown some effect in the treatment of lymphedema (Szuba et al. 2000).
A considerable proportion of patients who have received WPRT suffer from a change in bowel function that moderately to severely affects their quality of life. Very severe problems, including secondary malignancies, rectal bleeding necessitating transfusion, bowel obstructions, and fistula formations, occur in up to 10% of cases (Andreyev 2007).

PROGNOSIS

One-year and five-year survival of women with cancer of the uterine corpus were 95% and 87%, respectively, in Finland in 2009 to 2011 (Engholm et al. 2014). The outcome is highly dependent on the initial stage of the cancer. Overall five-year survival rates for each stage of endometrioid adenocarcinoma of the uterine corpus, as recorded in the National Cancer Institute’s Surveillance, Epidemiology, and End Results database from the United States, are shown in Table 6 (Lewin et al. 2010).

<table>
<thead>
<tr>
<th>FIGO stage</th>
<th>Proportion</th>
<th>Five-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>59.0%</td>
<td>89.6%</td>
</tr>
<tr>
<td>IB</td>
<td>10.3%</td>
<td>77.6%</td>
</tr>
<tr>
<td>II</td>
<td>2.0%</td>
<td>73.5%</td>
</tr>
<tr>
<td>IIIA</td>
<td>2.6%</td>
<td>56.3%</td>
</tr>
<tr>
<td>IIIB</td>
<td>0.4%</td>
<td>36.2%</td>
</tr>
<tr>
<td>IIC1</td>
<td>2.3%</td>
<td>57.0%</td>
</tr>
<tr>
<td>IIC2</td>
<td>1.2%</td>
<td>49.4%</td>
</tr>
<tr>
<td>IVA</td>
<td>0.2%</td>
<td>22.0%</td>
</tr>
<tr>
<td>IVB</td>
<td>4.1%</td>
<td>21.1%</td>
</tr>
</tbody>
</table>

Stage undefined in 18%. Lymph node sampling was performed in 45.5% of patients.
AIMS OF THE STUDY

This study was undertaken to develop new, clinically applicable methods for the risk-stratification of EC, and to evaluate the reliability of currently available methods to allow evidence-based decisions regarding the surgical treatment of patients with EC.

The specific aims of the study were:

1. To develop a preoperative risk-scoring model that might predict the probability of lymph node and distant metastasis in EC (Study I).

2. To determine whether the finding of grossly metastatic pelvic lymph nodes can predict para-aortic LNM in EC, and evaluate whether patients can be stratified to para-aortic lymphadenectomy by using macroscopic pelvic node findings as an intraoperative test (Study II).

3. To evaluate the validity of preoperative histology and pelvic MRI in the risk-stratification of EC and to compare routine and selective pelvic lymphadenectomy, based on preoperative histology and MRI, as surgical treatment strategies in EC (Study III).

4. To perform a systematic review and meta-analysis on the reliability of contemporary MRI techniques in the assessment of deep MI, CSI, and LNM in EC (Study IV).
MATERIAL AND METHODS

SUBJECTS

Studies I, II, and III were based on a cohort of women who were surgically treated for EC at the Department of Obstetrics and Gynecology, Helsinki University Hospital, between January 2007 and December 2013. The number of women varied for each study because new patients were included in the database both retrospectively and prospectively (Table 7). The final cohort consisted of 1166 patients whose clinicopathologic data are shown in Table 8. During the course of the study, most histology slides of the primary tumors were re-evaluated by a pathology working group (Table 7). Institutional review board approval was obtained for the study.

Table 7. Number of patients, study periods, and re-evaluated histology slides in Studies I, II, and III.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Study period</th>
<th>Final histology re-evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>774</td>
<td>1/2008-11/2012</td>
<td>–</td>
</tr>
</tbody>
</table>

SURGERY

The proportion of laparoscopic hysterectomies was 66.7% (778/1166) and that of robotic hysterectomies 6.2% (72/1166) during the study period (conversions to open surgery excluded). Pelvic-aortic lymphadenectomy was recommended for patients at high risk for extraperitoneal spread, i.e., those with deeply invasive grade 1-2 endometrioid carcinomas, grade 3 endometrioid carcinomas, and nonendometrioid carcinomas. Pelvic lymphadenectomy only was initially recommended in patients with superficial grade 1-2 endometrioid carcinomas, the depth of MI being assessed by gross visual inspection. As of January 2012, lymphadenectomy was omitted in grade 1-2 endometrioid carcinomas if MRI showed <50% MI. There was some variation in practice patterns because the decision to perform lymphadenectomy and the extent of the procedure depended on patient comorbidities and surgical risks. Lymphadenectomy rate was 64.8% (755/1166) across the whole study population. Additionally, 1.2% (14/1166) of the patients had pelvic SLN assessment. Of the patients with stage I-IIIB carcinoma and high-risk features according to the Mayo criteria in the final pathologic evaluation, 65.2% (497/762) underwent pelvic or pelvic-aortic lymphadenectomy.
LABORATORY ANALYSES

Pretreatment serum CA125 concentration was quantitated with a chemiluminescent microparticle immunoassay on the Abbott Architect 2000i Analyzer (Abbott Diagnostics, Abbott Park, IL, USA). The value of CA125 was not available for 122 patients. Variables of the last pretreatment complete blood count were analyzed by photometric measurement (hemoglobin) and electrical impedance technology and flow cytometry (cells). Blood count variables were not available for one patient.

### Table 8. Clinicopathologic data (n = 1166).

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (mean ± SD)</td>
<td>67.5 ± 10.5</td>
</tr>
<tr>
<td>BMI (kg/m2) (mean ± SD)</td>
<td>28.6 ± 6.3</td>
</tr>
<tr>
<td>Pelvic lymphadenectomy (number of cases, percent)</td>
<td>580 (49.7%)</td>
</tr>
<tr>
<td>Pelvic-aortic lymphadenectomy (number of cases, percent)</td>
<td>175 (15.0%)</td>
</tr>
<tr>
<td>Lymph node yield, pelvic lymphadenectomy (mean ± SD)</td>
<td>15.2 ± 8.1</td>
</tr>
<tr>
<td>Lymph node yield, pelvic-aortic lymphadenectomy (mean ± SD)</td>
<td>26.8 ± 11.1</td>
</tr>
<tr>
<td>Laparoscopic hysterectomies (number of cases, percent)</td>
<td>850 (72.9%)</td>
</tr>
<tr>
<td>Histology (number of cases, percent)</td>
<td></td>
</tr>
<tr>
<td>Endometrioid carcinoma</td>
<td>1070 (91.8%)</td>
</tr>
<tr>
<td>Clear cell carcinoma</td>
<td>41 (3.5%)</td>
</tr>
<tr>
<td>Serous carcinoma</td>
<td>34 (2.9%)</td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
<td>20 (1.7%)</td>
</tr>
<tr>
<td>Neuroendocrine carcinoma</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Grade (number of cases, percent) (For endometrioid only, n = 1070)</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>645 (60.3%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>268 (25.0%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>157 (14.7%)</td>
</tr>
<tr>
<td>FIGO stage (number of cases, percent)</td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>679 (58.2%)</td>
</tr>
<tr>
<td>IB</td>
<td>226 (19.4%)</td>
</tr>
<tr>
<td>II</td>
<td>66 (5.7%)</td>
</tr>
<tr>
<td>IIIA</td>
<td>54 (4.6%)</td>
</tr>
<tr>
<td>IIIB</td>
<td>11 (0.9%)</td>
</tr>
<tr>
<td>IIIIC1</td>
<td>56 (4.8%)</td>
</tr>
<tr>
<td>IIIIC2</td>
<td>33 (2.8%)</td>
</tr>
<tr>
<td>IVA</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>IVB</td>
<td>41 (3.5%)</td>
</tr>
</tbody>
</table>

1 Number of cases 1165 (BMI of 1 patient unknown); 2 Number of cases 571 (lymph node yield was not available for 9 patients); 3 Number of cases 173 (lymph node yield was not available for 2 patients); 4 Traditional laparoscopic hysterectomies, n = 778; robotic hysterectomies, n = 72; 5 Including 19 carcinosarcomas
PREOPERATIVE HISTOLOGY

Preoperative endometrial histology was assessed in tissue samples obtained by endometrial biopsy or curettage. Endometrial biopsy was the primary sampling method, while curettage was performed when biopsy was insufficient for diagnosis or failed due to cervical stenosis. Endometrial sample was not taken or it was nondiagnostic in 26 patients. Two samples for which the original pathology review did not unequivocally differentiate between low-risk histology (EH or grade 1-2 endometrioid carcinoma) and high-risk histology (grade 3 endometrioid or nonendometrioid carcinoma) were re-evaluated for the current study.

IMAGING

The endometrial thickness of 768 women was measured by TVUS as the anteroposterior diameter of the uterine cavity (Study I). Preoperative MRI was performed in 229 patients using either 1.5-T or 3-T magnetic field strengths (Study III). Intravenous anti-peristaltic agent was used when no contraindications were present. High-resolution T2-weighted images were obtained from the uterus in sagittal plane and perpendicular to the long axis of the uterine body, together with T1-weighted axial images of the pelvis and T2-weighted axial images up to the renal hila. The protocol included diffusion-weighted (DW) and contrast-enhanced (CE) imaging with one pre-contrast T1-weighted fat-saturated image and gadolinium-enhanced T1-weighted fat-saturated images in different phases (arterial, venous, and equilibrium).

STATISTICAL ANALYSES

In Study I, Pearson $\chi^2$ analyses were used to compute odds ratios (OR) along with 95% confidence intervals (CI) for the associations between putative risk factors and stage IIIC and stage IV disease. Factors identified as potential risk factors in unadjusted analyses ($P < 0.05$) were used to create a logistic regression model with lymph node and distant metastasis as the dependent variable. Statistically significant ORs in the multivariable model were rounded to the nearest whole number. These rounded values served as the estimated weights for each factor that were summed to generate a total score that might predict the probability of lymph node and distant spread. Additional models were created by eliminating individual factors from the model. The areas under curve (AUC) of the models were compared with the receiver-operator characteristic (ROC) curve area comparison test.

In Study II, a 2x2 table was constructed to calculate the sensitivity and specificity of grossly positive pelvic lymph nodes at surgery in predicting the likelihood of para-aortic LNM. Nodes were considered positive when described as metastatic based on size and morphology. Specifically, confluent nodes with an irregular contour and multiple dense nodes were considered positive. Macroscopic lymph node findings were extracted from operative reports without reference to pathology reports. The power of the test was expressed by positive (PLR) and negative (NLR)
likelihood ratios. Bayes’ nomogram was used to compute predictive values. Grossly positive pelvic nodes and selected uterine risk factors (MI \(\geq 50\%\), grade 3 endometrioid histology, nonendometrioid histology) were used to create a logistic regression model with positive para-aortic lymph nodes as the dependent variable.

In Study III, the capabilities of preoperative histology, MRI and their combination to predict final pathologic findings were evaluated in ROC analyses. Cohen’s kappa statistics were calculated to measure the agreement between pre- and postoperative findings.

Statistical significance was set for P values <0.05 in all studies. Data were analyzed using SPSS version 20 software (SPSS Inc., Chicago, IL, USA).

**META-ANALYSIS**

For the meta-analysis (Study IV), studies of interest were identified from the PubMed and Scopus databases with no time limit (from their commencement to March 1, 2014). The following search terms were used: (magnetic OR mri OR mr imaging) AND (endometrial OR endometrium OR uterine OR uterus) AND (adenocarcinoma OR carcinoma OR cancer). The search was restricted to English-language articles. Clearly irrelevant studies were excluded after reading the title and abstract. The reference lists of relevant articles were checked for cross-references. Of the articles published by the same group (n = 7), only the most recent reports were included.

Studies on the reliability of CE, dynamic, and DW MRI in the assessment of MI \(\geq 50\%\), CSI, and/or LNM in EC were included in the meta-analysis. The postoperative pathology served as a reference. When diagnostic indices for different MRI scan types were provided in the same article, the most contemporary imaging technique was considered (i.e., dynamic imaging before CE imaging, and DW imaging before CE and dynamic imaging). If diagnostic indices for the detection of pelvic and para-aortic LNM were reported separately, the indices for pelvic metastasis were used. If separate results for two different observers were reported, a mean value of the diagnostic indices was computed. Studies that did not differentiate between cervical stromal and cervical mucosal infiltration were excluded, as were studies that did not report the radiological criteria of a metastatic lymph node (n = 8).

Since there was significant heterogeneity across studies for all diagnostic indices (I\(^2\) > 30%), their pooled values were determined by random-effects analysis. Sensitivity was the main end-point of the study. When not reported, the diagnostic indices were computed from the numbers of true and false positive and negative cases and prevalence when appropriate. The effect on sensitivity of publication year, MRI scan type, number of patients, and imaging criteria for pathologic lymph nodes were tested using a meta-regression module. For the assessment of the possible publication bias, Egger test and funnel plots were used. P < 0.05 was considered statistically significant.
Comprehensive Meta-Analysis version 2 statistical software was used for the analyses (Biostat, Englewood, NJ, USA).
RESULTS

RISK-SCORING MODEL

In the first study, a preoperative risk score utilizing previously recognized risk factors of lymph node and distant metastases was generated. Of the selected putative risk factors, the following were associated with stage IIIC-IV disease in unadjusted analyses: normal weight (BMI <25 kg/m2), thick endometrium (>10 mm), anemia (hemoglobin <117 g/l), leukocytosis (leukocytes >8.7 x 10⁹/l), thrombocytosis (thrombocytes >360 x 10⁹/l), elevated CA125 (>35 U/ml), and high-risk histology (i.e., grade 3 endometrioid, clear cell, serous, undifferentiated, neuroendocrine). The association of old age (>68 years) was not significant.

A logistic regression model was generated by including the risk factors that had statistically significant associations with the risk of metastasis in unadjusted analysis. Lymph node and distant metastasis served as the dependent variable in the model. Only those patients with available data for all variables (n = 683) were included in the analysis.

In the logistic regression model, leukocytosis, thrombocytosis, elevated CA125, and high-risk histology had a significant effect on the dependent variable. The total score to predict stage IIIC-IV disease was created by rounding the statistically significant ORs in the regression model to the nearest whole number, which were the estimated weights for each significant risk factor. The weighted risk factors were then summed to generate a total score for predicting a stage IIIC-IV disease. The ORs in the logistic regression model are presented in Table 9.

The total score can be expressed as: (2 x leukocytosis) + (3 x thrombocytosis) + (7 x elevated CA125) + (4 x high-risk histology). Depending on the number of risk factors of an individual patient, the score ranged from 0 to 16 points. Using 6 as the cut-point for positive and negative test results, the AUC for the total score in predicting stage IIIC-IV disease was 0.823, with a sensitivity of 71.6%, specificity of 75.2%, PPV of 25.9%, and NPV of 95.7%. To test the capability of the score to predict LNM solely, stage IV carcinomas were excluded from the dataset. There was no statistically significant difference between the AUC for the total score in predicting stage IIIC-IV disease (AUC 0.823) and the AUC for predicting stage IIIC disease (AUC 0.813, P = 0.82). The total score predicted a stage IIIC-IV disease significantly better than CA125 alone (AUC 0.721, P = 0.022).
Table 9. Odds ratios in the logistic regression model with lymph node and distant metastasis as the dependent variable.

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal weight 1</td>
<td>1.3 (0.72-2.2)</td>
<td>0.42</td>
</tr>
<tr>
<td>Thick endometrium 2</td>
<td>1.3 (0.63-2.7)</td>
<td>0.48</td>
</tr>
<tr>
<td>Anemia 3</td>
<td>1.3 (0.59-2.7)</td>
<td>0.55</td>
</tr>
<tr>
<td>Leukocytosis 4</td>
<td>1.8 (1.0-3.3)</td>
<td>0.037</td>
</tr>
<tr>
<td>Thrombocytosis 5</td>
<td>3.0 (1.3-6.6)</td>
<td>0.007</td>
</tr>
<tr>
<td>Elevated CA125 6</td>
<td>6.5 (3.7-11)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>High-risk histology 7</td>
<td>3.6 (2.0-6.6)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

1 BMI <25 kg/m2; 2 endometrium >10 mm; 3 hemoglobin <117 g/l; 4 leukocytes >8.2 x 10⁹/l; 5 thrombocytes >360 x 10⁹/l; 6 CA125 >35 U/ml; 7 grade 3 endometrioid and nonendometrioid carcinoma

**Prediction of para-aortic lymph node metastasis**

In patients who underwent comprehensive lymphadenectomy (n = 117), grossly positive pelvic nodes predicted para-aortic LNM with a sensitivity of 52.4% and specificity of 93.8%. PLR and NLR were 8.4 and 0.51, respectively. The predictive power of grossly positive pelvic nodes remained significant (OR 18, 95% CI 4.1-78; P < 0.0001) after correcting for deep MI, poor tumor differentiation and nonendometrioid histology as confounders. The whole sample of 854 patients was employed for Bayesian calculations. The cut-off for a clinically useful test was set at an NPV of 98.0%.

NPV of the test (i.e., grossly positive pelvic nodes at surgery in predicting the likelihood of para-aortic LNM) was 99.7% for patients with superficial grade 1-2 endometrioid carcinomas and 98.0% for patients with deeply invasive grade 1-2 endometrioid carcinomas. For patients with grade 3 endometrioid and nonendometrioid carcinomas, NPVs were 97.3% and 92.2%, respectively. For the whole study population, NPV was 98.4%. PPVs varied between 4.8% and 58.4%. The values were very similar when calculations were made with the result of the preoperative endometrial sample as the histologic diagnosis.
**RISK-STRATIFICATION BY PREOPERATIVE HISTOLOGY AND MAGNETIC RESONANCE IMAGING**

Table 10 shows the capability of preoperative histology to detect grade 3 endometrioid and nonendometrioid carcinomas, MRI to detect deep MI, and the combination of both methods to detect grade 1-2 endometrioid carcinomas with deep MI, grade 3 endometrioid carcinomas, and nonendometrioid carcinomas. Based on the subgroup of patients who underwent both endometrial sampling and MRI as preoperative tests (n = 229), routine and selective pelvic lymphadenectomy algorithms were constructed to simulate the two different lymphadenectomy strategies (see the figure of the algorithms in the original article). In the selective pelvic lymphadenectomy algorithm, patients with high-risk carcinoma on preoperative evaluation (i.e., grade 1-2 carcinoma with MI ≥50% on the MRI, or high-risk histology with any invasion on the MRI) underwent pelvic lymphadenectomy. According to this algorithm, the rate of preoperative high-risk carcinomas was 52.8% (121/229), which was also the lymphadenectomy rate. Of the postoperative low-risk patients, 25.0% (31/124) underwent lymphadenectomy. Of the postoperative high-risk patients, 14.3% (15/105) did not receive lymphadenectomy. According to the NPV of the combined method, 13.9% (15/108) of patients with preoperative low-risk carcinomas moved to the high-risk group following the final pathologic evaluation in the selective lymphadenectomy algorithm. In the routine lymphadenectomy algorithm, the lymphadenectomy rate was, by definition, 100%. Of the lymphadenectomies in this algorithm, 54.1% (124/229) were performed in patients with low-risk carcinoma.

Of the low-risk patients who underwent pelvic or pelvic-aortic lymphadenectomy in the cohort of 1166 patients, 2.3% (9/389) had pelvic LNM. The incidence was 18.3% (64/350) in high-risk patients. Since the lymphadenectomy rate in the selective lymphadenectomy strategy was 25.0% for low-risk patients and 85.7% for high-risk patients, missed positive pelvic nodes were estimated to occur in 2.1% of patients when following the selective lymphadenectomy strategy. Based on surgical findings and follow-up data, the risk of isolated para-aortic LNM was estimated to be 2.1% for both treatment strategies, when stage IV carcinomas were excluded.

CSI occurred in 22 of 229 patients (9.6%) who had both endometrial sample and pelvic MRI as preoperative tests. A positive finding was predicted by MRI in 14 patients (63.6%). CSI was associated with deep MI, as assessed by MRI, and/or preoperative high-risk histology in 15 of 22 patients (68.2%).
Table 10. Examination performance of preoperative histology, MRI, and the combination of both methods in detecting high-risk ECs.

<table>
<thead>
<tr>
<th>End-points</th>
<th>Preoperative histology</th>
<th>MRI</th>
<th>Combined method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 1140)</td>
<td>(n = 229)</td>
<td>(n = 229)</td>
</tr>
<tr>
<td>Sensitivity (95% CI)</td>
<td>58.1% (51.6%-64.4%)</td>
<td>84.6% (74.7%-91.8%)</td>
<td>85.7% (77.5%-91.8%)</td>
</tr>
<tr>
<td>Specificity (95% CI)</td>
<td>96.3% (94.9%-97.5%)</td>
<td>75.5% (67.8%-82.1%)</td>
<td>75.0% (66.4%-82.3%)</td>
</tr>
<tr>
<td>PPV (95% CI)</td>
<td>80.9% (74.3%-86.5%)</td>
<td>64.1% (54.0%-73.3%)</td>
<td>74.4% (65.7%-81.9%)</td>
</tr>
<tr>
<td>NPV (95% CI)</td>
<td>89.6% (87.5%-91.4%)</td>
<td>90.5% (84.0%-95.0%)</td>
<td>86.1% (78.1%-92.0%)</td>
</tr>
<tr>
<td>AUC</td>
<td>0.772</td>
<td>0.801</td>
<td>0.804</td>
</tr>
<tr>
<td>Kappa value</td>
<td>0.607 ^4</td>
<td>0.558 ^4</td>
<td>0.600 ^4</td>
</tr>
</tbody>
</table>

End-points: ^1 detection of grade 3 endometrioid and nonendometrioid carcinomas; ^2 detection of ≥50% MI; ^3 detection of grade 1-2 endometrioid carcinomas with ≥50% MI, grade 3 endometrioid carcinomas, and nonendometrioid carcinomas; ^4 P < 0.0001

META-ANALYSIS ON MAGNETIC RESONANCE IMAGING

The PubMed and Scopus database searches returned 260 and 96 articles, respectively. Of these, 52 articles met the inclusion criteria, resulting in a total sample size of 3,816 patients with EC. A summary of pooled diagnostic indices is found in Table 11.

A univariate meta-regression analysis was performed to investigate the impact of study characteristics on pooled sensitivity. In detecting deep MI, dynamic imaging was associated with a higher sensitivity than CE imaging (P = 0.021), and the improvement related to DW imaging had borderline significance (P = 0.057). No statistically significant difference between the sensitivities of dynamic and DW imaging was found. A comparison of the sensitivities of the different scan types in detecting CSI or LNM was not possible due to the limited number of eligible studies.

The number of included patients (per 10) was associated with a lower sensitivity of MRI in detecting deep MI (P = 0.005), but no significant association existed between the publication year and sensitivity of MRI in detecting deep MI. Neither of these variables was associated with the sensitivity of MRI in detecting CSI or LNM. Adherence to nodal size criteria alone (lymph node size ≥10 mm in minimal diameter) was associated with a higher sensitivity of MRI in detecting LNM (P < 0.0001).

The possible effect of publication bias on the results was tested using Egger test, which revealed a significant small study effect for the sensitivity of MRI in detecting deep MI (P < 0.0001). This finding was confirmed by apparent visual asymmetry in a funnel plot (see the figure in the original article). With regard to the sensitivity of MRI in detecting CSI, the observed small study
effect was of borderline significance (P = 0.049). The test revealed no significant publication bias for the sensitivity of MRI in detecting LNM.

**Table 11.** Pooled values for diagnostic indices by random-effects analysis.

<table>
<thead>
<tr>
<th></th>
<th>Deep MI</th>
<th>CSI</th>
<th>LNM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of studies</td>
<td>50</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Number of patients</td>
<td>3,720</td>
<td>1,153</td>
<td>862</td>
</tr>
<tr>
<td>Sensitivity (95% CI)</td>
<td>80.7% (76.8%-84.1%)</td>
<td>57.0% (45.9%-67.4%)</td>
<td>43.5% (31.7%-56.1%)</td>
</tr>
<tr>
<td>Specificity (95% CI)</td>
<td>88.5% (85.3%-91.1%)</td>
<td>94.8% (92.1%-96.6%)</td>
<td>95.9% (92.9%-97.6%)</td>
</tr>
<tr>
<td>PPV (95% CI)</td>
<td>77.6% (73.4%-81.2%)</td>
<td>68.7% (60.5%-75.8%)</td>
<td>66.3% (54.8%-76.1%)</td>
</tr>
<tr>
<td>NPV (95% CI)</td>
<td>89.5% (87.5%-91.1%)</td>
<td>90.5% (87.7%-92.8%)</td>
<td>92.2% (88.5%-94.8%)</td>
</tr>
</tbody>
</table>
DISCUSSION

IMPORTANCE OF THE STUDY

Since patients with early-stage EC do not seem to benefit from lymphadenectomy (Benedetti Panici et al. 2008, ASTEC study group 2009), the treatment paradigm has shifted towards selective lymphadenectomy based on individual risk assessment. Consequently, it is of paramount interest to develop clinically applicable and reliable methods for predicting LNM in EC, as well as to evaluate the performance characteristics of existing ones.

The acceptable risk for missed LNM in the selective lymphadenectomy strategy remains debatable. In EC and some other cancers, such as those of the vulva and breast, a negligible risk of LNM has been suggested to be one of 4% or less (Boronow 1997, Krag et al. 2007, Levenback et al. 2012). Besides the acceptable risk for missed positive nodes, the ideal method for predicting LNM in EC has not been agreed upon.

PREOPERATIVE PREDICTION OF AN ADVANCED DISEASE AND HIGH-RISK TUMOR FEATURES

Risk-scoring model

Various uterine, biochemical and demographic factors have been shown to contribute to the risk of extraterine spread in EC. It was of interest to develop a new, cost-effective risk-scoring model to predict the probability of lymph node and distant metastasis in EC by combining these previously recognized risk factors of an advanced disease. Our Study I included a fairly large cohort of patients with detailed information on multiple demographic and disease-related factors. The well-characterized study population made the conduction of the first study both reasonable and possible.

The logistic regression analysis proved that leukocytosis, thrombocytosis, elevated CA125 and preoperative high-risk histology are independent predictors of an advanced stage in EC. The performance of the total score (combining all risk factors with an independent effect on disease spread) in detecting lymph node and distant metastasis was tested. The total score ranged from 0 to 16, depending on the number of existing risk factors of the patient. Six score points was the optimal cut-point for a positive compared with negative test result, since, at this cut-point, the total score had a good discriminatory power (AUC 0.823), moderate sensitivity and specificity (71.6% and 75.2%, respectively) and a fairly high NPV (95.7%). It was important to define a cut-point in such a way as to result in maximal NPV to minimize the risk of mislabeling a patient with stage IIIC or stage IV disease.
The capability of the calculatory score to identify an advanced disease was also tested in a dataset from which stage IV carcinomas were excluded. The discriminatory power did not significantly differ from that of the original analysis, suggesting that the total score predicts not only distant metastasis, but also LNM.

Although the total score reached a relatively high NPV, the 4% risk for lymph node or distant metastasis in a patient with a negative test result might be considered too high to allow omission of lymphadenectomy based solely on a negative test result. It is noteworthy, however, that the NPV of the calculatory score in detecting lymph node and distant metastasis was fairly similar to those of FDG PET/CT and SLN biopsy in detecting LNM in EC. The NPV of FDG PET/CT has been varied between 83.3% and 93.1% (Kitajima et al. 2008, Signorelli et al. 2009), while that of the SLN biopsy was 97% in a prospective multicenter study (Ballester et al. 2011).

The advantage of the risk-scoring model is that it allows the recognition of at-risk patients prior to surgery without advanced technology, suggesting a possible cost-effective approach to risk-stratification. One of the weaknesses of the study is that the model has not been validated on an external cohort; thus, there is a possibility that the results are specific to the population in question. Nevertheless, although the patients were treated in a single referral center, it is improbable that selection bias significantly influenced the results, as the demographics of the study population did not remarkably differ from those in studies from other developed countries (Lewin et al. 2010, Crosbie et al. 2012, Werner et al. 2012). Another weakness is that the actual lymph node status of all patients was not known because, in Study I, lymphadenectomy was not performed on 31% of the patients. Nevertheless, the risk calculations for the population that underwent lymphadenectomy were very similar to those for the whole study population.

**Magnetic resonance imaging**

The recognition of high-risk features of EC (deep MI, CSI and LNM) by MRI has gained interest over the past two decades (Gien et al. 2009), and, at many institutions, MRI has become a part of the standard preoperative risk-estimation protocol. The paradigm shift towards selective lymphadenectomy resulted in the implementation of pelvic MRI in the assessment of EC at our institution in the beginning of 2012. The diagnostic indices of MRI in predicting high-risk features of EC vary considerably in the literature, which prompted us to conduct a meta-analysis on the subject. As we had gained experience from the use of MRI in EC at our institution, we also had a particular interest in evaluating the reliability of the method in our own study population.

In the meta-analysis, the pooled sensitivity of 80.7% in detecting MI ≥50%, as well as the NPV of 89.5%, suggests that a negative MRI finding should be confirmed by a backup method (e.g., frozen section analysis) for the safe omission of lymphadenectomy. By contrast, the specificity (88.5%) and PPV (77.6%) were high enough to favor lymphadenectomy when MRI finding is positive for deep MI. At our institution, MRI predicted MI ≥50% with a sensitivity of 84.6%,
specificity of 75.5%, PPV of 64.1%, and NPV of 90.5%. These values are fairly consistent with those of the meta-analysis.

The presence of tumor in the uterine isthmus or cervix doubles the risk of pelvic LNM from 8% to 16% (Werner et al. 2012). In the meta-analysis, the pooled sensitivities of MRI in detecting CSI and LNM were too low to allow omission of lymphadenectomy in patients with negative findings. The NPVs were relatively high (>90%), presumably in part because of the low prevalence of stage II and IIIC carcinomas. On the other hand, similar to deep MI, the specificity and PPV of MRI in detecting CSI and LNM were sufficiently high to support lymphadenectomy after positive findings.

In our study population, the association of CSI with other high-risk features was evaluated in patients for whom the findings of both preoperative histology and MRI were available. CSI occurred in only 9.6% of these patients (22/229). A positive finding was predicted by MRI in 63.6% (14/22). On the other hand, CSI was associated with other preoperative high-risk features (MI ≥50% on MRI and/or preoperative high-risk histology) in more than two-thirds of the cases (15/22). Based on these observations it could be argued that the detection of CSI by MRI adds little to the value of MRI in recognizing patients who are at risk for LNM.

Dynamic MRI enhances the contrast between the primary tumor and normal myometrium and cervical stroma. Since its introduction in the 1990s, dynamic MRI has replaced the standard morphology imaging of EC by plain and CE MRI in many centers. Dynamic MRI has been found to achieve a better staging accuracy of EC than older techniques in some but not all studies (references found in the original publication). DW MRI is a functional imaging technique that displays information about water mobility, tissue cellularity, and the integrity of cell membranes (Koh & Collins 2007). In comparative studies, its accuracy regarding the assessment of MI depth has not been clearly superior to that of dynamic MRI (references found in the original publication).

In a meta-regression analysis, a significant difference in the sensitivities of dynamic and DW MRI in detecting deep MI was not detected. Nevertheless, the sensitivity of dynamic MRI in detecting deep MI was higher than that of CE MRI, and the increase in sensitivity caused by DW MRI was of a borderline significance. Thus, modern scanning techniques may improve the reliability of MRI in the preoperative evaluation of patients with EC. Meta-regression analysis also revealed that a larger study population was associated with a lower sensitivity of MRI in detecting deep MI. This is in agreement with the finding of significant small-study effects according to the funnel plot and Egger test.

MRI may be most useful under circumstances where risk-stratification cannot be based on intraoperative assessment of the uterus. An obvious example is that of a woman desiring fertility-
sparing treatment with progestins for complex atypical hyperplasia or nonmyoinvasive EC (Kudesia et al. 2014).

**Combination of preoperative histology and magnetic resonance imaging**

The change in the surgical treatment strategy at our institution from routine to selective lymphadenectomy prompted us to compare the two strategies retrospectively. According to the protocol launched in 2012, preoperative histology was used for the identification of grade 3 endometrioid and nonendometrioid carcinomas, and MRI for the identification of carcinomas with MI ≥50%. Tumors with any of these features were considered high-risk cases in which comprehensive lymphadenectomy was indicated. The combination of preoperative histology and MRI recognized high-risk carcinomas with a good discrimination power (AUC 0.804). Kappa statistics showed a moderate agreement between preoperative and postoperative findings (AUC 0.600).

The PPV of preoperative risk-stratification in predicting final high-risk cases was 74.4%, which indicates that lymphadenectomy should be performed on all eligible patients with preoperative high-risk tumor features. However, the NPV of 86.1% may be too low for a clinically applicable test because stratification of patients to lymphadenectomy by this method alone translates into a relatively high proportion of unstaged high-risk patients. Missed positive pelvic nodes were estimated to occur in 2.1% of patients in the selective strategy, assuming a lymphadenectomy rate of 25.0% for low-risk carcinomas and 85.7% for high-risk carcinomas. Of the women who underwent pelvic or pelvic-aortic lymphadenectomy in the complete cohort, the rate of pelvic LNM was 2.3% in final low-risk carcinomas and 18.3% in final high-risk carcinomas.

Adjuvant treatments for patients with stage IIIC1 and IIIC2 EC do not usually differ; however, the two IIIC substages have different prognoses (Werner et al. 2012). Since para-aortic spread cannot be diagnosed by pelvic lymphadenectomy alone, it was of interest to evaluate the incidence of isolated para-aortic LNM in the study population. The risk for isolated para-aortic LNM was estimated as 2.1%, based on para-aortic skip metastases that were found at primary surgery and relapses that were interpreted as a manifestation of positive para-aortic nodes that initially remained undiagnosed. This risk is fairly comparable to the risk of about 1% in earlier reports (Abu-Rustum et al. 2009, Chiang et al. 2011). About 80% of the skip metastases occurred in patients with high-risk carcinomas, suggesting that para-aortic lymphadenectomy might be a useful diagnostic adjunct in the selective lymphadenectomy strategy.
INTRAOPERATIVE PREDICTION OF PARA-AORTIC LYMPH NODE METASTASIS

Para-aortic lymphadenectomy, especially when performed by minimally invasive techniques, can be a challenging procedure. Even among expert surgeons, the extent of para-aortic lymph node dissection may be restricted to the level of inferior mesenteric artery. A failure in the cranial dissection may diminish the reliability of para-aortic lymphadenectomy because 88% of patients with para-aortic LNM have high para-aortic metastasis and 35% have only high para-aortic metastasis (Kumar et al. 2014). Further, para-aortic lymphadenectomy is not without risks; it is a powerful independent predictor of grade 2 or higher postoperative complications (Dowdy et al. 2012). Thus, selective para-aortic lymphadenectomy could be a reasonable option in EC if a reliable method for predicting para-aortic LNM were available.

Two previous observations triggered the theory that macroscopic pelvic lymph node findings at surgery might help in predicting para-aortic LNM in patients with EC. Firstly, in the presence of histologically positive pelvic nodes, para-aortic LNM exists in 51% of cases (Kumar et al. 2014). Consistent with this, we found para-aortic LNM concomitantly with positive pelvic nodes in 60% of patients in our study. Secondly, according to two reports (Abu-Rustum et al. 2009, Chiang et al. 2011), the prevalence of isolated para-aortic metastases in EC is low (about 1%).

The rate of isolated para-aortic LNM (5.1%) was somewhat higher than expected in our sample of 117 patients who underwent comprehensive lymphadenectomy. This could be explained by the fact that the sample consisted mainly of high-risk cases. The proportion of isolated para-aortic LNM was presumably much lower in the whole study population of 854 women, since 416 of the 455 patients who received pelvic lymphadenectomy only had no lymphatic spread. Over a median follow-up time of 33 months (range 1 to 64), a primary para-aortic relapse occurred in 11 patients (2.6%). One patient relapsed exclusively in the para-aortic space. Three of the 117 patients who underwent pelvic and para-aortic lymphadenectomy had a para-aortic relapse during follow-up. Only one of these patients relapsed exclusively in the para-aortic space. These findings suggest that para-aortic dissection was generally reliable in the study population, with few false negative cases.

Grossly positive pelvic nodes predicted para-aortic LNM with a moderate sensitivity (52.4%) and high specificity (93.8%). Since the incidence of para-aortic metastasis in EC varies depending on the features of the primary tumor, we used likelihood ratios to better describe the risk in a general population with EC. According to likelihood ratios, grossly positive pelvic nodes increased the probability of para-aortic LNM by about eight-fold, whereas the probability was halved when pelvic nodes were grossly negative. After correcting for deep MI, grade 3 endometrioid histology and nonendometrioid histology as confounders, grossly positive pelvic nodes remained a significant predictor of para-aortic LNM.
Bayesian calculations were applied to evaluate the usefulness of pelvic node findings in predicting para-aortic LNM in different clinical scenarios. The cut-off for a clinically useful test was set at an NPV of 98.0%, and the predictive values of the test were calculated for patients at various risks for stage IIIC2 carcinoma. The test reached NPV ≥98.0% for the study population as a whole and for patients with grade 1-2 endometrioid carcinomas, regardless of MI depth.

Data on macroscopic lymph node findings were presumably reliable, despite the fact that they were based on a retrospective analysis of operative reports. The criteria for grossly positive lymph nodes were strict, and there were no false positive cases when a postoperative pathologic evaluation served as the reference. In all eight cases of grossly negative but histologically positive pelvic nodes, an evaluation of the nodes was given in the operative report. A description of the nodes (typically “normal” or “unsuspicious”) was given in all such cases.

In conclusion, patients with grade 1-2 endometrioid carcinomas, regardless of MI depth, are unlikely to benefit from routine para-aortic lymphadenectomy. This findings could have a major impact on the planning of surgical staging procedures when adhering to a selective lymphadenectomy strategy, since grade 1-2 carcinomas with MI ≥50% are more common (179 cases in our sample) than either grade 3 endometrioid carcinomas (115 cases) or nonendometrioid carcinomas (70 cases). When adhering to the routine lymphadenectomy strategy, the diagnostic and therapeutic value of routine para-aortic lymphadenectomy in addition to pelvic lymphadenectomy appears to be minimal.

**STRENGTHS AND LIMITATIONS**

The interpretation of the findings in Studies I through III is strengthened by the large cohort size and detailed clinicopathologic data, including data on follow-up. Our institution adhered to the strategy of routine pelvic and selective para-aortic lymphadenectomy until the end of 2011. As a result, a relatively large proportion of patients with low-risk EC underwent lymphadenectomy which facilitated the recognition of patients whose disease stages were higher than expected. The lymphadenectomy rate for the total cohort was fairly high at 64.8%.

The limitations of Studies I through III are intrinsic to all single-institution retrospective studies. Specifically, it is not possible to rule out selection bias or the presence of confounding factors in the study population. However, it should be noted that the demographics of our study population, as well as the tumor distribution by histology and stage, were very similar to study cohorts from other developed countries (Lewin et al. 2010, Crosbie et al. 2012, Werner et al. 2012).

Meta-analysis, the statistical process for combining data from multiple studies, increases the overall sample size and may thereby provide a more reliable estimate of the true underlying effect than any individual study. A potential limitation of all meta-analyses is that their reliability is determined by the reliability of the methods used in the primary studies. As an attempt to reduce
the chance of bias in Study IV, a comprehensive search strategy and specified inclusion criteria were used. Meta-analyses do not correct biases that stem from selective publication, which was also recognized as a potential source of bias in Study IV.

**FUTURE PROSPECTS**

Although prospective randomized trials have failed to observe a survival benefit from lymphadenectomy in women with preoperative early-stage EC, published trials were not able to resolve whether patients at high risk for LNM benefit from lymphadenectomy (Benedetti Panici et al. 2008, ASTEC study group 2009). According to cohort and registry-based studies, lymphadenectomy may be associated with improved survival in patients at high risk for recurrence (Chan et al. 2006, Todo et al. 2010, Mahdi et al. 2013). Thus, if new randomized trials will be planned to validate the therapeutic effect of lymphadenectomy, the role of lymphadenectomy as an independent prognostic factor should be evaluated especially in high-risk patients.

Several risk-stratification methods associated with a negligible risk of undetected LNM have been developed. Unfortunately, these methods are not ideal because a relatively high lymphadenectomy rate is a prerequisite for their high reliability. Future studies should explore whether similarly low rates of undetected LNM can be achieved with methods associated with lower lymphadenectomy rates. Based on the findings of an integrated genomic and proteomic analysis, it can be predicted that molecular prognosticators will ultimately allow individualized risk-assessment and treatment of patients with EC (Cancer Genome Atlas Research Network 2013). The economic efficiency of routine lymphadenectomy and selective lymphadenectomy, based on different risk-stratification methods, can be compared with cost-effectiveness analyses. Such analyses may help in choosing between competing treatment alternatives.
CONCLUSIONS

This study sought to develop new, clinically applicable methods for the risk-stratification of EC, as well as to evaluate the reliability of currently available methods to allow evidence-based decisions regarding the surgical treatment of patients with EC.

The results of the study can be summarized as follows:

Study I The risk-scoring model that was developed predicts stage IIIC-IV ECs with an NPV that is comparable to that of FDG PET/CT and SLN biopsy in predicting LNM. The advantage of the current model is that it allows the recognition of at-risk patients prior to surgery without advanced technology, suggesting a possible cost-effective approach to the risk-stratification of EC.

Study II When uterine factors are used for the risk-stratification of EC, selective para-aortic lymphadenectomy, based on gross findings of pelvic nodes, is feasible for patients with grade 1-2 endometrioid carcinomas, regardless of the depth of MI. Similarly, gross pelvic node findings can be used to evaluate the need for para-aortic lymphadenectomy in the strategy of routine pelvic lymphadenectomy.

Study III The combination of preoperative histology and pelvic MRI mislabels a relatively high proportion of postoperative high-risk ECs. This limitation should be taken into account if the method is applied in clinical practice.

Study IV Considering the poor-to-moderate sensitivity of MRI in detecting deep MI, CSI and LNM, patients with negative findings may not safely forego lymphadenectomy unless the findings are confirmed by a backup method, such as frozen section analysis. The high specificities allow targeting of staging procedures by MRI alone in patients with positive findings. Compared with CE imaging, dynamic and DW imaging may be more reliable in the radiological staging of EC.
ACKNOWLEDGEMENTS

This study was carried out at the Department of Obstetrics and Gynecology, Helsinki University Hospital, during 2011-2015. I wish to express my gratitude to the former and present administrative heads of our institution, namely Docent Jari Sjöberg and Professor Seppo Heinonen, and former and present academic heads of the Department, Professor Jorma Paavonen and Professor Juha Tapanainen for creating an inspiring academic environment and providing me with great facilities for performing this study.

My deepest gratitude belongs to my supervisors, Docent Mikko Loukovaara and Docent Arto Leminen. I am sincerely thankful to Docent Mikko Loukovaara for introducing me to this project and to the world of scientific research. I admire his clear and systematic thinking that leads him to great achievements in different fields of work and life. His contribution to this project has been immeasurable. I want to express my deepest gratitude to Docent Arto Leminen for giving me a chance to get to know the field of gynecologic oncology. I warmly thank him for sharing his vast knowledge on the subject with me and providing me with excellent teaching on clinical skills. During this project his views have been guiding us through many difficult situations.

During these years many people have contributed to this work in various ways. I want to express my gratitude to all of them:

The official reviewers of this thesis Docent Maarit Anttila and Professor Ben Davidson, for their professional and thorough evaluation that helped me to improve this work.

Co-authors Docent Ralf Bützow, Docent Jouko Lohi and Arja-Riitta Pauna, MD, for sharing their valuable clinical and scientific expertise for the benefit of this study. Without them this work would not have been possible.

All my colleagues in Kätilöopisto Maternity Hospital, HUH Women’s Hospital and Päijät-Häme Central Hospital. It has been a privilege to work in such educating, encouraging and supporting atmospheres. Special thanks belong to all my colleagues and friends at Kätilöopisto Maternity Hospital. Hanna Rouhe, MD, PhD, and Docent Anna Kanerva in particular, for all the enjoyable conversations that have brightened my working days and for all the support and advice they have given.

Pia Ebert, MD, my friend and also my tutor during specialization, for always having time and patience for my questions and me.

Our group from medical school: Anna Luukkonen, Ilona Mikkola and Riitta Vehkamäki, for all the great weekend ”conferences” during and after the study years. You always cheer me up and make me laugh.
My dear friends Päivi Galambosi, Johanna Hautala, Anna-Mari Laulumaa, Henna Oksanen and Heini Patokoski, for sharing all the moments of happiness and sadness, for being true friends. Without you I would be lost.

Teemu Haapala, for bringing lots of happiness into my life and for designing the cover of this book.

My parents Lena and Tapani, my sister Henna and my brother Matti, for always being there for me.

This study was financially supported by the grants of the Finnish Society for Gynecological Surgery, the Cancer Foundation of Irja Karvonen and the Finnish Cancer Foundation.

Helsinki, October 2015


Andreyev, H.J. 2007, "Gastrointestinal problems after pelvic radiotherapy: the past, the present and the future", *Clinical oncology (Royal College of Radiologists (Great Britain))*, vol. 19, no. 10, pp. 790-799.


Huang, M., Chadha, M., Musa, F., Friedmann, P., Kolev, V. & Holcomb, K. 2010, "Lymph nodes: is total number or station number a better predictor of lymph node metastasis in endometrial cancer?", Gynecologic oncology, vol. 119, no. 2, pp. 295-298.


