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Endometrial cancer: diagnostic accuracy of preoperative imaging and oncologic outcome and treatment complications after implementation of a sentinel lymph node algorithm

Doctoral thesis

NTNU
Norwegian University of Science and Technology
Thesis for the Degree of
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Department of Clinical and Molecular Medicine

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SUMMARY IN ENGLISH

Endometrial cancer is the most common gynecologic malignancy in the western world, affecting approximately 800 women in Norway every year. Around 80% of patients are diagnosed at an early stage with a favorable prognosis. In this study, we have investigated the diagnostic accuracy of preoperative imaging and oncologic outcome and treatment complications in women treated surgically in accordance with the sentinel lymph node method.

Preoperative imaging in endometrial cancer includes ultrasound, MRI, and CT, where we look for metastatic disease, and where the lymph nodes are of particular interest. The sensitivity of CT and MRI in the detection of lymph node metastasis is limited. Therefore PET/CT has been included as part of the preoperative investigation, with the hope of improving the detection of lymph node metastasis. In the first paper, we investigated the detection rate of lymph node metastasis for CT, MRI, and PET/CT. Our findings indicated that PET/CT is better than CT and MRI in the detection of lymph node metastasis, especially regarding lymph nodes located along the aorta.

The cornerstone treatment of endometrial cancer is surgery, with removal of the uterus, ovaries, and fallopian tubes. The presence of lymph node metastasis entails an increased risk of recurrence and a worsened prognosis. To minimize the risk of recurrence, patients with lymph node metastasis should have adjuvant treatment with chemotherapy after surgery. To determine whether or not the disease has spread to the lymph nodes, it is necessary to remove lymph nodes for microscopic examination. Removal of lymph nodes has been heavily debated both in relation to who would benefit from it, and to what extent it should be performed.

Lymph node removal entails an increased risk of complications, especially in terms of lymphedema. Lymphedema is a condition with swelling of the lower extremities caused by accumulation of lymph fluid in the tissue following impaired drainage. To reduce the risk of complications, a method has been developed to remove only the lymph node with the highest risk of metastasis. This lymph node is called the sentinel lymph node and is the first lymph node into which a tumor drains. If the sentinel lymph node is free of metastasis, the lymph nodes that follow in the lymph chain are also cancer free.

The sentinel lymph node method was implemented for the treatment of endometrial cancer at St Olavs hospital in 2012. The second paper investigates the oncologic outcome of patients treated in accordance with the sentinel lymph node method, to ensure that the survival was not impaired. Of 108 patients, five (4.6%) recurred from the disease during the first five years. These results are at least as good as previously reported following traditional lymph node removal. Our study supports other research showing no detriment of prognosis after implementation of the sentinel lymph node method.

The third paper investigated the prevalence of lymphedema in patients operated for endometrial cancer between 2006 and 2021 at Oslo University hospital or at St Olavs hospital. The patients were invited to complete a questionnaire. We found that women who had undergone surgery with the sentinel lymph node method had less lymphedema than women who had undergone complete lymph node removal; moreover, they had no more lymphedema than women who had not undergone lymph node removal at all.

We also found that, in addition to full lymph node removal, high BMI and chemotherapy were associated with higher prevalence of lymphedema. Patients who developed lymphedema had lower quality of life compared to those who did not. Surprisingly, we found that women with musculoskeletal complaints had higher prevalence of lymphedema. This brings up the question, whether the questionnaires we have used can distinguish between lymphedema and musculoskeletal complaints, possibly reporting too high prevalence of lymphedema.

In conclusion, we believe that PET/CT may be helpful in the detection of lymph nodes. The survival in patients treated according to the sentinel lymph node method is excellent, and the method is favorable considering the prevalence of lymphedema. This supports the decision of continuing imaging with PET/CT scanning in patients with endometrial cancer, as well as continuation of the sentinel lymph node method.

SAMMENDRAG PÅ NORSK

Livmorkreft er den vanligste gynekologiske kreftformen i den vestlige verden, og i Norge rammes drøyt 800 kvinner hvert år. Omtrent 80 % av pasientene diagnostiseres på et tidlig stadium med god prognose. I denne studien har vi sett på verdien av bildediagnostikk, samt overlevelse og behandlingskomplikasjoner hos pasienter som er operert i henhold til vaktpostlymfeknutemetoden.

Bildediagnostikk før operasjon inkluderer ultralyd, MR og CT. På slike bilder ser en etter spredning, og da er lymfeknutene av spesiell interesse, i og med at lymfeknutespredning er den vanligste spredningsformen. CT og MR har vist seg å ha begrenset treffsikkerhet når det gjelder å påvise lymfeknutespredning. Derfor har vi begynt å gjøre PET/CT i tillegg for å se om dette kan gjøre at vi oppdager slik spredning bedre. I den første artikkelen undersøkte vi hvor stor andel av de kvinnene som har lymfeknutespredning som får dette oppdaget ved CT, MR og PET/CT. Funnene indikerte at PET/CT var bedre enn CT og MR til å oppdage lymfeknutespredning, spesielt når det gjelder de lymfeknutene som ligger høyere oppe langs hovedpulsåren.

Standard behandling av livmorkreft er operasjon med fjerning av livmor, eggstokker og eggledere. For å finne ut om sykdommen har spredt seg til lymfeknuter eller ikke, tar man også ut lymfeknuter slik at disse kan undersøkes mikroskopisk. Spredning til lymfeknuter gir økt risiko for tilbakefall, og medfører en dårligere prognose. For å redusere risikoen for tilbakefall bør pasienter med lymfeknutespredning ha etterbehandling med cellegift etter operasjon. Lymfeknutefjerning hos pasienter med livmorkreft har vært omdiskutert, både når det gjelder hos hvilke pasienter det skal gjøres, og omfanget av lymfeknutefjerningen. Ulempen med fjerning av lymfeknuter er at det gir økt risiko for komplikasjoner, særlig i form av lymfødem. Lymfødem er en tilstand som gir hevelse i beina på grunn av opphopning av væske (lymfe) i vevet som følge av redusert drenasje.

For å redusere risikoen for komplikasjoner har man utviklet en metode for å kun fjerne den lymfeknuten hvor det er størst risiko for spredning. Denne lymfeknuten kalles vaktpostlymfeknuten. Dette er den lymfeknuten som tumor først drenerer til, altså den lymfeknuten hvor man tidligst finner eventuell spredning. Prinsippet er at dersom det ikke er

spredning til denne lymfeknuten, er det heller ikke spredning til de lymfeknutene som ligger etter vaktpostlymfeknuten i kjeden av lymfeknuter.

Teknikken med fjerning av vaktpostlymfeknuter ble tatt i bruk ved St Olavs hospital i 2012. Den andre artikkelen er en gjennomgang av pasienter som har fått fjernet vaktpostlymfeknuter, der vi ville se hvordan det hadde gått med disse pasientene. Dette for å forsikre oss om at denne nye metoden ikke fører til dårligere overlevelse. Vi fant at av 108 pasienter, var det fem (4,6%) som fikk tilbakefall i løpet av de 5 første årene. Dette er minst like gode tall som man tidligere har sett etter tradisjonell lymfeknutefjerning, og støtter annen forskning som ikke viser dårligere prognose etter vaktpostlymfeknutefjerning.

Den tredje artikkelen tok for seg pasienter operert for livmorkreft i perioden 2006 til 2021, ved Oslo Universitetssykehus eller St Olavs hospital. Vi sendte ut spørreskjema for å finne ut om det var forskjell på forekomsten av lymfødem hos kvinner som hadde fått fjernet lymfeknuter ved tradisjonell teknikk, vaktpostlymfeknuteteknikk og hos de som ikke hadde fått fjernet lymfeknuter. Vi fant at pasienter som var behandlet etter vaktpostlymfeknutemetoden hadde lavere risiko for lymfødem sammenliknet med de som hadde fjernet lymfeknuter på tradisjonell måte, og faktisk ikke høyere forekomst enn dem som ikke hadde fått fjernet lymfeknuter i det hele tatt. I tillegg til lymfeknutefjerning var også høy BMI og cellegiftbehandling assosiert med høyere forekomst av lymfødem. Vi fant dessuten at pasienter som utviklet lymfødem hadde dårligere livskvalitet enn de som ikke gjorde det. Noe overraskende fant vi at kvinner med muskel/skjelettplager hadde større forekomst av lymfødem sammenliknet med kvinner uten slike plager. Dette gjør at vi stiller spørsmål ved om spørreskjemaene bare fanger opp pasienter med lymfødem, eller om de også fanger opp pasienter med muskel/skjelettplager, som da feilaktig blir kategorisert som lymfødem.

Konklusjonen av arbeidet er at PET/CT sannsynligvis gir en gevinst i oppdagelse av lymfeknutespredning. Pasienter som er operert med fjerning av vaktpostlymfeknuter har utmerket prognose, og denne behandlingsformen er assosiert med lavere forekomst av lymfødem enn tradisjonell lymfeknutefjerning. Dette styrker beslutningen om å fortsette med PET/CT hos pasienter med livmorkreft og å fortsette å behandle pasientene i henhold til vaktpostlymfeknutemetoden.

***Kandidat**:* *Nina Jebens Nordskar*

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***Biveiledere**:* *Bjørn Hagen*

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LIST OF PAPERS

This thesis is based on the following three papers:

Paper I

Initial experience with positron emission tomography/computed tomography in addition to computer tomography and magnetic resonance imaging in preoperative risk assessment of endometrial cancer patients.

Nordskar NJ, Hagen B, Ogarkov A, Vesterfjell EV, Salvesen Ø, Aune G.

Eur J Obstet Gynecol Reprod Biol. 2021;259:46-52.

doi: 10.1016/j.ejogrb.2021.01.052. Epub 2021 Feb 15.

Paper II

Long-term outcomes in endometrial cancer patients after robot-assisted laparoscopic surgery with sentinel lymph node mapping

Jebens Nordskar N, Hagen B, Vesterfjell EV, Salvesen Ø, Aune G.

Eur J Obstet Gynecol Reprod Biol. 2022;271:77-82.

doi: 10.1016/j.ejogrb.2022.02.003. Epub 2022 Feb 7

Paper III

Self-reported lower extremity lymphedema and quality of life after surgical staging of endometrial carcinoma: A population based cross-sectional study

Bjerre Trent P, Jebens Nordskar N, Wangen K, Engeskaug I, Opheim L, Aune G, Staff A, Thorsen L, Falk R, Eriksson A

Gynecol Oncol 2023;15:72-80.

https://doi.org/10.1016/j.ygyno.2023.05.070

ABBREVIATIONS

AJCC	American Joint Committee on Cancer
ASTEC	A Study in the Treatment of Endometrial Cancer
BMI	Body mass index
CAP	The College of American Pathologists
CDT	Complex decongestive therapy
CI	Confidence interval
CINDEIN	Circumflex iliac nodes distal to the external iliac nodes
CT	Computed tomography
DFS	Disease-free survival
DL	Deep learning
DSS	Disease specific survival
EBRT	External beam radiotherapy
ECLAT	Endometrial Cancer Lymphadenectomy Trial
EORTC	European Organisation for Research and Treatment of Cancer
ER	Estrogen receptor
ESGO	European Society of Gynaecological Oncology
ESP	European Society of Pathology
ESTRO	European SocieTy for Radiotherapy and Oncology
EUGENIE	Improving Endometrial cancer assessment by combining the new techniQue of GENomic profiling with surgical Extra uterIne disEase assessment
FDG	Fluorodeoxyglucose
FIGO	International Federation of Gynecology and Obstetrics
FILM	Near-infrared fluorescence for detection of sentinel lymph nodes in women with cervical and uterine cancers
FIRES	Fluorescence imaging for robotic endometrial cancer sentinel node mapping
GLUT	Glucose transport proteins
HDI	Human development index
HE	Hematoxylin and Eosin
HER2/Neu	Human epidermal growth factor receptor 2
HRD	Homologous recombination deficient
IHC	Immunohistochemistry
IQR	Interquartile range
ITC	Isolated tumor cell
LEL	Lower extremity lymphedema
LELSQ	Lower Extremity Lymphedema Screening Questionnaire

LND	Lymphadenectomy
LVC	Limb volume change
MMRd	Mismatch repair deficient
MRI	Magnetic resonance imaging
MSI	Microsatellite instable
MSKCC	Memorial Sloan Kettering Cancer Center
NGS	Next generation sequencing
NIR	Near-infrared
NJN	Nina Jebens Nordskar
NPV	Negative predictive value
NSMP	No specific molecular profile
OS	Overall survival
OSNA	One-step nucleic acid amplification
OUH	Oslo University Hospital
PARP	Poly (ADP-ribose) polymerase
PD1	Programmed cell death protein 1
PET	Positron emission tomography
PFS	Progression-free survival
POLE	Polymerase epsilon
PORTEC	Post Operative Radiation Therapy in Endometrial Carcinoma
PPV	Positive predictive value
PRO	Patient-reported outcome
PROM	Patient-reported outcome measure
QALYw	Quality-adjusted life year weight
QoL	Quality of life
RCT	Randomized controlled trial
RFS	Recurrence-free survival
SD	Standard deviation
SELECT	SEntinel Lymph node Endometrial Cancer Trial
SLN	Sentinel lymph node
SUV	Standard uptake volume
TCGA	The Cancer Genome Atlas
TVUS	Transvaginal ultrasound
VAS	Visual Analog Scale

INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy in Norway, affecting approximately 800 women every year (1, 2). Endometrial cancer often presents with vaginal bleeding, which is why many women seek medical attention and are diagnosed at an early stage (3). Among patients with early-stage disease, approximately 80% have a favorable prognosis with high survival rates. However, in the remaining 20%, unfavorable histopathological features entail an increased risk of recurrence and cancer-related death (4). The latter group have an increased risk of lymph node metastasis, the most common form of extrauterine spread. Based on histologic subtype and extent of disease, the patients are categorized into risk groups, determining the treatment to be offered.

The cornerstone treatment of endometrial cancer is surgery, with removal of the uterus, ovaries, and fallopian tubes, with or without removal of lymph nodes. The extent of lymph node removal has been heavily debated, as the therapeutic effect in early-stage disease remains uncertain and systematic lymphadenectomy (LND) carries a significant risk of developing lymphatic-specific morbidity, such as lower extremity lymphedema (LEL) (5-8). Since most of the women diagnosed with endometrial cancer do not have lymph node metastasis and carry a good prognosis, it is of greatest importance to avoid unnecessary treatment causing adverse effects and reduced quality of life (QoL). The diagnostic challenge is to identify patients with low risk of nodal metastasis who can be treated with surgery alone, in contrast to those with high-risk disease needing adjuvant therapy.

Preoperative investigation that includes imaging is important in assessing the extent of disease, ensuring that the patient receives the most optimal and tailored treatment possible. Findings from preoperative imaging are crucial in determining the surgical approach and extent. Due to the potential adverse effects, the treatment must be sufficient, but not too extensive. Traditionally, CT and MRI have been performed to investigate the presence of lymph node metastases. The sensitivity is, however, limited (9). Since 2016, PET/CT has been introduced as part of the preoperative investigation of endometrial cancer patients at St Olavs hospital, with the hope to improve the preoperative detection of lymph node metastasis. The **first paper** in this thesis investigates if PET/CT provides additional

information compared to CT and MRI in the detection of lymph node metastasis, thereby justifying the continuation of PET/CT as preoperative assessment.

Importantly, although preoperative imaging and endometrial biopsy can guide risk-stratification, allocating patients to risk groups can only be done based on postoperative histopathological findings. The sentinel lymph node (SLN) algorithm has been developed as a compromise between comprehensive LND in high-risk patients and omittance of lymph node removal in low-risk patients. This algorithm was implemented in our department in 2012, as the first hospital in Norway, but is established in hospitals where cancer care is centralized today.

When introducing a new algorithm such as SLN, it is of greatest importance to ensure that the oncologic outcome of the patients is not impaired, yet studies providing information on oncologic outcome after implementation of SLN are limited and often with short follow-up. **Paper II** contributes to filling this knowledge gap with long time survival data in patients staged according to the SLN algorithm.

A reduction in LEL is one of the expected benefits of SLN compared to LND. However, lack of consensus on how to diagnose LEL makes it difficult to determine its occurrence. To offer the best possible treatment and surveillance of these women it is of great importance to obtain information about the prevalence of LEL, and how the presence of LEL affects the patient's quality of life (QoL). These are the issues in focus in **paper III**.

In the last decade, there has been a significant development in terms of investigation and treatment of patients with endometrial cancer. Novel methods in imaging, surgical staging with transition to the SLN algorithm, and molecular classification with its possible implications for adjuvant treatment all contribute to opportunities for more detailed diagnostics than previously available.

The rationale for this thesis was to evaluate preoperative imaging in women diagnosed with endometrial cancer, focusing on the diagnostic accuracy of preoperative PET/CT compared to standard CT and magnetic resonance imaging (MRI) in identifying lymph node metastasis. Further objectives were to evaluate long term outcomes after implementation of the SLN algorithm, regarding recurrence rate and survival, treatment complications with lower extremity lymphedema, and QoL.

BACKGROUND

Endometrial cancer

Epidemiology

Endometrial cancer is the sixth most common cancer in women worldwide and the most common gynecological cancer in developed countries with 417,000 new cases and 97,000 deaths in 2020 (10, 11). The incidence varies across regions, with the highest rates seen in countries with a very high Human Development Index (HDI) such as Northern America, Europe, Micronesia/Polynesia, and Australia/New Zealand and the lowest rates seen in most African regions and South-Central Asia (10, 12). In Norway, 817 women were diagnosed with endometrial cancer in 2022 (1). In 2020, the age-standardized rate (ASR) in Norway was 25.5 pr 100,000 women years (13) , compared to 8.7 pr 100,000 worldwide (11). The incidence increased from 232 new cases per year in the period from 1963-67, to 802 in the period from 2018-22 (Figure 1) (1). Worldwide, the number of newly diagnosed endometrial cancers increased by 132% between 1990 and 2019 (14). The majority of patients are diagnosed with localized disease, with five-year survival rates nearly 98%. However, with regional or distant spread, the survival rates are 73% and 39% respectively (1). The mortality-to-incidence ratio is higher in developing than in developed regions (Figure 2). The majority of patients diagnosed with endometrial cancer are postmenopausal, as 90% are more than 50 years old. In Norway the median age at diagnosis is 69 years (1), compared to 63 years worldwide (4).

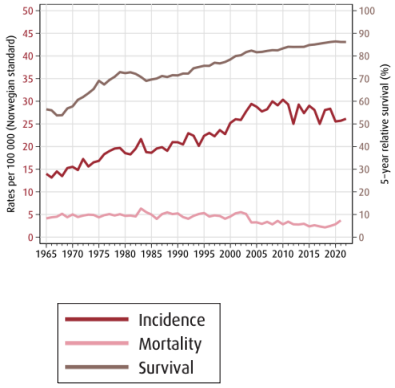


Figure 1: Trends in the Norwegian incidence and mortality rates and 5-year relative survival proportions. Reprinted with permission from Cancer Registry of Norway. Cancer in Norway 2022 - Cancer incidence, mortality, survival and prevalence in Norway. Oslo: Cancer Registry of Norway, 2023 (1) .

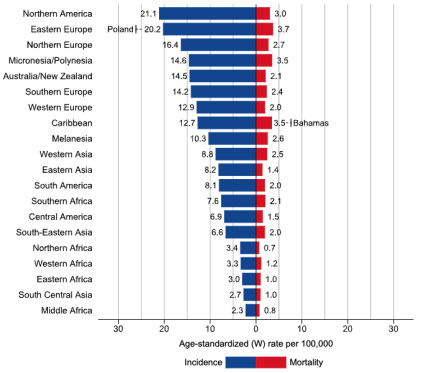


Figure 2: Region-specific incidence and mortality age-standardized rates (2020).
Reprinted with permission from Sung et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Available from: https://gco.iarc.fr/today (10).

Clinical presentation and diagnosis

Abnormal vaginal bleeding, including bleeding after menopause, is the cardinal symptom that occurs in 90% of women who have endometrial cancer. Bleeding often occurs early, which is why most women are diagnosed with early-stage disease confined to the uterus. The risk of endometrial cancer in women with postmenopausal bleeding is approximately 9%, increasing when other risk factors are present (3). Women presenting with postmenopausal bleeding should undergo gynecological examination with transvaginal ultrasound (TVUS) and endometrial biopsy. In women with endometrial cancer, TVUS will often present thickened endometrium. In the presence of postmenopausal bleeding, several guidelines recommend using a sonographic cutoff value of 5 mm to recommend further investigation of the endometrium (15).

Women with advanced endometrial cancer often have symptoms similar to those seen in patients with advanced ovarian cancer, such as abdominal or pelvic pain, abdominal distention, bloating, early satiety, as well as change in bowel or bladder function.

Etiology and risk factors

Prolonged exposure to unopposed estrogens is an essential contributor to most of the risk factors for endometrial cancer, including nulliparity, early menarche, late menopause, use of hormone replacement therapy, and obesity (16-18). Other risk factors are family history of endometrial cancer (19), hypertension (20, 21), and diabetes. However, the latter two are controversial as they may be confounded by body weight (22, 23). High parity, late age at first and last birth, combined estrogen-progesterone oral contraceptives, physical activity, and smoking are associated with reduced risk of endometrial cancer (24-27).

Overall, for every 5-unit increase in body-mass index (BMI), the risk of endometrial cancer increases by more than 50% (Figure 3). The risk clearly increases for BMI over 25 kg/m^2, but some risk increase is also observed within the normal BMI range (28). High BMI alone is estimated to account for 34% of the total endometrial cancer incidence worldwide (17). The rapidly increasing global prevalence of obesity (29, 30) combined with an aging population is the main contributor to the increasing incidence of endometrial cancer. As a consequence of the obesity pandemic, the incidence of endometrial cancer is therefore expected to continue increasing in the near future (31).

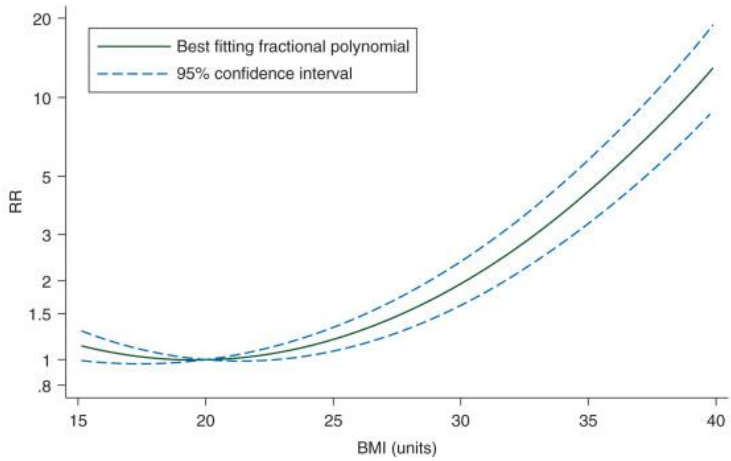


Figure 3: Body-mass index and endometrial cancer incidence, non-linear dose-response.
From Aune D, Navarro Rosenblatt DA, Chan DS, Vingeliene S, Abar L, Vieira AR, et al. Anthropometric factors and endometrial cancer risk: a systematic review and dose-response meta-analysis of prospective studies. Ann Oncol. 2015;26(8):1635-48.
Reprinted with permission from Elsevier(28).

High BMI is responsible for increased incidence of endometrial cancer through different mechanisms. First, synthesis and bioavailability of sex steroids is influenced by excess weight. Second, adiposity after menopause causes increased levels of insulin and insulin-like growth factors, leading to higher levels of free estrogens. Additionally, adiposity is associated with insulin resistance and increased risk of type 2 diabetes, which in turn is assumed to be a risk factor for endometrial cancer. Finally, estrogens can stimulate cellular proliferation, inhibit apoptosis, and induce angiogenesis. (28, 32).

Although most endometrial cancers occur due to sporadic mutations, approximately 5% of all endometrial cancers are caused by genetic predisposition. Lynch syndrome results from pathogenic variants in the mismatch repair (MMR) genes MLH1, MSH2, MSH6, and PMS2, portending a 13-49% lifetime risk of endometrial cancer (33). Other, less frequent, hereditary causes of endometrial cancer include Cowden syndrome, BRCA1 and BRCA2 mutations (34, 35).

Histopathology

Cancer of the uterine corpus is usually referred to as endometrial cancer. Endometrial cancer arises from the epithelial lining of the uterine cavity (endometrium); this is unlike sarcomas which arise from the stromal and muscle tissues of the myometrium. The latter will not be further discussed in this thesis.

Endometrioid adenocarcinoma is the most common histologic subtype, accounting for 75-80% of cases (36). Endometrioid adenocarcinoma develop from hyperplasia, often because of prolonged unopposed exposure to estrogen. Endometrioid adenocarcinomas are graded using the International Federation of Gynecology and Obstetrics (FIGO) grading criteria (37), which assesses the architectural pattern and nuclear grade. Grade 1 exhibits ≤ 5% solid growth patterns, grade 2 exhibits 6-50% solid growth patterns and grade 3 > 50% solid growth (36). Binary grading is recommended, classifying grade 1 and 2 tumors as low-grade and grade 3 tumors as high-grade (38). Most endometrioid adenocarcinomas are low-grade, diagnosed at an early stage with favorable prognosis.

Serous endometrial carcinoma accounts for approximately 10% of the endometrial cancer cases (36), but as many as 40% of endometrial cancer-related deaths. Serous carcinomas

develop from endometrial atrophy or in an endometrial polyp. The incidence is higher in black women than in other populations, and affected women are often multiparous with a history of breast carcinoma and/or tamoxifen use.

Clear cell carcinoma accounts for less than 10% of the endometrial cancers (36). Patients with clear cell carcinoma tend to be older, are more likely to present at higher-stage disease, and carry a worse prognosis than patients with endometrioid carcinoma.

Carcinosarcoma (36) is a biphasic cancer with both epithelial (carcinomatous), typically serous, and mesenchymal (sarcomatous) components. These are clinically aggressive tumors with 45% likelihood of extrauterine spread at presentation, accounting for 5% of the endometrial cancers.

Molecular classification of endometrial cancers

Traditionally, endometrial cancer has been classified into type I and type II, based on Bokhman's dualistic model from 1983 (39). **Type I** is typically seen in perimenopausal women with high BMI and is described as estrogen dependent, usually with low-grade endometrioid histology with favorable prognosis. **Type II** is often seen in postmenopausal women with normal BMI, is unrelated to estrogen and comprises a diverse mix of high-grade, clinically aggressive histologic subtypes with p53 mutations and poor prognosis. Both histologic subtype and grade assignment have been shown to be poorly reproducible between gynecological pathologists (40, 41), making the risk stratification inconsistent, and leading to imprecise risk estimation of recurrence and death, again leading to both over- and under-treatment.

In 2013, The Cancer Genome Atlas (TCGA) Research Network classified endometrial cancers into four molecular categories: polymerase epsilon (POLE)-mutated, mismatch repair deficient (MMRd), p53-abnormal (p53abn), and tumors with no specific molecular profile (NSMP) (42). This classification defines biologically and clinically distinct diseases, and is, unlike the traditional classifications which were based on histological subtypes, objective and reproducible (43, 44). Molecular classification has important prognostic and therapeutic implications that may provide a basis for personalized treatment. TCGA uses whole genome sequencing for evaluation, which is neither clinically nor economically feasible for a large

population. Two researcher groups in Leiden and Vancouver have developed more feasible techniques of immunohistochemistry (IHC) and Sanger or next generation sequencing (NGS) analysis (45-47), where TCGA molecular stratification is possible using surrogate markers, enabling identification of subgroups analog to the four described by TCGA.

POLEmut endometrial cancers have pathogenic mutations in the exonuclease domain of DNA POLE-protein which is involved in DNA replication. This results in ultra-mutated tumors. This molecular subclass includes 10% of the endometrial cancers and affects relatively young patients without association to metabolic syndrome. The prognosis is excellent, independent of adjuvant treatment (48). Targeted sequencing of POLE exonuclease domain is performed by NGS (46).

MMRd endometrial cancers are also called microsatellite instable (MSI) tumors, accounting for 25-30% of all endometrial cancers. Damage in the DNA MMR pathway leaves unrepaired post-DNA replication errors, resulting in a high mutational burden. MMRd can be identified through MSI testing or IHC testing for the loss of expression of one or more MMR proteins (MLH1, PMS2, MSH2, MSH6) (49). Germline mutations in one of the MMR proteins are known as Lynch syndrome, accounting for 10% of the MMRd endometrial cancers. The prognosis is intermediate.

p53abn endometrial cancers, also called copy number high, account for approximately 15% of the endometrial cancers, but are, however, responsible for 50-70% of the endometrial cancer mortality, because of the poor prognosis. These tumors are identified by IHC staining for p53 and are shown to benefit from adjuvant treatment with platinum-based chemotherapy. Many of these tumors are homologous recombination deficient (HRD), a known marker for clinical response to both platinum-based chemotherapy and poly (ADP-ribose) polymerase (PARP) inhibitors (50).

No specific molecular profile (NSMP) endometrial cancers have a low number of somatic copy number alterations (copy-number low), low mutational burden, and high levels of estrogen- and progesterone receptor expression. This group accounts for approximately half of all endometrial cancers, and the prognosis is intermediate. Obesity and diabetes are common in women with endometrial cancer with NSMP subtype. Low-grade (1-2) and

estrogen receptor (ER) positive NSMP endometrial cancers carry a low risk of recurrence and an exceptionally favorable prognosis (50-52).

Figure 4 describes a diagnostic algorithm for molecular classification.

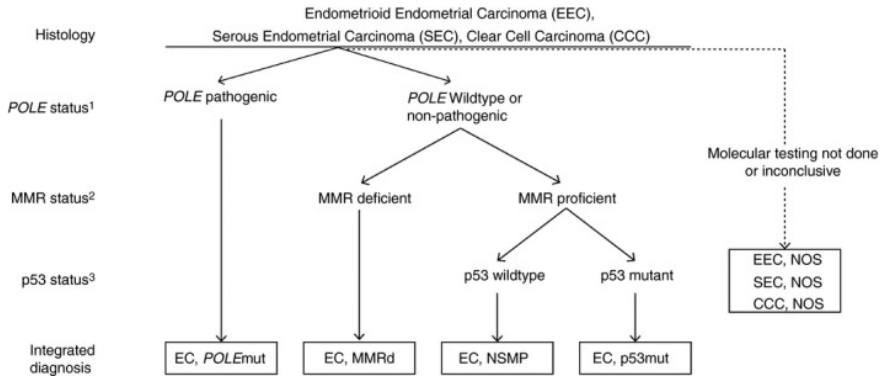


Figure 4: Diagnostic algorithm for the classification of the four molecular subgroups in endometrial cancer. Reprinted from Vermij et al., Incorporation of molecular characteristics into endometrial cancer management (53).

While most endometrial cancers can be classified based on a single classifier (POLEmut, MMRd, p53mut), 3-6% of tumors harbor more than one molecular classifying feature and are referred to as “multiple classifier” endometrial cancers (54).

The European Society of Gynaecological Oncology (ESGO) recommends testing with MMR IHC, p53 IHC and ER IHC in all endometrial cancers. Because of its limited availability, testing for POLE mutations is restricted but is recommended in cases of p53mut and MMRd tumors where the presence of a pathogenic POLE mutation could alter the indication for adjuvant treatment (55).

Human epidermal growth factor receptor 2 (HER2/Neu) is a tyrosine kinase providing critical signaling for cancer cell growth, survival, and proliferation. HER2/Neu is overexpressed in approximately 30% of serous endometrial cancers and appears to be a poor prognostic factor. Overexpression of HER2/Neu may be utilized for targeted treatment with monoclonal antibodies that attach to the HER2 on the surface of some cancer cells, blocking it from tumor growth (56).

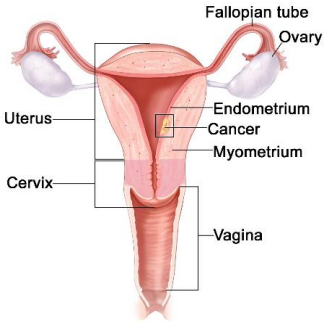
Staging of endometrial cancer

FIGO staging of endometrial cancer is based on depth of myometrial invasion, involvement of the cervical stroma, and the presence of extrauterine disease (37), as the TNM-classification describes the primary **tumor** site and size, regional lymph **node** involvement and **metastatic** spread of the disease (57). The staging classification systems are shown in Table 1 and Figure 5. The stage at diagnosis is the strongest predictor of 5-year survival (58). Staging is also important for treatment planning, it serves as a research tool to assess treatments among patient groups and for stratification in clinical trials (59). The first FIGO staging system for endometrial cancer was adopted in 1950. It was a simple system, based on only two criteria. Stage I had tumor clinically confined to the uterus, and stage II had disease spread beyond the uterus (60). The FIGO system has undergone multiple revisions, and in 1962 it was expanded into a four-stage system. The GOG 33-study showed that a significant number of patients with endometrial cancer presumed to be confined to the uterus actually had extrauterine disease (58). This is why surgical staging was introduced in 1988, replacing clinical staging (61).

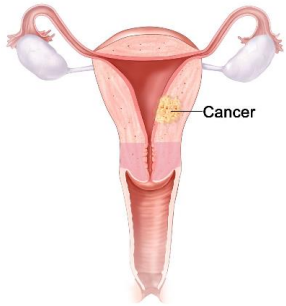
Table 1: FIGO and TNM classifications of endometrial cancer according to surgical and histological characteristics. From Morice P, Leary A, Creutzberg C, Abu-Rustum N, Darai E. Endometrial cancer. Lancet. 2016;387(10023):1094-108. Reprinted with permission from Elsevier (62).

	FIGO stage*	TNM category
Primary tumour cannot be assessed	..	TX
No evidence of primary tumour	..	T0
Carcinoma in situ	..	Tis†
Tumour confined to the corpus uteri	Stage I	T1
Tumour limited to endometrium or invades less than 50% of the myometrium	Stage IA	T1a
Tumour invades 50% or more of the myometrium	Stage IB	T1b
Tumour invades cervical stroma but does not extend beyond uterus	Stage II	T2
Tumour with local or regional extension	Stage III	T3 or N1–2, or both
Tumour involves serosa or adnexa, or both	Stage IIIA	T3a
Vaginal involvement or parametrial involvement	Stage IIIB	T3b
Regional lymph node metastasis	Stage IIIC	
Regional pelvic lymph node metastasis	Stage IIIC1	N1
Regional para-aortic lymph node metastasis with or without pelvic lymph node metastasis	Stage IIIC2	N2
Tumour invades bladder or bowel mucosa, or distant metastatic disease present (or any combination thereof)	Stage IV	
Tumour invades bladder or bowel, or both	Stage IVA	T4
Distant metastatic disease (includes inguinal lymph node, intraperitoneal disease, lung, bone, or liver)	Stage IVB	M1

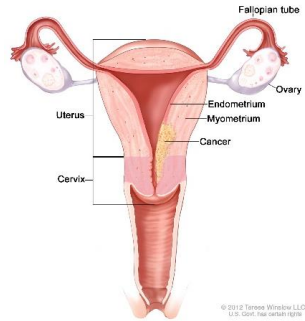
TNM classification: NX (regional lymph nodes cannot be assessed), N0 (no regional lymph node metastasis), and M0 (no distant metastasis). FIGO=International Federation of Gynecology and Obstetrics. *Either G1, G2, or G3. †FIGO does not include stage 0 (Tis) in its classification.



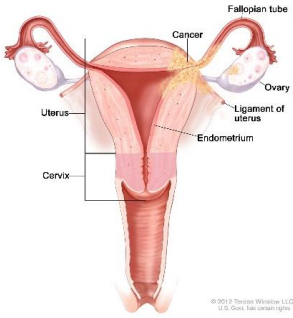
Stage IA



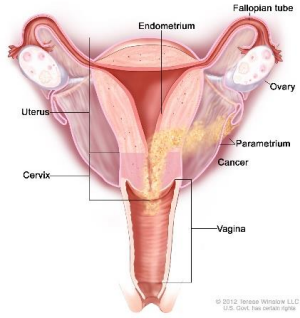
Stage IB



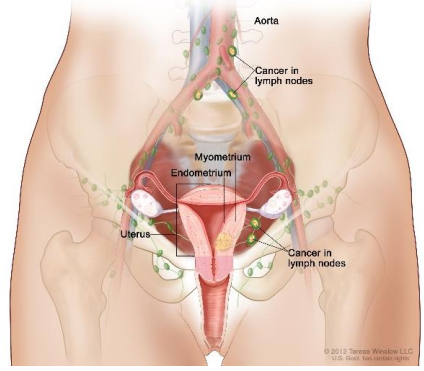
Stage II



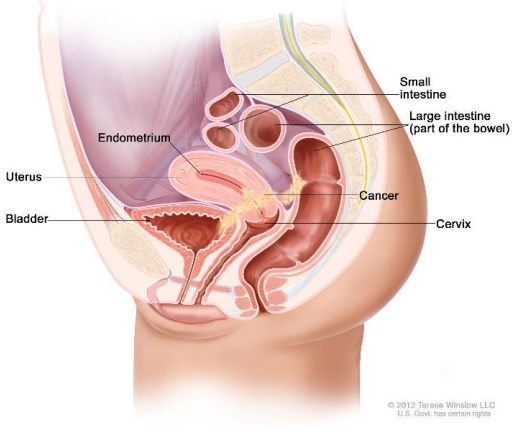
Stage IIIA



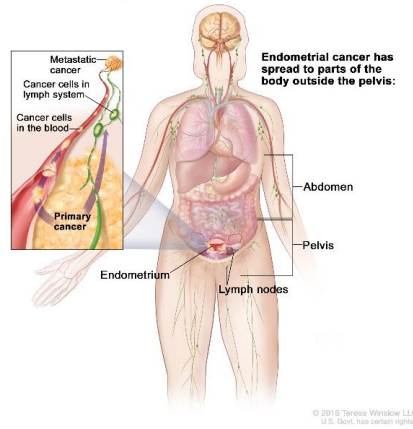
Stage IIIB



Stage IIIC



Stage IVA



Stage IVB

Figure 5: FIGO staging of endometrial cancer
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Preoperative assessment in endometrial cancer

The preoperative assessment of endometrial cancer includes histologic samples from the endometrium, TVUS, and imaging with MRI, CT and eventually PET/CT. The preoperative imaging should provide information about depth of myometrial infiltration, cervical stromal involvement, lymph node metastases in the pelvic and paraaortic region, and possible distant metastases. Diagnostic imaging is an essential part of the preoperative assessment to tailor the surgical procedure. Detection of suspicious paraaortic lymph nodes leads to removal of bulky paraaortic nodes, in many centers by laparotomy instead of minimally invasive surgery and SLN. There are, however, multiple institutions that have reported minimal invasive surgery, including SLN, also for the removal of paraaortic lymph nodes (63, 64).

Standard preoperative diagnostic tools in Norway are TVUS, CT and MRI (65), which are well-established diagnostic tools for preoperative risk classification (66). CT thorax/abdomen/pelvis is mandatory, while MR pelvis is recommended when TVUS is not sufficient to clarify the extent of myometrial invasion, cervical affection, or invasion of nearby organs in cases of locally advanced disease. PET/CT combines CT with radiolabeled ^{18}F-fluorodeoxyglucose (FDG) and has become more established in the management of gynecologic malignancies during the last decade. There is, however, currently no international consensus on optimal diagnostic imaging strategies in endometrial cancer, and the clinical routines vary across institutions and countries, mainly motivated by tradition, interpretation of published studies, and access to imaging facilities.

Transvaginal ultrasound

TVUS is traditionally performed by the gynecologist. Endometrial cancer is typically seen as hyper- or isoechoic compared to the surrounding myometrium, whereas cervical stroma invasion is seen as thickened hyper- or isoechoic endometrium extending into the cervical canal and stroma. When performed by a trained clinician, TVUS can be used to assess both the depth of myometrial infiltration and cervical invasion. The examination is easily accessible and low in cost. It is, however, highly dependent on a skilled examiner, and thus prone to interobserver variation. In a meta-analysis evaluating the accuracy of subjective

assessment in the detection of deep myometrial invasion, the overall pooled sensitivity and specificity was 82% (95%CI, 76-87%) and 81% (95% CI, 76-85%), respectively (67).

CT

CT of the thorax, abdomen and pelvis is part of the standard preoperative assessment in endometrial cancer. CT is widely available and not too expensive, providing fast reproducible image acquisition. CT makes it possible to get a complete survey of the entire pelvis, abdominal cavity, and thorax for local and distant tumor staging, including lymph node metastasis (66), the main purposes of the examination. For local staging however, CT is considered inferior to both ultrasound and MRI, due to its lower contrast resolution in soft tissue (9). Endometrial cancer tissue will appear slightly hypodense compared to the surrounding myometrial tissue. Identification of metastatic lymph nodes on CT is based on the measured node size. A common threshold for considering a lymph node metastatic is 8-10 mm (68-73). However, it may be challenging to differentiate metastatic lymph nodes from benign reactive nodes of similar size, and metastatic lymph nodes of normal size; this is why enlarged reactive lymph nodes may be misclassified.

MRI

Preoperative pelvic MRI is widely used and considered the best preoperative imaging method for local staging of the uterus in endometrial cancer (9). As deep myometrial invasion is associated with increased risk of lymph node metastasis and inferior outcome, predicting deep myometrial invasion preoperatively is important (74). MRI performs well in the detection of deep myometrial invasion and cervical stroma invasion. It has, however, low sensitivity in identifying metastatic lymph nodes, and the diagnostic criteria are primarily based on lymph node size (short axis diameter >8-10 mm) (71, 72, 75). Myometrial invasion is best assessed using T2-weighted and contrast-enhanced imaging. Novel MRI techniques such as diffusion-weighted imaging may potentially increase diagnostic accuracy in the preoperative assessment of endometrial cancer (76).

PET/CT

PET integrated with CT using ^{18}F-FDG provides both anatomic and metabolic information, at the same time allowing structural and functional data depicted in fused images. FDG is a glucose analog radiolabeled with ^{18}F, which is transported intracellularly via glucose transport proteins (GLUT). Because of their high metabolic activity, tumor cells have an increased number of GLUT proteins, allowing an increased amount of ^{18}F-FDG to enter the cell. Tumor cells prefer anaerobic metabolism, which increases the demand for glucose utilization. The cell membrane is impermeable for FDG, which will be concentrated intracellularly. Together, all this leads to retention and high levels of FDG in tumor cells compared to normal cells. The intracellular accumulation of FDG is directly proportional to the metabolic activity of the cell and can be quantified by the calculated standard uptake volume (SUV) index. In highly metabolically active cancer, the SUV will therefore be increased (77).

As increased glucose metabolism in malignant cells enables PET/CT to provide functional data, PET/CT may have the potential to detect smaller lymph node metastases than CT and MRI. Current PET/CT technology has a spatial resolution of 4-6 mm, still depending upon a sufficient number of metabolically active malignant cells to detect metastatic lesions (71, 78, 79). Although the resolution is superior to that in CT, small lymph node metastases may be hardly detectable.

PET/CT is proposed as an alternative or supplement to CT in detection of lymph node metastasis and distant spread of endometrial cancer and is reported to outperform TVUS and MRI (80). Whole-body FDG-PET/CT has the potential to detect lymph node metastasis which may be overlooked on CT and MRI. The sensitivity and specificity of detecting lymph node metastasis is reported to be in the range 63-85 %, and 91-96%, respectively (78, 81, 82) (Figure 6).

Preoperative PET/CT is increasingly used for staging of various cancers, including endometrial cancer. Some studies have proposed incorporating preoperative FDG-PET/CT to identify nodal metastasis, but there is limited data on the diagnostic and prognostic value of preoperative PET/CT imaging and no consensus on the use of it (55, 82, 83). The importance of PET/CT in assumed low-risk endometrial cancer is debated due to the low prevalence of

lymph node metastasis. However, it is more commonly recommended in endometrial cancer patients with high risk clinical and histologic features (65, 84, 85). In addition to CT, it is possible to combine the PET technology with MRI. The diagnostic accuracy of PET/MRI is reported to be equal or superior to PET/CT in endometrial cancers (86). However, in most countries, the availability of PET/MRI scanners is currently lower than PET/CT, limiting the use of PET/MRI in routine diagnostics of endometrial cancers.

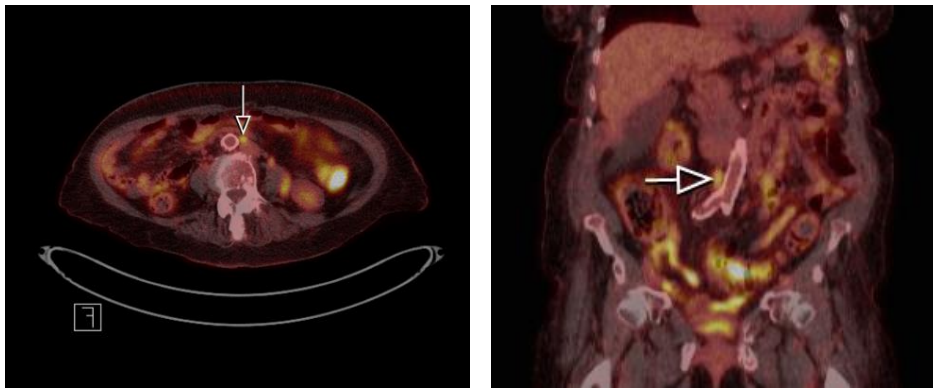

Figure 6: PET/CT images showing metastatic paraaortic lymph node.
Published with the patient's consent.

Lymph node status

Lymph nodes are the most common site of extrauterine spread, and lymph node status is a significant prognostic factor in apparent uterine-confined endometrial cancer (87). Although the risk of lymph node metastasis in apparent early-stage endometrial cancers with low grade tumors is relatively low, a significant number of patients with apparent early-stage endometrial cancer do have extrauterine disease. Poorly differentiated tumors, lymphovascular space invasion (LVSI) and deep myometrial invasion are factors that increase the risk of lymph node metastases (58).

The selection for and extent of lymph node removal in endometrial cancer primary surgery has been debated during recent decades. There has been disagreement about whether the clinical benefits of routine LND may outweigh the potential morbidity of the procedure (6, 58, 88, 89) and what the optimal procedure for lymph node assessment might be. Multiple retrospective studies have evaluated the impact of routine LND on survival. Kilgore et al. found that patients undergoing multi-site pelvic node sampling had significantly better survival than patients without sampling, even when the patients were categorized into low- or high-risk group. They therefore supported LND for all patients (88). Trimble et al. found a survival benefit in patients with high grade disease (90), and Chan et al. suggested that the number of nodes removed may be a prognostic factor for improved survival in intermediate/high-risk patients (91). A reason for the survival differences could be upstaging of patients with an inaccurately staged stage I disease to a true stage IIIC disease, and thereby correctly comparing with the survival for patients with stage IIIC disease instead of comparing with stage I patients.

The therapeutic effect of lymph node removal remains uncertain. Two large, randomized studies failed to prove any therapeutic benefit from LND in early-stage endometrial cancer (7, 8). Benedetti Panici et al. found that systematic pelvic LND improved surgical staging by identifying 10% more cases of lymph node metastases. However, it did not improve recurrence-free survival (RFS) or overall survival (OS) and the rate of lymphedema was significantly increased (7). The ASTEC (A Study in the Treatment of Endometrial Cancer) trial demonstrated similar findings, with no survival benefits and increased rate of lymphedema (8). However, these studies have been heavily disputed (92), and there are gynecologic

oncologists who still support a therapeutic benefit from LND. The ongoing Endometrial Cancer Lymphadenectomy Trial (ECLAT) may provide answers to this question (93).

Treatment of endometrial cancer

Surgical treatment

Surgery is the mainstay of treatment for endometrial cancer, and the standard surgical procedure is total hysterectomy and bilateral salpingo-oophorectomy (55, 65). Surgery was traditionally performed by laparotomy. However, randomized controlled trials (RCTs) show non-inferior oncological outcomes with shorter hospital stay and decreased blood loss, pain and perioperative morbidity after minimally invasive hysterectomy compared with open surgery. Minimally invasive surgery, with laparoscopy or robot-assisted surgery, has become the new standard of surgical treatment, including patients with high-risk endometrial cancer (94-96). Infracolic omentectomy is advised in clinical stage I serous endometrioid carcinoma, carcinosarcoma and undifferentiated carcinoma because of the risk of omental metastasis (97). Vaginal hysterectomy with or without bilateral salpingo-oophorectomy might be considered as an alternative for presumed early-stage disease where comorbidities in the patient prohibit an abdominal approach (98). In Norway, SLN biopsy is added to the surgical staging with hysterectomy and bilateral salpingo-oophorectomy as the standard surgical procedure in endometrial cancer stage I and II (65). ESGO recommends SLN biopsy in low- and intermediate-risk patients (described in Table 2), however, SLN biopsy is also proposed as an acceptable alternative to systematic LND in high-intermediate risk and high risk disease (55). When systematic LND is performed, pelvic and paraaortic infrarenal LND is suggested. The SLN algorithm will be described later in this thesis.

Adjuvant treatment

Adjuvant treatment in endometrial cancer is a topic of discussion, and the recommendations across different regions in the world are not universal. The Norwegian guidelines regarding adjuvant treatment in endometrial cancer are organized according to risk groups. The Norwegian risk groups are based on the risk groups defined in the ESGO guidelines (55) (Table 2), but with modifications (Table 3). They are based on clinicopathological factors such as histologic type, grade, and myometrial invasion. According to the ESGO guidelines, LVSI should also be assessed and taken into account when categorizing women in to a risk

group as this is a strong prognostic factor for pelvic recurrence, distant metastasis, and decreased OS (99). However, LVSI status is not included in the Norwegian risk groups.

Table 2: Definition of prognostic risk groups according to the ESGO guidelines.
Reprinted from Concin et al., ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma, Radiother Oncol, 2020. With permission from Elsevier (55).

Risk Group	Molecular Classification Unknown	Molecular Classification Known[Δ],*
Low	• Stage IA endometrioid + low-grade** + LVSI negative or focal	• Stage I-II ***POLE*mut** endometrial carcinoma, no residual disease • Stage IA **MMRd/NSMP** endometrioid carcinoma + low-grade** + LVSI negative or focal
Intermediate	• Stage IB endometrioid + low-grade** + LVSI negative or focal • Stage IA endometrioid + high-grade** + LVSI negative or focal • Stage IA non-endometrioid (serous, clear cell, undifferentiared carcinoma, carcinosarcoma, mixed) without myometrial invasion	• Stage IB **MMRd/NSMP** endometrioid carcinoma + low-grade** + LVSI negative or focal • Stage IA **MMRd/NSMP** endometrioid carcinoma + high-grade** + LVSI negative or focal • Stage IA **p53abn** and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion
High-intermediate	• Stage I endometrioid + substantial LVSI, regardless of grade and depth of invasion • Stage IB endometrioid high-grade**, regardless of LVSI status • Stage II	• Stage I **MMRd/NSMP** endometrioid carcinoma + substantial LVSI, regardless of grade and depth of invasion • Stage IB **MMRd/NSMP** endometrioid carcinoma high-grade**, regardless of LVSI status • Stage II **MMRd/NSMP** endometrioid carcinoma
High	• Stage III-IVA with no residual disease • Stage I-IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease	• Stage III-IVA **MMRd/NSMP** endometrioid carcinoma with no residual disease • Stage I-IVA **p53abn** endometrial carcinoma with myometrial invasion, with no residual disease • Stage I-IVA **NSMP/MMRd** serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Advanced Metastatic	• Stage III-IVA with residual disease • Stage IVB	• Stage III-IVA with residual disease of any molecular type • Stage IVB of any molecular type

[Δ]For stage III-IVA ***POLE*mut** endometrial carcinoma, and stage I-IVA MMRd or NSMP clear cell carcinoma with myometrial invasion, insufficient data are available to allocate these patients to a prognostic risk-group in the molecular classification. Prospective registries are recommended

* see text on how to assign double classifiers (e.g. patients with both *POLE*mut and p53abn should be managed as *POLE*mut)

** according to the binary FIGO grading, grade 1 and grade 2 carcinomas are considered as low-grade, and grade 3 carcinomas are considered as high-grade.

p53abn: p53 abnormal, MMRd: Mismatch Repair Deficient, NSMP: nonspecific molecular profile, *POLE*mut: polymerase Ɛ mutated

Table 3: Risk groups for guidance to adjuvant treatment in Norway.
Reprinted with permission from Helsedirektoratet (65)

Risk group	
Low risk	• Stage I, endometrioid histology, grade 1-2, <50% myometrial invasion
Intermediate risk	• Stage I, endometrioid histology, grade 1-2, >50% myometrial invasion • Stage I, endometrioid histology, grade 3, <50% myometrial invasion
High risk	• Stage I, endometrioid histology, grade 3, >50% myometrial invasion • Stage I, non-endometrioid histology (serous, clear cell, carcinosarcoma, undifferentiated and dedifferentiated • Stage > I

Adjuvant treatment is recommended for patients in the high risk group, including stage IB with high-grade endometrioid histologic subtype, non-endometrioid histologic subtype, and all patients with stage > I disease (65, 100). The standard adjuvant treatment is chemotherapy with Carboplatin and Paclitaxel, 6 cycles. Adjuvant treatment is not recommended in low-risk patients (65). The ESGO guidelines have included molecular classification in the recommendations for adjuvant treatment (55), this has not yet been implemented in Norway.

In other countries, and according to the ESGO guidelines, adjuvant radiation therapy has been used to prevent local pelvic recurrence (55, 101). However, no survival benefit from this treatment has been demonstrated (102, 103), although reduced locoregional recurrences have been found (104). Radiation therapy is associated with significant toxicity, without improved progression-free survival (PFS) or OS, and is thus not recommended as adjuvant treatment according to Norwegian guidelines. The lack of benefit in PFS or OS was confirmed in the GOG-258 study presented at the Society of Gynecologic Oncology (SGO) recently (105). Furthermore, local pelvic recurrences in radiotherapy-naïve women can be successfully salvaged with radiotherapy (106), advocating the omittance of adjuvant

radiotherapy in primary settings. However, according to the Norwegian guidelines, women with stage II disease including cervical stroma involvement with narrow tumor margins could be considered for adjuvant radiation therapy (107).

Targeted treatment

In Norway, there are two types of targeted therapy approved for endometrial cancer patients. In a nonrandomized phase I trial, the programmed cell death protein 1 (PD1)-inhibitor Dostarlimab is associated with clinically meaningful and durable antitumor activity in patients with MMR deficient advanced or recurrent endometrial cancer after prior platinum-based chemotherapy and could be advised in these patients (108). These results were confirmed in a recent randomized, placebo-controlled trial. Dostarlimab plus Carboplatin and Paclitaxel significantly increased PFS among patients with primary advanced or recurrent endometrial cancer, with a substantial benefit in MMRd endometrial cancer patients (109).

Further, patients with advanced or recurrent uterine serous carcinomas with overexpression of Her2/Neu are in a randomized phase II trial demonstrated to have increased PFS and OS when adding the HER2 antibody Trastuzumab to traditional chemotherapy with Paclitaxel and Carboplatin (56).

Hormonal treatment

There are no data supporting the use of adjuvant hormonal therapy in early-stage endometrial cancer (62). Endocrine treatment is however well tolerated and is an option to be considered in patients who are too frail for chemotherapy, and especially in patients with systemic recurrent disease (55, 110). Progesterone is the hormonal treatment of choice, and the effect relies on the presence of estrogen and progesterone receptor. Loss of progesterone receptor appears to be common, emphasizing the need for sampling of the recurrent tumor for hormone receptors when hormonal therapy is considered.

Pelvic lymphatic drainage pathways

The pelvic lymphatic drainage pathways are well known. The external iliac nodes, lying on the external vessels drain from the leg, abdominal wall, bladder, uterus, and vagina. The common iliac nodes form a medial group of nodes receiving drainage from the pelvic viscera, and a lateral group receiving drainage from the lower limb and pelvis (111).

The routes of lymphatic spread in endometrial cancer are less clear; various studies show heterogenous distributions. An experimental study in female cadavers proposed two lymphatic connections: one extending to the external iliac area and one to the paraaortic area (112). Mariani et al. described the routes of lymphatic spread and the location of lymph node metastases in 625 patients with endometrial cancer, 112 of these having lymph node metastasis. External iliac lymph nodes were the most commonly involved lymph nodes, followed by paraaortic, obturator, and the common iliac nodes (113). Odagiri described the paraortic region to be the most prevalent site of lymph node metastases, followed by obturator, internal iliac, and common iliac nodes (114).

In a retrospective study, Persson et al. described the uterine pelvic lymphatic drainage as following two major pathways (64) (Figure 7):

1) **The upper paracervical pathway (UPP**) running along the uterine artery to the medial *external iliac and obturator nodes*, continuing lateral to the common iliac artery to the paraaortic nodes, and
2) **The lower paracervical pathway (LPP**) running medial to the internal iliac artery to *presacral nodes* and continuing medial of the common iliac artery to the paraaortic area.

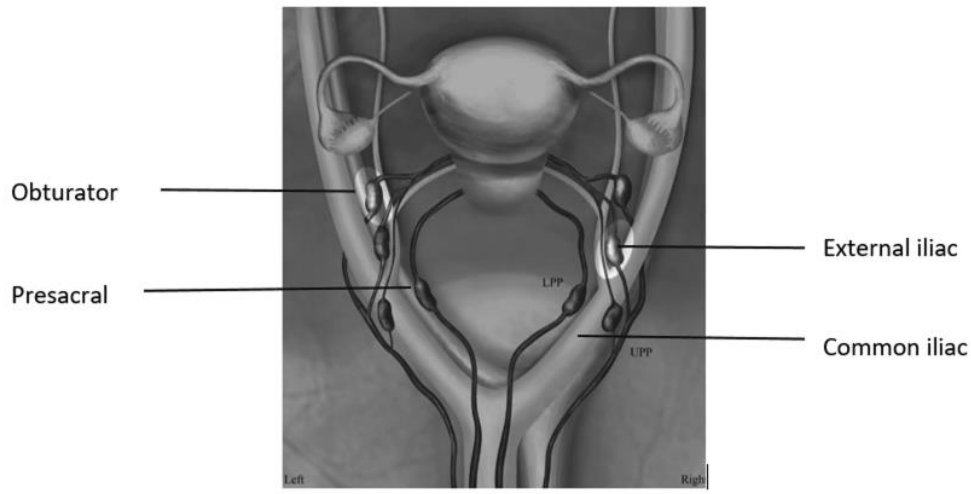

Figure 7: The pelvic uterine lymphatic pathways. **UPP** = Upper Paracervical pathway; **LPP** = Lower paracervical pathway. From Persson J, Geppert B, Lönnerfors C, Bollino M, Måsbäck A. Description of a reproducible anatomically based surgical algorithm for detection of pelvic sentinel lymph nodes in endometrial cancer. Gynecol Oncol. 2017;147(1):120-5. With permission from Elsevier (64).

Persson et al. described the location of the metastatic and non-metastatic lymph node according to the described pathwways. They found that presacral lymph node metastases were discovered in 33% of the node positive patients (64).

Circumflex iliac nodes distal to the external iliac nodes (CINDEIN) are described as the most distal external iliac nodes. These nodes are located in the enlarged adipose tissue immediate above the pelvic wall, and are commonly removed when performing systematic pelvic LND, exposing the external iliac vessels. CINDEINs are seen in almost all patients, and they are commonly macroscopically enlarged. However, the incidence of lymph node metastasis in the CINDEINs is very low, and these lymph nodes are seldom SLNs (111).

Sentinel Lymph Node (SLN)

The sentinel lymph node is defined as the first lymph node or group of nodes into which a tumor drains (Figure 8). Theoretically, if the SLN is negative, the lymph nodes that follow in the lymph node chain should be negative (115).

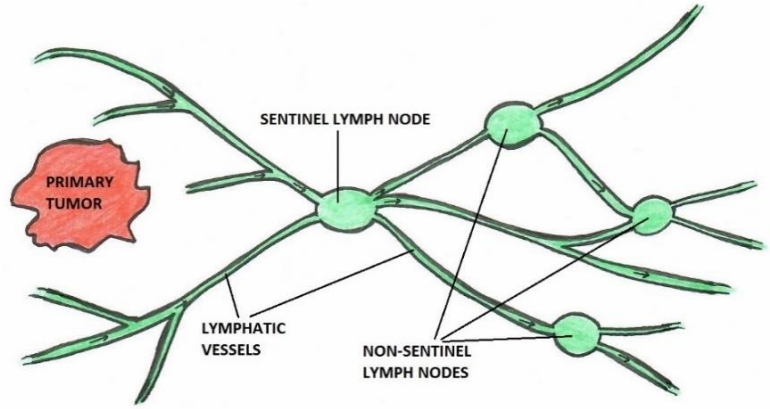

Figure 8: Sentinel lymph node.
Modified and reprinted from researchgate.net with permission from Rick G Pleijhuis.

History of SLN mapping

The first description of a sentinel node was made in 1951 by Gould et al. in patients treated for cancer of the parotid gland. The sentinel node was examined by the pathologist, and the presence or absence of metastatic cells could guide the surgeon in deciding whether or not to perform a radical neck dissection (116). In 1977, Cabañas, using lymphangiography of the penis, observed the existence of a sentinel node that appeared to be the primary site of metastatic disease (117). The SLN procedure is now well established in the treatment of different cancers, like breast cancer (118), malignant melanoma (119), vulvar (120), cervical (121), and, eventually, endometrial cancer (55). The latter has been more challenging, given the complexity and bilaterality of the nodal basins draining the uterus.

The SLN procedure

The SLN strategy has emerged during the last decades and represents an evolution of nodal assessment; it is a compromise between comprehensive LND in high-risk patients and

omittance of lymph node removal in low-risk patients. This allows sufficient lymph node assessment in patients in all risk categories and is proposed as a more “targeted” alternative to complete pelvic LND (122).

SLN mapping involves injecting a tracer material that helps the surgeon locate the SLNs during surgery. Various tracers have been evaluated, either alone or in combination, including blue dye, technetium and indocyanine green (ICG) (123, 124). ICG with NIR imaging is, based on results from the FILM trial, considered the gold standard for SLN maaping (55, 125, 126). However, a combination of blue dye and technetium is an acceptable alternative in institutions where ICG and NIR cameras are not available. Blue dye is visible to the naked eye, a gamma-probe is used for detection of SLNs when using technetium. ICG is water soluble and emits a fluorescent signal in the near-infrared (NIR) light range. ICG is safe and effective and is found to be superior regarding SLN mapping when compared to the use of blue dye, especially in obese patients (126-128). The risk of adverse events is extremely low, but ICG should be avoided in patients with severe iodine allergy or liver failure.

Regarding the injection site of the tracer, three techniques have been evaluated, including cervical injection, hysteroscopic fundal injection and laparoscopic fundal injection (64, 129). Cervical injection has been the preferred method due to the high detection rate for SLN metastasis through a safe and feasible method (55, 130). However, there has been a concern that isolated paraaortic lymph node metastasis may be missed with this method, as some of these nodes can only be reached via the infundibulo-pelvic ligament pathway (125). A multicenter prospective RCT found that detection of SLNs in the paraaortic area was slightly higher in patients after hysteroscopic injection of tracer compared to cervical injection, but the differences were not statistically significant (131). Cervical injection has, due to a feasible approach and the highest SLN detections rates, become the most favorable technique (132).

After entering the abdomen, the pelvis is during surgery assessed in NIR mode for identification of lymphatic trunks leading to SLN(s) (Figure 9). The SLN(s) are then removed and analyzed. If the SLN(s) are negative, metastatic disease is unlikely.

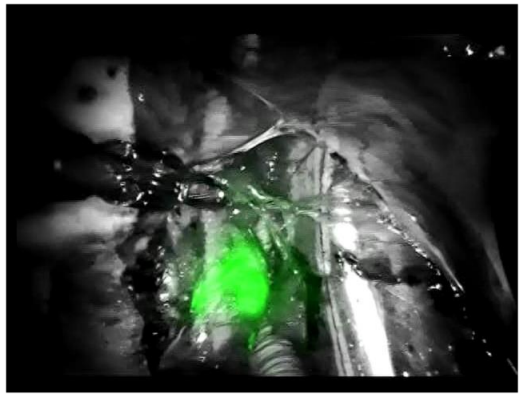

Figure 9: Assessment of SLN in NIR modus.
With permission from B. Hagen.

An algorithm for a standardized lymph node examination and resection using SLN mapping was developed at Memorial Sloan Kettering Cancer Center (MSKCC) in 2005 (122). Following the algorithm, both SLNs and other suspicious nodes are removed, and the strategy is to perform SLN biopsy in the pelvis in the majority of patients, rather than comprehensive LND in selected high-risk patients (Figure 10). In cases of no mapping on a hemipelvis, a side-specific pelvic (external, iliac, and obturator), common iliac, and interiliac LND should be performed, according to the algorithm. Paraaortic LND is left to the surgeon's discretion (122).

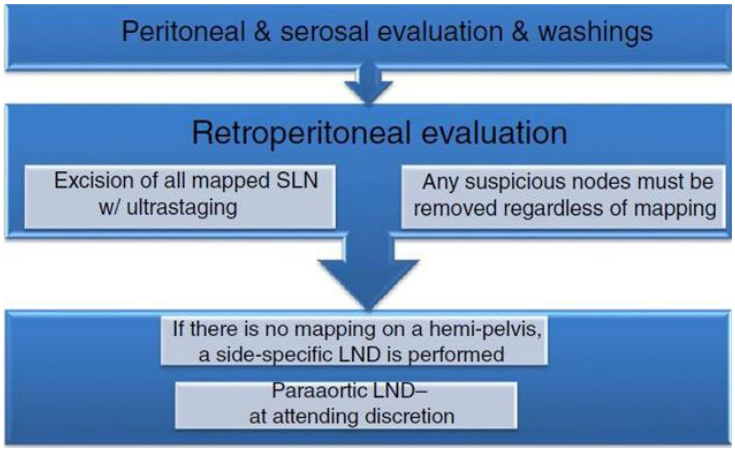

Figure 10: The SLN surgical algorithm.
From Barlin JN, Khoury-Collado F, Kim CH, Leitao MM, Jr., Chi DS, Sonoda Y, et al. The importance of applying a sentinel lymph node mapping algorithm in endometrial cancer staging: beyond removal of blue nodes. Gynecol Oncol. 2012;125(3):531-5. With permission from Elsevier (122).

Since the introduction of the SLN algorithm, the method has been widely implemented. The goal is to achieve bilateral SLN mapping to identify the lymph nodes at most risk for metastasis by adhering to the surgical SLN algorithm in order to limit the need for side specific LND (122).

As previously mentioned, Persson et al. have described the anatomy of the uterine lymphatic drainage. They aimed to enable standardization of an anatomically based, reproducible pelvic SLN concept. Nineteen percent of the patients were node positive, nearly one third of these had presacral lymph node metastases along the LPP. The LPP was less often displayed after tracer injection, and the study group therefore suggested that ideally, a bilateral detection of at least one SLN should be identified in both the UPP and LPP to secure that no lymph node metastases were missed (133). This is however not included in the surgical algorithm from MSKCC.

Pathologic ultrastaging

Ultrastaging refers to the utilization of enhanced pathology techniques, including deeper serial sections and IHC stains. The intention is to increase the detection of malignant cells in SLNs (59).

Initially, at macroscopic evaluation, the SLNs are sliced longitudinally into 2-3 mm thick sections and stained with Hematoxylin and Eosin (HE). SLNs negative upon microscopic examination of the HE-sections are further examined with ultrastaging. Two new adjacent sections are made at two different levels, 50 µm apart. At each level, one section is stained with HE and the other with IHC and cytokeratin. Cytokeratins are structural proteins found in all epithelial cells. In lymph nodes these are expressed only in the presence of tumor metastasis (134). Thus, there are totally four new sections per SLN block. Cytokeratin-positive cells not confirmed in the corresponding HE-sections are not classified as metastases (Figure 11).

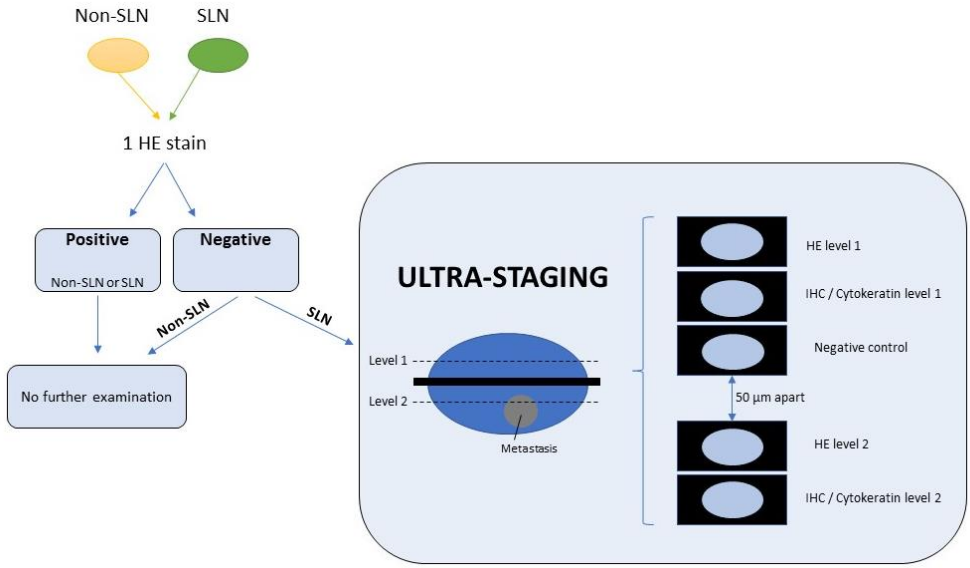

Figure 11: Memorial Sloan-Kettering Cancer Center's Pathologic Ultrastaging Algorithm for Sentinel Lymph Nodes. From Kim et al., Pathologic Ultrastaging Improves Micro-metastasis Detection in Sentinel Lymph Nodes during Endometrial Cancer Staging, Int J Gynecol Cancer 2013. Modified and reprinted with permission from Int J Gynecol Cancer (135).

There have been various strategies for the pathologic processing of SLNs, both regarding the number of level sections examined by routine HE staining, the depth of the sectioning into the tissue blocks, the intervals of microns between sections, and the use of IHC to detect tumor cells not detected on HE staining. The mostly used method refers to the guidelines for breast cancer, proposed by The College of American Pathologists (CAP) (136).

Size of lymph node metastases

According to the American Joint Committee on Cancer (AJCC) Staging guidelines for the staging of breast cancers, lymph node metastases are divided into **macro-metastases** (tumor clusters ≥ 2.0mm), **micro-metastases** (tumor clusters between 0.2 and 2.0mm), and **isolated tumor cells (ITCs)** (single tumor cells or small tumor clusters ≤ 0.2mm) (137). The size of the SLN metastasis is associated with an increased likelihood of non-SLN metastasis (138).

Low-volume metastasis

Ultrastaging with ultra-sectioning and IHC staining provides increased detection of low volume metastases, including micro-metastases and ITCs, potentially resulting in an upstaging to stage IIIC disease and thereby increased use of adjuvant treatment (135, 139). Presence of both macro- and micro-metastases is regarded as metastatic lymph node involvement. The prognostic significance of ITCs is however still uncertain. Various institutions handle the occurrence of ITC differently, as some consider ITC as nodal metastasis and use it to guide adjuvant therapy while others do not. According to Norwegian guidelines, ITC are not considered to be nodal metastasis (140).

Lymphedema

Lymphedema is a chronic disorder with accumulation of fluid, especially in the extremities, often caused by cancer treatment such as surgery and radiation therapy. Because of lymph node assessment, patients treated for endometrial cancer are thought to be especially prone to this.

Normal lymphatic circulation

The lymph system plays an integral role in the immune functions of the body. The system is composed of lymphatic organs, such as lymph nodes, tonsils, thymus, and the spleen, all of which are connected via a network of lymphatic vessels running parallel to the venous circulation (Figure 12) (141). Lymph from gynecologic organs drains mainly into the pelvic, paraaortic, and inguinofemoral lymph node beds (142).

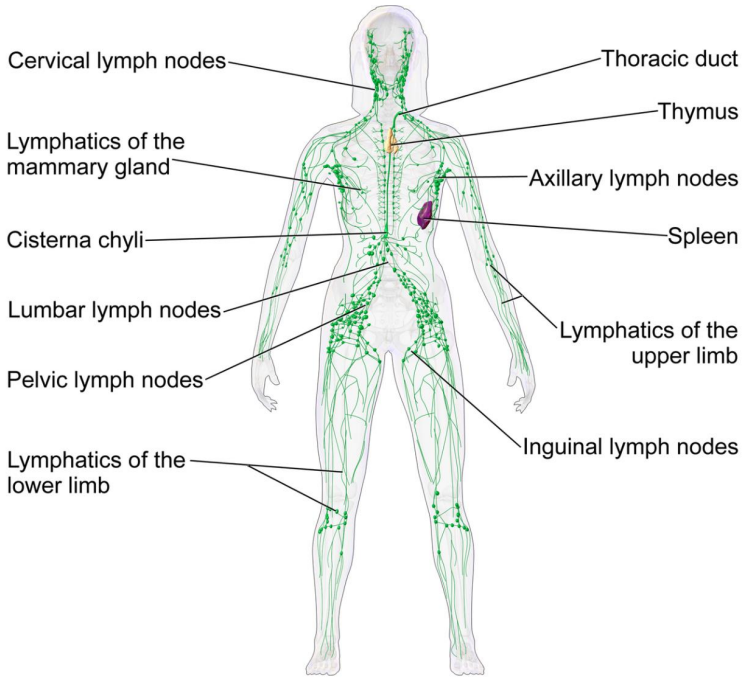

Figure 12: The lymphatic system.
Reprinted with permission from Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". WikiJournal of Medicine 1 (2). DOI:10.15347/wjm/2014.010. ISSN 2002-4436.

Lymphatic circulation is a one-way drainage route that removes unwanted material and excess interstitial fluid. The primary function of the lymphatic system is to collect and return proteins and colloids to the bloodstream. In addition, it is responsible for fat absorption and immunological functions. The lymphatic system contains two types of lymphatic vessels: small initial lymphatic capillaries and collecting lymphatic vessels.

About 90% of the interstitial fluid is reabsorbed via venous microcirculation and returns to the bloodstream (143). The remaining 10% of the interstitial fluid has a relative high protein concentration, with molecules too large for venous circulation. This protein-rich fluid is referred to as lymph once it is collected by the lymphatic capillaries. The lymphatic capillaries converge into larger collecting vessels, consisting of the same three layers as veins and arteries, but with a thinner wall with more valves than veins, ensuring one-way flow. The collecting lymphatic vessels also have smooth muscle walls able to contract to get the lymphatic fluid forward by intrinsic pumping. Lymph is then transported via the collecting lymphatic vessels, filtered through the lymph nodes, and reenters the circulatory system through the thoracic duct and the right lymphatic trunk, near the point where the peripheral venous blood enters the right heart (141) (figure 13). About 20 L of plasma leaks from the blood vessels by capillary filtration every day, 17 L is reabsorbed. The remaining 3 L, containing cell debris, bacteria, and foreign bodies, is transported by the lymphatic system.

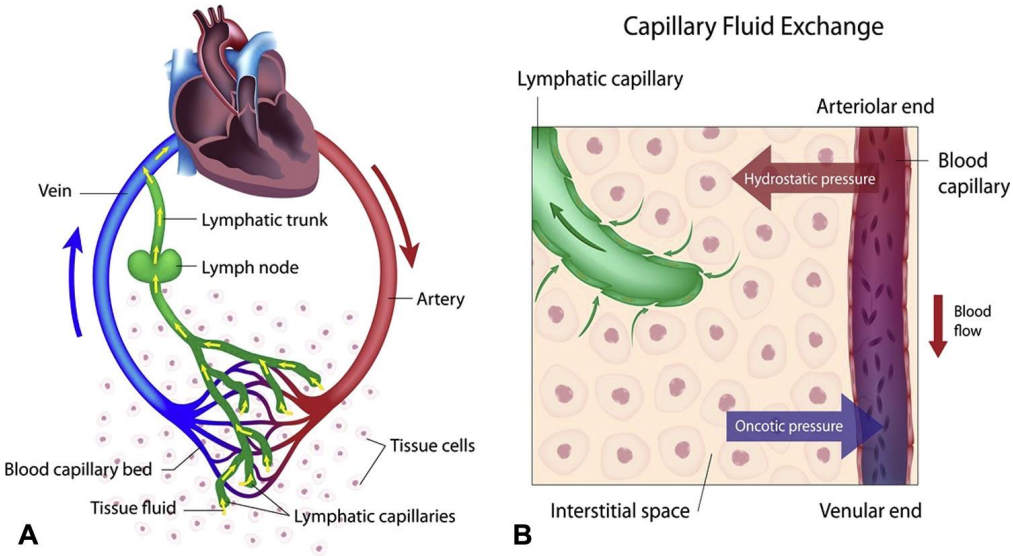

Figure 13: Normal lymphatic circulation. A: Tissue fluid returns to the bloodstream via lymphatic drainage. B: Protein-rich lymph is collected from the interstitial space by the lymphatic capillaries.
From Grada et al., Lymphedema: Pathophysiology and clinical manifestations, J Am Acad Dermatol, 2017.
Reprinted with permission from Elsevier (141).

Incidence of lymphedema

Lymphedema affects approximately 20 million people worldwide and causes significant discomfort, morbidity, and financial burden (142). Approximately 99% of all individuals with lymphedema have **secondary lymphedema,** which occurs when the lymphatics are damaged because of factors originating outside the lymphatic system. Secondary lymphedema is caused by medical conditions such as cancer, obesity, recurrent infections, surgery, trauma, radiation therapy, and other therapies (141). Malignancy and cancer-directed treatment, especially regional LND, are the most common causes in the western world (143, 144) .

A great deal of data has been collected regarding lymphedema in upper extremities after treatment for breast cancer. There is less data regarding lymphedema in the lower limbs following gynecologic cancer, and these are mostly based on self-reported data. There are, however, obvious differences in the upper and lower extremities with respect to limb size, volume, location, tissue composition and mechanical functioning; therefore, extrapolating data based on the upper extremities should be done with caution (145).

The incidence of LEL in patients surgically treated for endometrial cancer has been reported to range widely, from 1.2% in retrospective analyses to 67% in prospective studies utilizing QoL surveys (5, 6, 146-151).

Diagnosing lymphedema can be difficult, especially in early stages. This has led to under-diagnosis even for research purposes. Early and correct diagnosis of lymphedema is essential to proper intervention and prevention of the irreversible sequelae of later-stage disease (142). The onset of lymphedema may be gradient or sudden. If untreated, lymphedema generally progresses to more advanced stages, increasing patients' risk for cellulitis infections, functional decline, and chronic unhealing wounds (152). When lymphedema is established beyond the early stages, it often becomes a chronic condition that cannot be cured. It is therefore important to intervene early to halt or slow the progression of lymphedema. Although LEL most commonly presents within the first 12 months after cancer treatment, lymphedema can develop several years after the completion of cancer treatment, which explains why the incidence of secondary lymphedema might be greatly underestimated (153).

Pathophysiology of lymphedema

Lymphedema is defined as the accumulation of interstitial fluid caused by a malfunction of the lymphatic drainage system. This leads to accumulation of protein-rich lymph fluid in the subcutaneous tissue, seen as soft tissue swelling, chronic inflammation, reactive tissue fibrosis and abnormal adipose deposition.

Most examples of limb edema are caused by an *increase in capillary filtration*, overwhelming lymph drainage capacity in, for instance, heart failure or nephrotic syndrome. Lymphedema occurs when swelling is due to a *failure of lymph drainage* in circumstances in which capillary filtration is not increased (154). Impairment of the draining capacity caused by obstruction or lymphatic hypoplasia leads to an accumulation of interstitial fluid and swelling of the tissue, known as ***lymphedema***. This leads to decreased oxygen tension which in turn leads to chronic inflammation and reactive tissue fibrosis. As lymphedema progresses, the fluid increases in protein content with cellular infiltration, eventually developing tissue fibrosis and fat deposition in the skin and subcutaneous tissue.

The lymphatic system has an important immune-monitoring function as circulating lymph transports antigens and activated antigen-presenting cells into the lymph nodes to start an immune response. In the skin there are many lymphatic capillaries; patients with lymphedema are thus prone to recurrent skin infections because of the accumulation of peripheral tissue antigens (141).

Risk factors for developing LEL

Several studies have assessed risk factors for development of LEL in women treated for endometrial cancer. In addition to high BMI, LND and radiation therapy are the main contributors to LEL in these patients. LND directly disrupts the normal return of lymphatic fluid from the lower extremities. In general, the risk of lymphedema is proportional to the number of lymph nodes removed, with excision or certain lymph nodes and lymph node basins thought to be at a higher risk, although a threshold has not been established (5, 6, 111, 142, 155). Radiation-induced lymphedema is thought to be caused by lymph node and lymphatic vessel sclerosis, scarring, and subsequent obstruction of the upstream lymphatic flow (142).

The presence of metastatic lymph nodes, old age, addition of adjuvant chemotherapy, and decreased physical activity (6, 142, 144, 146, 156) are also known risk factors for LEL in endometrial cancer patients. SLN mapping alone has been shown to decrease the risk of LEL to less than 10%, across gynecologic malignancies.

Obesity and metabolic syndrome are known risk factors for development of LEL, due to etiologies such as chronic venous insufficiency and congestive heart failure. Both are, however, also risk factors for endometrioid adenocarcinoma, the most common histologic subtype of endometrial cancer (6, 144, 157). Thus, this population may have higher rates of baseline LEL that can be mistaken for, or exacerbated by, malignancy (142). Abu-Rustum et al., assessing rates of postoperative LEL in endometrial cancer patients prior to the introduction of SLN, reported that 5-6% of patients had clinically reported LEL preoperatively, potentially secondary to other comorbidity (5). Obesity, a comorbid condition in a large percentage of endometrial cancer patients, makes lymphedema clinically

harder to detect in its early stages because it may be difficult to distinguish from adiposity. Additionally, it may independently contribute to the pathogenesis of LEL (6).

The primary sites of lymphedema in patients treated for gynecologic malignancies are the lower extremities and, to lesser extent, the vulva and mons areas. Vulva and mons pubis are locations difficult to assess with objective measurements but may be detected by Patient Reported Outcome (PRO) questionnaires.

Symptoms of LEL

The symptoms of LEL are limb heaviness, swelling, numbness, pain, restricted range of motion, recurring infections, and hardening and thickening of the skin due to fibrosis (141, 158, 159). Signs and symptoms can range from mild to severe, and are staged into four groups (Figure 14):

0) Subclinical: Swelling is not present.
1) Mild edema. Fluid accumulates throughout the day but resolves overnight.
2) Lymphedema is always present but varies in severity.
3) Persistent, moderate-to-severe edema of the involved limb.

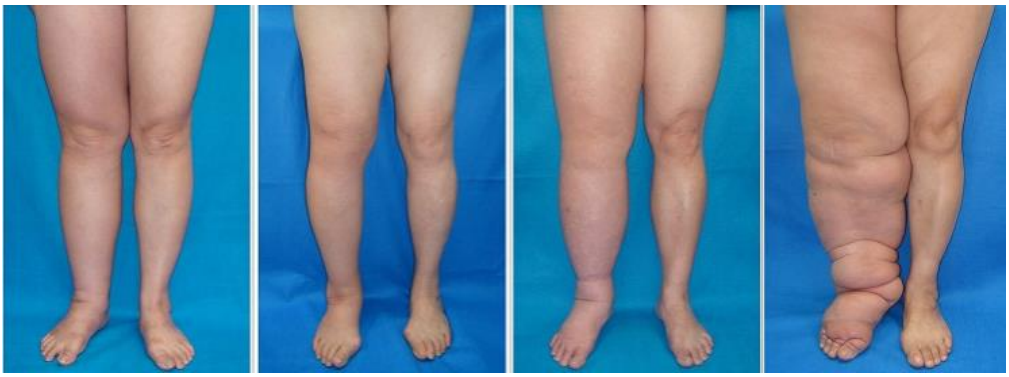

Figure 14: The four stages of lymphedema.
Reprinted from Cheng et al., "Principles and Practice of Lymphedema Surgery", with permission from Elsevier (160).

Assessment of LEL

There are many accepted methods for measuring LEL. These include various clinical evaluations, volume measurements, limb volume change (LVC), limb circumference, bioelectrical impedance spectrometry, MRI, and lymphoscintigraphy (149, 161-163). However, there is no consensus on a «gold standard» for the method to use for measuring lymphedema in clinical or scientific contexts. Several methods exist, including patient-reported outcome measures (PROMs).

Every change in limb circumference, volume or abnormal imaging study is indicative of clinically significant lymphedema. Lymphedema symptoms may be reported by patients before they become identifiable through circumference or volume changes (i.e., leg heaviness). This is why several studies have focused on patient-reported lymphedema, using validated surveys with good sensitivity and specificity for diagnosing clinically significant LEL.

Prevention and treatment of lower extremity lymphedema

The aim of the treatment of lymphedema is to prevent the progression of the condition, reduce the risk of infection and improve the QoL (145). An important issue is to identify the patients at risk for developing LEL. Informing the patients of early signs of LEL is also important, making them aware of the condition and the possibility of early intervention. Chronic LEL is difficult to treat and associated with severe health impacts including recurrent cellulitis and morbidity. Mobilization should be encouraged for these patients. An RCT in patients undergoing surgery for breast cancer demonstrated that increased upper extremity mobility and prophylactic physiotherapy significantly decreased the risk of chronic lymphedema from 25% to 7% (P=0.01) (164). Similar randomized studies have not been done in patients undergoing surgery for other malignancies.

Standard treatment of lymphedema is complex decongestive therapy (CDT), which consists of manual lymphatic drainage, skin care, compression bands or stockings, and exercise. CDT is reported to be effective in reducing lymphedema and thereby increasing QoL in patients with LEL following gynecological cancers (165, 166).

Surgical treatment of lymphedema includes microsurgical techniques, lymphatic-lymphatic bypass, lymphovenous bypass, allographic vascularized nodal tissue transplantation, and surgical removal of abnormal tissue. Pharmacological treatment is not documented to be effective in treatment of LEL (152, 167).

The rate of lymphedema is found to be significantly lower in women who have undergone SLN mapping compared with patients who have undergone lymphadenectomy, 1.3-27%, and 10-49% after SLN and LND, respectively (147, 168, 169). The acceptance of SLN mapping as a standard in the staging of endometrial cancer provides a method for reducing morbidity secondary to LND (142).

Patient-reported outcome measures (PROM)s and Quality of Life (QoL)

Lymphedema can limit mobility and the ability to perform daily activities and have adverse effects on psychological and social wellbeing. Patients with LEL following treatment for gynecological cancer experience significant reductions in QoL and have increased supportive care needs compared with those without lymphedema (145). The impact of LEL on QoL can best be examined by describing adverse effects on the following aspects of QoL: physical, daily life, psychological and emotional, sexuality and social concerns, as well as concerns related to lymphedema treatment. Physical symptoms, including swelling, heaviness, pain, and discomfort, can significantly reduce physical function, mobility, and ability to perform daily activities. LEL is reported to cause significant impact on everyday life, including difficulties in performing daily tasks and avoiding activities that worsen the physical symptoms. Patients with LEL have increased levels of distress and adverse changes in body image and self-confidence. Many of these patients experience unmet sexual needs, and one third of patients aged under 65 years are not at all or rarely sexually active or have difficulties with sexuality and intimacy. Women with LEL also report social concerns like difficulties in personal relationships caused by limited mobility, restricted activities, and feelings of embarrassment around friends.

During the last decades, QoL has gained increasing interest and is considered to be an important variable in oncological research. Measuring QoL as an outcome in research is challenging due to the wide range of different outcome measures and QoL tools. Several PROMs have been developed.

Lower Extremity Lymphedema Screening Questionnaire (LELSQ)

The LELSQ is a validated questionnaire consisting of 13 graded questions, sensitive and specific for detecting clinically relevant LEL among women, including those with BMI ≥30 kg/m^2 (153). At least seven questions must be answered to be evaluable. Scoring ≥5 points on LELSQ was defined as self-reported LEL. LELSQ has been translated and tested in a Norwegian population (170).

EQ-5D-5L

EQ-5D is a widely used standardized PROM of health-related QoL, developed by the EuroQoLGroup. It is a generic questionnaire for use in clinical and economic appraisal and population health surveys. EQ-5D is brief, widely tested, and includes five important aspects of health or dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, using five levels in each domain. (171, 172) .

EORTC QLQ-C30 and EORTC QLQ-EN24

The European Organisation for Research and Treatment of Cancer (EORTC) is an organization with the mission to improve QoL and survival rates of cancer patients, and in 1980 a separate QoL group was created. EORTC has proposed guidelines for module development of questionnaires (173).

EORTC QLQ-C30 (174) and EORTC QLQ-EN24 (173) have been developed to evaluate QoL in cancer patients. EORTC QLQ-C30 is one of the most widely used PRO questionnaires for assessing QoL, functional health, and symptom burden generally in cancer patients. EORTC QLQ-C30 incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a Global Health and QoL scale. Several single-item symptom measures are also included. EORTC QLQ-EN24 was designed to assess disease and treatment of specific aspects of the QoL in patients with endometrial cancer. It consists of 24 questions, divided into ten symptoms and three function domains, including lymphedema, urological symptoms, gastrointestinal symptoms, body image problems, sexual/vaginal problems, back/pelvis pain, tingling/numbness, muscular/joint pain, hair loss, taste change, sexual interest, sexual activity, and sexual enjoyment. All questions in the EORTC QLQ-C30 and -EN24 are graded; “not at all, “a little”, “quite a bit” or “very much”.

The EORTC QoL group has established thresholds for clinical importance for the five functioning and nine symptom scales of the absolute scores of EORTC QLQ-C30, based on external criteria reflecting the clinical importance of a health problem (175). Comparison of QoL between groups by applying these thresholds for clinical important changes has not previously been reported for survivors after endometrial cancer.

AIMS OF THE STUDIES

Paper I:

"Initial experience with positron emission tomography/computed tomography in addition to computer tomography and magnetic resonance imaging in preoperative risk assessment of endometrial cancer patients"

- To evaluate the diagnostic accuracy of PET/CT compared to standard CT/MRI in identifying lymph node metastases in endometrial cancer, particularly with regard to evaluation of the paraaortic region in candidates for SLN-mapping.

Paper II:

"Long-term outcomes in endometrial cancer patients after robot-assisted laparoscopic surgery with sentinel lymph node mapping"

- To report long-term outcome data in patients staged according to the SLN algorithm in terms of RFS, OS, and treatment-related complications.

Paper III:

"Self-reported lower extremity lymphedema and quality of life after surgical staging of endometrial carcinoma: A population based cross-sectional study"

- To explore the prevalence of self-reported LEL in endometrial carcinoma survivors stratified by nodal assessment.
- To identify patient- and treatment-related factors associated with lymphedema.
- To determine how LEL affects QoL in these women.
- To compare thresholds for clinical importance in QoL between patients with and without LEL.
- To assess correlation between different questionnaires.

MATERIALS AND METHODS

Study design, patient selection, and recruitment

This thesis utilizes data from patients treated for endometrial cancer at St Olavs hospital (all three papers) and from Oslo University Hospital (OUH) (paper III).

Paper I - Preoperative imaging and treatment

Paper I is a retrospective study. Inclusion criteria were histologically confirmed endometrial cancer, preoperative CT of the thorax, abdomen and pelvis, MRI of the pelvis, preoperative whole-body ^{18}FDG PET/CT, pelvic lymph node removal, and histologically confirmed presence of lymph nodes. We compared the ability of preoperative PET/CT versus preoperative CT/MRI to detect lymph node metastases, with histologically confirmed lymph node metastases as the standard of reference. In our hospital, PET/CT was implemented as routine preoperative assessment of endometrial cancer in 2016.

Women operated from January 2016 through July 2019 at St Olavs hospital were included as the study group. In addition, women who underwent surgery between November 2012 through December 2015 (before the introduction of routine preoperative PET/CT) were included as a reference group, to determine if the results from the PET/CT would influence interpretation of CT/MRI. Patients in the reference group who had a PET/CT scan performed during the preoperative workup of endometrial cancer were excluded.

Paper I included patients in all risk groups. The included women underwent robotic surgical treatment or laparotomy depending on preoperative risk group. Most women who underwent robotic surgery were staged in accordance with the SLN algorithm.

Paper II – Treatment and follow-up

Paper II is a retrospective cohort study of 108 women with apparently early-stage endometrial cancer who underwent robot-assisted laparoscopic surgery and SLN mapping using the MSKCC algorithm with NIR fluorescence detection of ICG at St Olavs hospital from

November 20th 2012 to January 1st 2016. Patients who did not undergo SLN mapping were excluded from the study.

The SLN algorithm was implemented at St Olavs hospital in 2012. All surgical procedures in paper II were performed by one of three surgeons who had SLN experience from 35 pilot procedures using blue dye.

The included patients were followed up in accordance with the Norwegian guidelines (65) with outpatient controls every 3rd month for the first two years, and every 6th month until a total follow up of five years. The outpatient follow-ups were performed at St Olavs hospital, at local hospitals in the region, or by contract specialists in gynecology. All patients with relapsed disease were referred to The Department of Gynecologic Oncology at St Olavs hospital. Follow-up data were registered from the date of surgery through December 2020. Median follow-up was 75 months (range 61-98).

The primary endpoint was RFS. Secondary endpoints were OS and treatment-related adverse effects.

Paper III – Treatment and study inclusion

Paper III is a multicenter, population-based cross-sectional study including women treated for assumed early-stage endometrial cancer between January 1st 2006 and December 31st 2020 at OUH and between November 20th 2012 and December 31st 2020 at St Olavs hospital. The patient group from OUH underwent surgery by robotic, laparoscopic, laparotomy or vaginal approach and were staged either by LND or the SLN algorithm; all patients included from St Olavs hospital underwent robotic surgery, staged in accordance with the SLN algorithm.

These hospitals were the first in Norway to implement the MSKCC SLN algorithm and the only two where the algorithm had been implemented during the study period. Patients from St Olavs hospital were included in the study to increase the number of participants with longer follow-up time after surgery, as St Olavs hospital implemented the SLN algorithm already in 2012, while OUH implemented the algorithm in 2018.

Nodal assessment was defined as *hysterectomy* if no nodal assessment was performed, as *sentinel lymph node biopsy (SLN)* if the MSKCC SLN algorithm was adhered to and as *lymphadenectomy (LND)* if pelvic LND with or without paraaortic LND was performed.

The women were invited to complete questionnaires regarding self-reported LEL and QoL. Differences in QoL between women with and without LEL were analyzed. The questionnaires are attached in Appendix.

A summary of the populations in the three papers is presented in table 4.

Table 4: Summary of the thesis population

	Paper I	Paper II	Paper III
Study population	Women undergoing surgery for EC (all stages) preoperatively staged with CT, MRI, and PET/CT. N=185	Women with apparent early-stage EC treated surgically in which SLN mapping with ICG was performed. N=108	Women who underwent surgical staging for apparent early-stage EC with LND, SLN or hysterectomy alone. N=1134.
	St Olavs hospital	St Olavs hospital	OUH and St Olavs hospital
Study period	January 2016 – August 2019	November 2012 – January 2021	January 2006 – January 2021
Study aims	Evaluate the diagnostic accuracy of PET/CT compared to standard CT/MRI in identifying lymph node metastasis.	Determine long-term outcome data after surgical staging with SLN mapping.	• Explore the prevalence of LEL stratified by nodal assessment approach • Identify factors associated with LEL • Compare QoL using thresholds for clinical importance • Assess correlation between various PROMs tools
Main study outcome	Preoperative detection rate for lymph node metastases for CT/MRI and for PET/CT.	RFS, OS and treatment complications.	• Prevalence of self-reported LEL, stratified by nodal assessment. • Risk factors associated with LEL. • Clinically important impact of QoL
Study design	Retrospective observational study	Retrospective cohort study	Multicenter, population-based cross-sectional study

Abbreviations: EC: endometrial cancer; LN: lymph node; SLN: sentinel lymph node; LND: lymphadenectomy; CT: computed tomography; MRI: magnetic resonance imaging, PET: positron emission tomography; RFS: recurrence-free survival; OS: overall survival, OUH: Oslo University Hospital, PROM: Patient-reported outcome measure, QoL: quality of life.

Study variables

Demographic, clinicopathologic, nodal characteristic, and disease-specific parameters were collected from electronic medical records, including outpatient and inpatient notes, imaging,

operative reports, pathology reports, information regarding postoperative treatment, including adjuvant chemotherapy, and reported adverse effects of the treatment. Date and location of recurrence, and date and disease status of last follow-up, including cause of death if deceased, were also retrieved from electronic medical records. All CT, MRI and PET/CT-images were interpreted by radiologists specialized in gynecologic oncology. All pathologic evaluations were performed by gynecologic pathologists. All surgical procedures were performed by gynecologic oncologists. Patient age was defined as age at date of surgery. BMI was calculated as weight divided by height squared (kg/m^2). Height and weight were recorded from the patient chart at initial visit.

Nodal status

Macro-metastasis and micro-metastasis were considered node-positive in all three papers. In paper I, evaluating the diagnostic accuracy of PET/CT, and in paper III, assessing development of LEL and QoL, ITCs were considered node negative. In paper II, evaluating the oncologic outcome, ITCs were considered node positive, however noted as ITCs, and the patients were staged to stage IIIC. Cytokeratin-positive cells in IHC sections not confirmed in corresponding HE sections, were however considered node-negative.

Ethical considerations and approval

The studies were approved by the Regional Committee for Medical and Health Research Ethics (REK Midt 7193/2019 and REK Sørøst D 149598).

For papers I and II, all patients signed informed consent prior to inclusion. For paper III, all patients received study information, including questionnaires and instructions to notify the study team if they did not wish to participate. Responding to PROMs was considered equivalent to informed consent.

The patients did not have any direct benefits from participating in the studies, but they contributed to new knowledge that may benefit future endometrial cancer patients as well as the existing patients. The disadvantages for the patients were time used to complete the questionnaires.

For papers I and II, signed consent forms were registered on a paper form marked with study ID. The SPSS file containing study ID and deidentified clinical patient information was stored in the university computer system, accessible only by one person (NJN). The key between patient ID and study ID was stored in the hospital computer system, in secured area only accessible by one person (NJN).

For paper III, data was stored at TSD (Sensitive Data Services), according to the rules of safe storage, with a two-step login. The files were zipped and secured with a password.

Statistical methods

Paper I

Patient characteristics were summarized using the median (range) for continuous variables and percentages for categorical variables. The result of the histological evaluation was set as a standard of reference for statistical analyses of lymph node metastases. Differences in sensitivity and specificity between PET/CT and CT/MRI were examined using McNemar's exact test. Comparison of lymph node detection with CT/MRI between the study group and the reference group was performed with the Chi square test. For all analyses, p-values less than 0.05 were considered statistically significant.

Paper II

Patient characteristics were summarized using the median (range) for continuous variables and percentages for categorical variables. RFS was defined as the time from surgery to the time of recurrence. Disease specific survival (DSS) was defined as the time from surgery to the time of death from disease. RFS, DSS and OS curves were estimated with the Kaplan-Meier method. Data for patients who died were censored at the time of death.

Paper III

A power analysis was performed prior to the study to determine the needed size of the study group. With a two-sided significance level of 5% and a power of 90%, 227 patients

were needed in each group to detect a 15% difference in rate of LEL between the cohorts. Based on previous studies, this was estimated to 35% in the SLN cohort and 50% in the LND cohort. The number of potential respondents was 2156, far more than required, allowing adjustments for several potential confounding variables in this observational design setting.

Descriptive statistics were provided for baseline variables for the entire cohort and subgroups. Categorical variables were presented as frequencies and proportions, continuous variables as mean with standard deviation (SD) or median with interquartile range (IQR). Comparison of cohorts stratified by nodal assessment (hysterectomy, SLN and LND) or LEL status (negative/positive) was performed by chi2 test, t-test or ANOVA and Mann-Whitney or Kruskal-Wallis tests, as appropriate.

Logistic regression analysis was used to investigate associations of baseline covariates with self-reported LEL. Variables included in the multivariable model were BMI at surgery, nodal assessment, and adjuvant therapy. Nodal count and histology were omitted from the model due to their high correlation with nodal assessment and adjuvant treatment.

To further explore a potential relationship with musculoskeletal complaints and LEL, regression analysis was stratified by presence or absence of musculoskeletal complaints. In addition to investigating type of nodal assessment, we also considered the number of nodes removed. A log transformation was applied due to its non-linear relationship with LEL.

The relationship between the global health status/QoL scale and Quality-adjusted life year weight (QALYw) and the Visual analog scale (VAS), and participants' individual scores from LELSQ and the lymphedema domain in EORTC QLQ-EN24 were assessed by Spearman's correlation coefficient with 95% confidence interval (CI) calculated by bootstrap estimation. A correlation coefficient of 0.40-0.69 was considered as moderate, and >0.70 as strong. The significance level was set to $p<0.05$.

Statistical analyses in papers I and II were performed using International Business Machines Corporation (IBM) Statistical Package for the Social Science (SPSS), version 27. Statistical analyses in paper III were performed using Stata/SE 17.0.

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SUMMARY OF THE RESULTS

Paper I

In this paper we found that PET/CT seems to be superior to CT/MRI for detection of lymph node metastases in the preoperative investigation of women with endometrial cancer, especially in the investigation of paraaortic lymph nodes.

We found that the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of PET/CT for the detection of lymph node metastases were 63%, 98%, 85%, 94%, and 93%, respectively. The sensitivity, specificity, PPV, NPV, and accuracy of CT/MRI were 41%, 98%, 73%, 91%, and 90%, respectively (p=0.07). For pelvic lymph node metastases, PET/CT had a sensitivity of 58%, compared to 42% for CT/MRI (p=0.22). Ten patients had paraaortic lymph node metastases, all of them were detected by PET/CT, for a sensitivity of 100%, compared to 50% for CT/MRI (p=0.06).

When differentiating by the size of lymph nodes, we found that 93% of macro-metastases and 31% of micro-metastases were detected by PET/CT. In comparison, CT/MRI detected 57% of macro-metastases and 23% of micro-metastases.

PET/CT has a diagnostic value, in particular in detecting paraaortic lymph node metastases in patients who are candidates for minimal invasive surgery with SLN mapping.

Paper II

In this study we demonstrated excellent oncologic outcome and long-term treatment-related complication rates more than 5 years after diagnosis in patients staged according to the SLN algorithm.

After a median follow-up of 75 months (range 61-98) for the 108 included patients, five (4.6%) patients had recurred, and three patients had died from disease. The 5-year RFS was 95.4% (95% CI, 91.5-99.3). The 5-year DSS was 97.2% (95% CI, 94.1 – 100.3). The 5-year OS was 92.6% (95% CI, 87.7 – 97.5). Peripheral neuropathy after chemotherapy was the most common adverse event (9.3%), followed by LEL (2%) and postoperative hernia (2%).

Paper III

In paper III we found a lower prevalence of LEL after SLN compared with LND. The prevalence of lymphedema stratified by nodal assessment was 51%, 36% and 40% after LND, adherence to SLN algorithm, and hysterectomy, respectively ($p<0.001$). Increased BMI (one unit increase), LND and adjuvant chemotherapy were identified as risk factors for self-reporting LEL with odds ratios 1.07 (95% CI 1.05-1.09), 1.42 (95% CI 1.03-1.97) and 1.43 (95% CI 1.08-1.89) respectively. Women with LEL were found to have clinically important worsened QoL in all domains.

The prevalence of LEL did not differ between nodal assessment groups in patients who also self-reported musculoskeletal disease. Self-reported musculoskeletal disease was evenly distributed amongst nodal assessment groups, but more prevalent in patients reporting lymphedema ($p<0.001$). In women *with* musculoskeletal complaints the prevalence of self-reported LEL was 59%, 50% and 53% for LND, SLN and hysterectomy ($p=0.115$). In women *without* musculoskeletal disease the prevalence of self-reported lymphedema was 39%, 17% and 18% for LND, SLN and hysterectomy, respectively ($p<0.001$).

DISCUSSION

Methodological considerations, strengths, and limitations

Study design

RCTs are the gold standard for drawing causal conclusions based on statistical associations. This is, however, often not feasible due to high costs, problems with generalizability, and loss to follow up. Retrospective observational studies are designed to analyze preexisting data. They lack conclusive results but are suitable for finding associations, thereby forming a basis for further research as they may generate hypotheses to be further explored in RCTs. Observational studies may be influenced by confounders and biases, necessitating cautious interpretation of causality (176). Cross-sectional studies provide information at a specific point of time, and are suitable to study prevalence of a condition (177). Cohort studies are longitudinal with a follow-up of a cohort of participants over time. A retrospective cohort study is suitable for estimating the incidence of outcomes of interest.

Paper I is a **retrospective observational study** exploring the diagnostic accuracy of PET/CT for detecting lymph node metastases as part of the preoperative assessment in endometrial cancer. Preexisting data from medical journals were extracted and analyzed. A weakness of this study is the retrospective design, as well as the limited number of patients with lymph node metastases, impairing the strength of the study.

Paper II is a **retrospective cohort-study** following 108 patients staged in accordance with the SLN algorithm for at least five years. The strength of this study is the long observation time. Most endometrial cancer relapses occur within the first two years (178), sufficiently covered in our study where none of the patients recurred later than 39 months after surgery. The weakness of this study is the retrospective design and the relatively small number of cases, especially the small number of relapsed cases, again reflecting that endometrial cancer despite its relatively high incidence often presents at early-stage with good prognosis and few patients recurring from the disease. In this population 45 (42%) were low-risk, 35 (32%) were intermediate-risk, and 28 (26%) were high-risk patients, reflecting a normal and expected distribution of risk groups.

Paper III is a **multicenter population-based cross-sectional study** investigating self-reported lymphedema and QoL after treatment for endometrial cancer. This is a large study, geographically covering 66% of the Norwegian population, a population which is unselected, providing real-world data. The satisfying response rate to the surveys of 61% is also a strength of this study. The retrospective design, with its inherent biases, is a limitation also in this study. Median follow-up in the SLN cohort was shorter than in the LND cohort. However, both median follow-ups were greater than two years, the time period in which LEL commonly develops (151).

Biases and confounders

Information bias occurs when information used in a study is either measured or recorded inaccurately. This is an issue in all three papers, as we collected information from electronic medical records; thus, there could be information bias due to errors in medical records, or errors due to the registration of the information. To limit the risk of information bias, all fields related to findings from preoperative imaging with CT/MRI and PET/CT were re-reviewed. Information regarding histologic subtype, grade, and stage of disease was assessed from the pathology reports, which were also re-reviewed.

A weakness of the second paper is that the treatment-related adverse effects are solely registered by assessing the electronic medical records. This demonstrates a very low prevalence of LEL, only 2%. The subsequent paper III, using self-reported LEL from PROMs, detects a significantly higher prevalence; this illustrates the information bias due to a less thorough focus on the occurrence of LEL in the routine follow up of endometrial cancer patients.

The third study is also exposed to **recall bias**. Recall bias is a systematic error occurring in studies that use self-reporting, when participants do not remember previous events or experiences or omit details.

Another issue is whether the patients included in the study differ from patients also eligible but not included. A strength of all three studies is the unselected population, as all endometrial cancer patients in Norway are treated in public hospitals. However, some patients are excluded from the studies due to lack of consent. Theoretically, these patients

could be different from the patients who consented to be included in the study, creating a selection bias. **Selection bias** is a systematic error occurring in the selection of participants, as some people are more likely than others to participate in such studies, resulting in a study population that does not represent the total population. Patients suffering from the current condition may have more interest in participating in the study than patients without such bothers, motivated both by their self-interest in contributing to the research and its results, and by the potential opportunity to receive attention and guidance in managing their condition. In the third study, the demographics of responders and non-responders were compared to address this, finding that responders were younger at time of survey, had shorter follow-up, lower BMI at surgery and received more chemotherapy than non-responders, possibly influencing the results of the study.

The evaluation of PET/CT and CT/MRI was performed unblinded by the radiologists, where the interpretation of PET/CT might possibly be influenced by the CT/MRI report, creating a **classification bias**. To address this, we investigated the detection of lymph node metastases by CT/MRI before and after PET/CT was introduced, without finding improved CT/MRI detection after the introduction of PET/CT.

There were several potential confounding variables. In the third paper, these were adjusted for by multiple logistic regression. Women who scored positive for LEL more often reported musculoskeletal complaints, possibly reflecting overlapping risk factors for development of LEL and musculoskeletal disorders such as increasing BMI and age. Further, LEL and musculoskeletal complaints may present many of the same symptoms such as pain, swelling, and stiffness, asked for in the questionnaires (179). Self-reported musculoskeletal disease may therefore influence subjective LEL scoring. To address this, we performed a regression analysis and stratified by presence or absence of musculoskeletal complaints. However, this is a cross-sectional study not able to determine if LEL leads to musculoskeletal pain or vice versa.

Validity

When using questionnaires in research, validity is essential. All questionnaires in paper III are validated and forward- and back-translated into Norwegian. However, in our study we found

that the prevalence of self-reported musculoskeletal complaints was significantly higher in patients with LEL, compared to those without. This causes a concern about the validity of the LEL-questionnaire regarding its ability to capture patients who truly suffer from LEL. It may be that the questions are not able to distinguish between LEL and musculoskeletal disease or actually capture musculoskeletal disorders, reflecting that the true prevalence of LEL is lower than the reported values. In the group without musculoskeletal complaints, the prevalence of LEL was 17% and 18% after SLN or hysterectomy, which is lower than the prevalence in a comparable American study (147), but more similar to prevalence reported in Scandinavian studies (168, 180). The Scandinavian studies had, however, shorter follow-up time (three and 12 months), possibly missing some cases of lymphedema with late onset. As a result of these observations, new assessment of the validity of the relevant questionnaires should be made.

Misclassification

Misclassification occurs when a participant is placed in the wrong category because of observational or measurement error. Paper I may be prone to differential misclassification as there was more than one radiologist reporting the interpretations of the CT, MRI, and PET/CT. We investigated the performance of PET/CT from a clinician's point of view. Although the classification of suspicious metastatic lymph nodes on PET/CT was based on the presence of focally increased FDG uptake compared to the background uptake as well as on the size, shape and location of the lymph node, these parameters were only guidance for the categorization of lymph nodes, as the total impression by experienced radiologist was also allowed. This may be considered a weakness of the study.

Interobserver variation between pathologists may also result in misclassification, possibly influencing the results of the study.

Type I and II errors

In statistics, type I error is a false positive conclusion, while a type II error is a false negative conclusion. The null hypothesis in our first study is that there is no difference in the

detection rate for lymph node metastasis between CT/MRI and PET/CT. **Type I errors** occur if we reject the null hypothesis and erroneously state that a new test (PET/CT) is better than the older (CT/MRI). We are then concluding that the results are statistically significant when, in reality, they came about purely by chance or because of unrelated factors. This corresponds to the p-value which is the probability of making a type I error. The lower the p-value, the lower the likelihood of the type I error to occur. **Type II errors** occur when one fails to reject a null hypothesis that is actually false, in this setting if the test is not able to show any difference (PET/CT being superior to CT/MRI), despite the fact that there is one. Type II errors often occur when sample size is too small, restricting statistical power. Paper I may be prone to type II errors, as the sample size is limited, especially the number of patients with lymph node metastasis, and thus may be lacking enough power to detect potential differences between PET/CT and CT/MRI. Power is defined as the extent to which a test can correctly detect a real effect or difference when there is one.

The PPV refers to the probability of having the condition given a positive test, while the NPV refers to the probability of *not* having the condition given a negative test. The predictive values strongly depend on the prevalence of the given condition. If the prevalence of the condition is low, the PPV will also be low. In our study this affects the probability of actually having lymph node metastasis given a positive PET/CT. Although endometrial cancer is the most common gynecologic cancer in the western world, most cases are diagnosed in an early stage, with a relatively low risk of lymph node involvement, and few patients with lymph node metastasis. Despite the relatively low number of patients with lymph node metastases in our materials, the PPV of 85% for PET/CT is considered satisfying, and better than the 73% for CT/MRI.

Interpretations of main findings, comparison with existing knowledge and clinical implications

Detection of lymph node metastasis with PET/CT

The first paper indicates PET/CT to be superior in detecting lymph node metastases compared to conventional CT and MRI. PET/CT seems to be better especially in detecting paraaortic lymph node metastasis, with a detection rate of 100% compared to 50% for CT/MRI (p=0.06).

For detection of lymph node metastasis overall we found a sensitivity of 63% for PET/CT, compared to 41% for CT/MRI (p=0.07). However, the differences are not significant, reflecting the limited cohort, totally counting 185 patients, 27 of those with lymph node metastasis. This is a weakness of the study. Our findings with a sensitivity of 63% and a specificity of 98% correspond to results in comparable studies, where Hu et al. and Bollineni et al. in two systematic reviews and meta-analyses found a sensitivity of 68% and 72% and a specificity of 96% and 94%, respectively (81, 181). The corresponding detection rate in comparable studies supports our findings, and we find it reasonable to believe that PET/CT may provide benefit in detecting lymph node metastases compared to CT/MRI.

Although PET/CT seems to be beneficial in detecting lymph node metastases in patients with endometrial cancer, the specificity is limited, possibly due to false positive lymph nodes as well as incidental findings. False positive findings could possibly lead to even more examinations, stress, and discomfort for the patients, leading to significant costs to the healthcare system. On the other hand, for some patients, incidental findings from the PET/CT scan may be fortunate, for example, when other cancers (i.e. lung cancer, colorectal cancer) are detected at an early stage with possible curative treatment.

PET/CT is a costly examination. In many countries, access to clinical PET/CT scanning facilities is limited; also in Norway, scanning is not routinely performed at most centers. PET/CT is an examination requested for a variety of conditions, exceeding the capacity. Therefore, it is highly relevant to consider where the benefit is greatest. There is an increasing focus on prioritizing in health care services, addressing the resources to where it is most needed, and

avoiding unnecessary examinations and other health services. For these reasons it is important to identify those endometrial cancer patients most likely to benefit from additional PET/CT as part of their primary diagnostic workup, based on preoperative characteristics. In a retrospective study, Fasmer et al. (182) performed MRI and PET/CT in all patients, finding that PET/CT yielded a better detection rate for lymph node metastases than MRI alone, with sensitivity and specificity of 56% and 90 % compared to 33% and 95%, respectively (p=0.04). The diagnostic performance was similar when restricting PET/CT to patients with MRI indicating FIGO stage ≥IB, with sensitivity 52% and specificity 91% (p=0.06). The diagnostic performance was also assessed when restricting PET/CT to patients with high-risk preoperative histology, but this yielded inferior diagnostic performance with sensitivity and specificity of 44% and 94%. Based on the results in this study, Fasmer et al. suggest tailoring the use of PET/CT based on preoperative MRI findings.

In the latter study, lymph node surgery was performed in 61% (220/361) of patients, whereas in our study, all patients had at least pelvic lymph node surgery. This means that for a significant number of patients in their study, there is no standard of reference in terms of lymph node status confirmed by histopathologic evaluation. The prevalence of lymph node metastases was 7.5% (27/361) in the Fasmer et al. study, compared to 15% (27/185) in our study. This difference makes it reasonable to question whether some lymph node metastases might have been overlooked in the Fasmer et al. study, as both study populations seem to be comparable regarding clinicopathologic factors. However, 70% of the patients in our study underwent robot-assisted laparoscopic surgery with SLN biopsy, which probably increased the amount of lymph node metastasis due to ultrastaging.

SLN and ultrastaging increases the detection rate for lymph node metastasis. Detection of lymph node metastases by preoperative imaging is challenging, especially for diagnosing micro-metastases smaller than the PET scanner's spatial resolution (5 mm), as the number of malignant cells in these lymph nodes often is insufficient to significantly alter their glucose metabolism (77). This is illustrated in our study, in which PET/CT detected 93% of the macro-metastases, but only 31% of the micro-metastases.

Tanaka et al. (183) compared the combined diagnostic accuracy of PET/CT and SLN biopsy in the prediction of pelvic lymph node metastases, finding that PET/CT had lower sensitivity for lymph node metastases compared to SLN biopsy (36.8% versus 57.9%), however not

statistically significant (p=0.1). Especially small lymph nodes less than 5mm were more frequently detected by SLN biopsy than by PET/CT, with sensitivity of 72.7% versus 18.2% (p=0.01). However, in the Tanaka et al. study, the sensitivity tended to be higher for PET/CT than for SLN biopsy in lymph node metastases ≥ 5mm (62.5% versus 37.5%, p=0.2). When stratifying by preoperative risk categories in our study we found a limited detection rate in low-/ intermediate-risk patients, where only 50% and 40% of the lymph node metastases were detected by PET/CT, respectively. This emphasizes the importance of SLN biopsy, and indicates a better utilization of the resources when PET/CT is performed in selected patients.

Lymph node evaluation, SLN and the tailoring of adjuvant treatment

The role and extent of lymph node removal in endometrial cancer surgery is still highly debated. Nodal status is the single most prognostic factor for women with apparent early-stage endometrial cancer. It is also essential in directing the use of adjuvant treatment. Omission of nodal assessment would result in improper staging, and undertreatment of some women.

Adjuvant treatment

It has been debated whether adjuvant therapy in endometrial cancer should consist of radiotherapy, chemotherapy, or a combination. The ESGO guidelines recommend adjuvant chemotherapy as standard treatment in all high-risk endometrial cancer patients (55). This recommendation is based on the results from the GOG209 trial, a phase III, randomized, noninferiority, open-label trial comparing Carboplatin plus Paclitaxel to Paclitaxel-Doxorubcin-Cisplatin in stage III, IV and recurrent endometrial cancers (184). The trial showed that Carboplatin-Paclitaxel is noninferior to Paclitaxel-Doxorubicin-Cisplatin with regard to efficacy. Carboplatin-Paclitaxel has a more favorable toxicity profile and slightly improved health related QoL, and is considered the first-line therapy for advanced or recurrent endometrial cancer.

Based on the recently published RUBY trial (109), evaluating Dostarlimab plus Carboplatin/Paclitaxel versus placebo plus Carboplatin/Paclitaxel in patients with recurrent or primary advanced cancer, there is also a role for immunotherapy in the adjuvant setting.

There have been multiple RCTs evaluating radiotherapy as adjuvant treatment in endometrial cancer. The Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC)-1 trial (published in 2000), GOG99 (published in 2004), and the ASTEC-trial (published in 2009) (101, 102, 104) showed that adjuvant pelvic radiation therapy significantly reduced the rates of vaginal and pelvic recurrence, but without benefit in OS. The PORTEC-1 trial showed that most pelvic relapses were located in the vaginal vault, and that the salvage rates in women without previous radiation therapy was high. To address this, PORTEC-2 (185, 186), an RCT, investigated if vaginal brachytherapy was as effective as pelvic external beam radiotherapy (EBRT) in prevention of vaginal recurrence in women with high/intermediate risk factors. The trial showed that vaginal brachytherapy was effective in ensuring vaginal control, with lower rates of gastrointestinal adverse effects and better QoL compared to pelvic EBRT.

The PORTEC-3 trial, published in 2019, demonstrated statistically significant improvement in both overall and failure-free survival (defined as the time from randomization to any relapse, or death related to endometrial cancer or treatment, whichever occurred first) when chemotherapy was added to radiotherapy alone in patients with high-risk endometrial cancer (100). In an RCT including patients with FIGO stage III or IV disease, chemotherapy with Doxorubicin and Cisplatin were compared to whole abdominal radiation, resulting in significantly greater PFS and OS in the chemotherapy group. The greatest difference in OS was seen in FIGO stage III disease (187). GOG249 was a randomized phase III trial published in 2019 to assess if vaginal cuff brachytherapy combined with chemotherapy increased RFS compared to pelvic radiation therapy in high-intermediate and high-risk early-stage endometrial cancer (188). The study did not demonstrate superiority of combined vaginal cuff brachytherapy and chemotherapy over pelvic radiotherapy. In more recent trials, adjuvant chemotherapy has been shown to provide a significant improvement in OS in patients with extrauterine disease, including nodal involvement. However, chemotherapy may increase the risk of lymphedema as well as other adverse events.

Lymph node removal

Theoretically, the removal of lymph nodes may also eradicate metastatic lymph node disease. However, the therapeutic effect of lymph node removal is uncertain, as the two RCTs from Benedetti Panici et al. and from Kitchener et al. (the ASTEC study) failed to demonstrate any survival benefit from LND in women with presumed early-stage endometrial cancer (7, 8). In the Benedetti Panici et al. study, the rate of postoperative complications and lymphedema increased after LND. The ASTEC study concluded that pelvic LND should not be recommended as routine procedure for therapeutic purposes outside clinical trials. Both these studies have, however, been heavily debated. A concern regarding these trials has been that they were not powered to detect a difference in outcome. Both studies included a large proportion of low-risk women, which diluted the possible therapeutic effect of lymphadenectomy. There was no clear indication for postoperative adjuvant therapy; the ASTEC trial did not assign postoperative treatment based on the results of the lymph node status and the trial from Benedetti Panici et al. did not control for postoperative treatment. However, the adjuvant therapy administration was similar in both study arms, a result that may have influenced postoperative outcomes. It has also been criticized that neither of the trials evaluated the role of paraaortic LND appropriately. Additionally, in the ASTEC trial, the number of pelvic lymph nodes yielded was low in many patients in the LND group, and 5% of the no LND group *had* lymph nodes removed, with nearly 30% of these patients demonstrating lymph node metastasis.

Despite the results from these studies, there is a lack of consensus regarding the role and extent of nodal assessment in women with endometrial cancer. In intermediate- and high-risk endometrial cancer, several retrospective observational studies suggest improved survival after LND (91, 189), which is why this has been recommended. A recent Cochrane review based mainly on the RCTs carried out by Benedetti Panici et al., and Kitchener et al. found no evidence of therapeutic benefit from LND in patients with stage I disease (190). To address these questions, ECLAT is an ongoing open label RCT evaluating the effect of comprehensive pelvic and paraaortic LND in the absence of bulky nodes on 5-year OS of patients with stage I and II endometrial cancer and a high risk of recurrence. The participants are randomized to total hysterectomy with bilateral salpingo-oophorectomy, with or without

addition of systematic pelvic and paraaortic LND up to the level of the left renal vein. For all patients, vaginal brachytherapy and adjuvant chemotherapy are recommended. Inclusion to the study is planned to be completed in 2025 with 640 patients, and the results are planned to be presented in 2031 (93).

An argument against LND in patients with endometrial cancer is the risk of treatment-related adverse effects, in particular lymphedema. The earlier described CINDEINs are lymph nodes seldom involved with metastatic disease, although appearing enlarged (111, 191). It has been observed that the removal of these nodes is likely a risk factor that contributes to more lymphatic obstruction of the lower extremity and lower abdominal wall and likely increases the risk of postoperative symptomatic LEL (192). Elimination of these lymph nodes could therefore be helpful in reducing the incidence of LEL.

SLN mapping

SLN biopsy is a staging procedure, where the most important feature is its negative predictive value; its ability to truly demonstrate an absence of nodal metastasis.

There are four published prospective trials, all performing cervical injection of tracer to determine the diagnostic accuracy of SLN mapping. The **SENTI-ENDO trial** performed SLN assessment with technetium and patent blue followed by systematic pelvic lymph node dissection in patients with stage I-II endometrial cancer of all histologic subtypes (193). The detection rate for at least one SLN was 89%; the NPV when considering the patient as one unit was 97% and the sensitivity 84%. In the **FIRES study**, Rossi et al. also performed SLN mapping with ICG followed by pelvic LND with or without paraaortic LND in patients with clinical stage I endometrial cancer of all histologic subtypes and grades. They reported 86% unilateral mapping, an NPV of 99.6% and a sensitivity of 97.2% (194). In Sweden, Persson et al. performed the **SHREC trial**, including patients with presumed stage I-II high risk endometrial cancer, and demonstrated a bilateral mapping rate of 95% after reinjection of ICG (195). The NPV was 100% and the sensitivity 100% of the overall SLN algorithm. Finally, the **SENTOR study** reported 77.6% bilateral mapping, an NPV of 99% and sensitivity of 96% (196) when ICG was used as tracer in patients with clinical stage I grade 2 endometrioid, or high grade endometrial cancer.

A prospective observational study from our department, validating the MSKCC SLN algorithm demonstrated a detection rate of 96% for at least one SLN and 78% bilateral mapping (197) when ICG was used as tracer.

Explanations for failed SLN mapping may be disruption of lymphatic channels, changes in anatomy after previous surgery or radiation, or a result of increased BMI (125, 128, 198). In case of failed SLN mapping, it has been discussed whether reinjection of tracer should be performed. There is no consensus regarding this (55), although it has been advocated by some trials (115, 195, 199).

Paraaortic lymph nodes

In addition to the debate about whether comprehensive LND improves survival, it has been debated if paraaortic lymph nodes should be removed in addition to pelvic LND (7, 8, 189). In the presence of pelvic lymph node metastasis, as many as 51% of the women also have paraaortic lymph node metastasis (200). Isolated paraaortic lymph node metastasis without pelvic lymph node metastasis is reported to occur in approximately 1-4% of all endometrial cancer patients (200-202). When retrospectively performing ultrastaging of negative pelvic lymph nodes in patients with isolated paraaortic lymph node metastasis, Multinu et al. found the prevalence of true isolated lymph node metastasis in their cohort to be 1.8%, compared to 2.5% before ultrastaging (203).

Especially when performing the SLN algorithm, paraaortic lymph nodes may be an issue of concern, as evaluation of this area is left to the surgeon's discretion and almost always omitted (125). Some paraaortic lymph nodes may be reached only via the infundibulo-pelvic ligament pathway, which is not reached by superficial cervical injection of ICG during SLN algorithm, and some paraaortic metastases may be missed because of this (115, 133).

In the presence of lymph node metastasis, the patient will be a candidate for adjuvant treatment. It may therefore be important to examine paraaortic lymph nodes in the absence of pelvic lymph node metastasis, to ensure detection of the isolated paraaortic lymph node metastasis and allocate the patient to adjuvant treatment. This is of particular importance in patients where uterine factors alone do not indicate adjuvant therapy. However, patients

with uterine factors that do not dictate adjuvant therapy are at the lowest risk for isolated paraaortic lymph node metastasis (201).

In paper II, three of the five women with relapsed disease had multifocal relapse including the paraaortic nodes, but no isolated paraaortic relapse was observed. One woman had stage IA disease at time of diagnosis, and did not receive adjuvant treatment. The second woman had stage IIIC1 disease at time of diagnosis and was recommended for adjuvant treatment, but refused. The third woman had stage IIIC1 disease at time of diagnosis and received adjuvant treatment with Paclitaxel and Carboplatin in accordance with the national guidelines. Peroperative paraaortic lymph evaluation were not performed in any of these women.

According to the first paper in this thesis and comparable studies, PET/CT may be superior to CT and MRI, especially in detecting paraaortic lymph node metastases. This could be a support in selecting patients with a need for paraaortic LND or a more thorough examination to detect paraaortic SLNs. Taskin et al. evaluated the complementary role of preoperative PET/CT in patients with high-risk features for lymph node metastasis in patients undergoing SLN mapping. The study demonstrated isolated paraaortic lymph node metastasis overseen by SLN mapping, but detected by PET/CT; the study concluded that PET/CT may be a feasible tool, especially in the detection of isolated, paraaortic lymph node metastasis in patients undergoing SLN mapping to properly stage the patient (204), even though isolated paraaortic lymph node metastasis rarely occurs.

When evaluating the location of paraaortic lymph node metastasis, a prospective study from the Mayo Clinic described 77% of these as being localized above the inferior mesenteric artery (202). The latter study therefore suggests the need for systematic LND of both the pelvic and paraaortic area, up to the level of the renal vessels in patients at risk, defined as myometrial invasion >50%, tumor diameter >2 cm, grade 3 endometrioid or non-endometrioid histologic subtype. Routine LND has, however, never demonstrated survival benefit by any level 1 evidence.

Many studies suggest improved survival following removal of paraaortic lymph nodes in high-risk patients, especially where lymph node metastasis is present (90, 189, 205, 206). This improved survival may, however, be explained by stage migration. The patient will be

correctly staged as stage IIIC2, and no longer part of the survival analysis in the stage I/II cohorts. This may thus not represent a true benefit of the removed lymph nodes.

At present, the ESGO/European Society for Radiotherapy and Oncology (ESTRO)/European Society of Pathology (ESP) guidelines recommend either routine systematic pelvic and paraaortic LND or the SLN approach in high-risk patients, and LND is used primarily for staging (55). The Norwegian guidelines recommend a SLN approach, which includes removal of bulky lymph nodes, also in the paraaortic region (140).

Low volume metastases

Staging in accordance with the SLN algorithm which includes deeper serial sections and IHC staining, increases the detection of low volume metastases comprised of micro-metastasis and ITCs. This entails a potential upstaging to stage IIIC, especially in low risk patients (135). Four (24%) of the 17 patients with lymph node metastasis in paper II were detected by ultrastaging only, six (35%) of the 17 patients were detected with low volume metastasis, five with micro-metastasis and one with ITC.

According to the ESGO/ESTRO/ESP guidelines, adjuvant treatment is recommended in patients with stage IIIC disease, especially in the presence of macro-metastases (55). The presence of ITCs alone does not seem to influence the oncologic outcome (207, 208), although the prognostic significance of low volume disease in endometrial cancer is debated, and there is no consensus regarding the potential benefit from adjuvant treatment in patients with ITCs. ITCs are detected with ultrastaging in 2-14% of assumed early-stage endometrial cancer patients that are node negative on routine examination with HE (208-210). Deep myometrial invasion and large tumor size are associated with increased risk of ITCs (209). The FIRES (Fluorescence imaging for robotic endometrial cancer sentinel node mapping) and FILM (Near-infrared fluorescence for detection of sentinel lymph nodes in women with cervical and uterine cancers) trials found low volume metastases overall accounting for >50% of positive SLNs in endometrial cancer, demonstrating that >30% of lymph node metastases might have been missed without ultrastaging (126, 194). As low volume metastases occur most frequently in apparently low-risk patients, it is of greatest

importance to ascertain the clinical significance, knowing that these patients otherwise would be omitted from adjuvant treatment.

Evidence tends to suggest the use of adjuvant treatment in the presence of micro-metastasis. Compared to negative lymph nodes in patients, the presence of micro-metastasis is associated with adverse prognosis (211, 212), however, it is associated with improved oncologic outcome in comparison to patients with macro-metastasis (213, 214). Both Bogani et al. and Ignataov et al. found that patients with micro-metastases who underwent adjuvant treatment had improved long-term oncologic outcome compared to those who did not, advising the use of adjuvant treatment in these patients (211, 215). However, both Plante and Backes et al. demonstrated that patients with ITCs may not derive the same benefit from adjuvant treatment, as they have a good prognosis independent of adjuvant treatment. Adjuvant treatment is therefore suggested based on uterine and/or molecular factors (208, 216).

One-step nucleic acid amplification (OSNA) reaction is a novel and automated diagnostic assay for analyzing the entire lymph node tissue, eliminating sampling bias. It is routinely used for SLN examination in other solid tumors such breast cancer; some centers have adopted the method also in the evaluation of SLNs in endometrial cancer. Prospective observational studies have suggested a possible improvement in the detection of SLNs by approximately 20% compared to standard ultrastaging (217); the potential role of OSNA must be further explored.

Oncologic outcome after SLN mapping

After the introduction of a novel method like the SLN algorithm it is of greatest importance to ensure that oncologic outcome is not compromised. The second paper in this thesis was one of the first studies, apart from data from pioneer institutions, to report long-term oncologic outcome data in patients where the SLN algorithm was applied. Our study, which included patients of all histologic subtypes, demonstrates excellent oncologic outcome in endometrial cancer patients treated in accordance with the SLN algorithm, with 5-year RFS of 95.4%. This is in line with other studies, although most of the studies have limited follow-up time. The strength of our study is the long follow-up time, with a median of 75 months

(range 61-98). There is a lack of RCTs comparing the oncologic outcome after SLN biopsy with comprehensive LND, as available trials are all retrospective observational studies.

In a systematic review, Bogani et al. demonstrated an overall recurrence rate of 4.3% after SLN compared to 7.3% after LND (218). A review comprising studies from MSKCC also describes non-inferior oncologic outcome after SLN compared to LND (125). Eriksson et al. compared the oncologic outcome after SLN mapping and after selective LND in women with low-risk endometrial cancer with endometrioid histology and <50% myometrial invasion, demonstrating 3-year disease-free survival (DFS) of 94.9% and 96.8% (219). Schlappe et al. investigated women with endometrioid histology and >50% myometrial invasion, finding 3-year DFS of 78.7% for patients treated according to the SLN algorithm compared to 77.7% for patients undergoing LND (220). The same research group also compared the oncologic outcome after lymph node assessment via the SLN algorithm versus comprehensive pelvic and paraaortic LND in patients with serous and clear cell endometrial carcinoma. They demonstrated a non-significant decreased RFS after SLN mapping, but the OS was not compromised (63). Basaran et al. confirmed similar outcomes when comparing SLN mapping to more extensive LND in patients with uterine serous carcinoma (221). Finally, Zammarrelli found no difference in PFS or OS when comparing SLN mapping and systematic LND in patients with carcinosarcoma (222). The described studies are summarized in Table 5.

Table 5: Oncologic outcomes of patients with endometrial cancer having undergone SLN mapping.
Reprinted and modified with permission from Eriksson et al., Update on Sentinel Lymph Node Biopsy in Surgical Staging of Endometrial Carcinoma, J Clin Med, 2021, (125).

Study	Study population	Nodal assessment	n	Metastatic nodes	p-value	Disease-free survival	p-value	Overall survival	p-value
Eriksson (219)	Endometrioid MI < 50%	SLN LND	642 493	5.1% pelvic 2.6% pelvic	0.03	94.9% 96.8% (3 year)	Not reported	97.4% 95.4% (3 year)	0.07
Schlappe (220)	Endometrioid MI > 50%	SLN LND	82 94	33.3% pelvic 14.8% pelvic	0.005	78.7% 77.7% (3 year)	Not reported	91.8% 77.6% (3 year)	Not reported
Schlappe (63)	Serous and clear cell	SLN LND	118 96	22% pelvic 20% pelvic	0.83	69% 80% (3 year)	0.32	88% 77% (3 year)	0.06
Basaran (221)	Serous carcinoma	SLN LND	79 166	26.5% 29.5%	0.63	58.8% 64.9% (2 year)	0.48	89.1% 83.9% (2 year)	0.85
Zammarrelli (222)	Carcinosarcoma	SLN LND	99 100	23.2% 22%	0.4	62.9% 52.3% (3 year)	0.13	72.1% 71.6% (3 year)	0.68

The results of our study support the continued implementation of the SLN algorithm. The comparable studies from larger institutions provide knowledge supporting the use of the SLN algorithm, not only in low-risk patients, but also in patients with high-risk histologic subtypes. Importantly, the risk categories are postoperative knowledge, finally depending on information in the histology report. A study from our department demonstrated that 9% of preoperatively early-stage, low-risk patients in the cohort were upstaged postoperatively with the findings of lymph node metastasis (197), emphasizing the importance of SLN in patients in all risk categories.

ENDO-3 and SELECT are current trials assessing oncologic outcome after SLN. ENDO-3 is an open label, phase III RCT comparing SLN biopsy with no retroperitoneal dissection in apparent early-stage endometrial cancer. In this study, patients with endometrial cancer are randomized to receive laparoscopic/robotic hysterectomy and bilateral salpingo-oophorectomy, with or without the addition of SLN biopsy. The trial is divided into two stages. In stage 1 the aim is to compare the recovery of the participants, the incidence of adverse events, LEL, health related QoL, and costs to the health care system. Stage 2 will compare DFS between groups after 4.5 years (223). SELECT (SEntinel Lymph node Endometrial Cancer Trial) is a prospective multicenter international single-arm observational study assessing the oncologic safety of the SLN algorithm in stage I intermediate-risk endometrial cancer. The primary aim in this trial is to assess the 36-month incidence of pelvic/non-vaginal recurrences in women with pathologically confirmed stage I intermediate-risk endometrioid endometrial cancer with bilateral negative pelvic SLNs (224).

Lymphedema and quality of life following SLN mapping

Prevalence of LEL after SLN mapping, LND and hysterectomy alone

The third paper examining the prevalence of lymphedema after endometrial cancer surgery demonstrates that SLN mapping is not associated with increased prevalence of LEL compared to hysterectomy alone but is associated with a significantly lower prevalence of LEL compared to LND. QoL is significantly influenced by the presence of lymphedema, showing better patient-reported outcomes after SLN compared to LND.

According to these results, the risk of LEL should not be used as an argument against SLN mapping. We found that every lymph node removed contributed to an increased risk of LEL. This emphasizes the importance of bilateral mapping, as the SLN algorithm in cases of failed mapping requires performance of side-specific LND, possibly removing multiple lymph nodes.

The higher prevalence of LEL in women after LND (51%) compared to SLN (36%) or hysterectomy alone (40%) are in line with previous studies. Leitao et al. compared the prevalence of patient reported LEL after SLN mapping and after LND, and reported the prevalence to be 27% and 41%, respectively (147). Yost et al. aimed to estimate LEL prevalence in patients surgically treated for endometrial cancer in order to identify predictors of LEL, and to evaluate the effect of LEL on QoL. The prevalence in patients undergoing hysterectomy alone was compared to patients undergoing additional LND, finding a LEL prevalence of 36% and 52%, respectively. Yost et al. also compared the prevalence of LEL in patients undergoing pelvic LND with patients undergoing pelvic and paraaortic LND, finding no higher risk among women who had paraaortic LND in addition to pelvic LND, 52.4% compared to 49.4% (p=0.63) (6). Both the referred studies used LELSQ, EORTC-QLQ-C30, and EORTC-QLQ-EN24, which are the same PROMs as we used in our study.

Our findings of similar prevalence of LEL after SLN and hysterectomy alone are not previously reported in large studies. Unlike previous studies, our SLN cohort reflects outcomes of the SLN algorithm as women with failed mapping undergoing uni- or bilateral side-specific LND according to the SLN algorithm are included as intention-to-treat in this cohort, irrespective of the number of lymph nodes removed.

Risk factors for developing LEL

In addition to LND, we found that high BMI and adjuvant chemotherapy were independent risk factors for development of LEL. This corresponds to the study by Yost et al., reporting higher BMI, congestive heart failure, LND, and radiation therapy as factors associated with increased prevalence of LEL. We also found the number of lymph nodes removed to be associated with increased prevalence of LEL. This differs from the study of Yost et al., finding no association either with the number of lymph nodes removed or the extent of LND.

Since adjuvant radiotherapy is not recommended by the national guidelines in primary setting, the population in our study is mainly radiotherapy naïve. Our reported prevalence of LEL after combined surgery and adjuvant chemotherapy is in line with previously published findings where radiotherapy has been administered, indicating that the receipt of any adjuvant therapy may negatively influence the development of LEL. Forsse et al. conducted a prospective cohort study, investigating the longitudinal effects of adjuvant chemotherapy and lymph node staging on patient-reported outcomes in endometrial cancer survivors. The PROMs EORCT QLQ-C30 and EORTC QLQ-EN24 were assessed preoperatively, and at one and two years of follow-up. The patients were divided into three treatment groups. The first group underwent hysterectomy only, the second group hysterectomy with addition of lymph node staging (but without adjuvant chemotherapy), and the third group had adjuvant chemotherapy (irrespective of staging procedure). Patients receiving adjuvant chemotherapy more often reported lymphedema, but also long-term neuropathy, fatigue, and inferior physical function. This study demonstrated no difference between women undergoing lymph node staging compared to those treated with hysterectomy and bilateral salpingo-oophorectomy alone (225). This differs from our findings where both LND and adjuvant chemotherapy were associated with LEL. Despite chemotherapy being more commonly administered in the SLN cohort compared to the hysterectomy cohort, this does not seem to increase LEL prevalence for the SLN cohort.

Musculoskeletal complaints and LEL

In our study, 56% of responders reported musculoskeletal complaints, 98% of these reported that these problems affected activities of daily living. This is in line with the prevalence of musculoskeletal complaints in the general population of elderly females in Norway (50%) (226). Patients reporting musculoskeletal complaints more often scored positive for self-reported LEL compared to patients without musculoskeletal complaints. To our knowledge, there are no previous studies reporting prevalence of musculoskeletal disease in endometrial cancer survivors and its potential influence on scoring positive for LEL in PROMs. This may possibly reflect overlapping risk factors for development of LEL and musculoskeletal disorders such as increasing BMI and age, in addition to overlapping symptoms such as swelling, stiffness and pain.

In our study, 17% and 18% of women without musculoskeletal complaints scored positive for LEL after SLN or hysterectomy. This prevalence is lower than previous results from cross-sectional studies in an American population: 27% and 40% after SLN or hysterectomy (147) and, 36% after hysterectomy (6). Our study may indicate that the prevalence of LEL may not be as high as previously reported in endometrial cancer survivors, since underlying musculoskeletal disorders could mimic both signs and symptoms of LEL. A study based on self-reported symptoms is especially prone to bias such as this and should be investigated further. LND was not associated with LEL in women reporting musculoskeletal complaints, however this association was present both for the total study population, as well as for patients not reporting musculoskeletal complaints.

Quality of life and thresholds for clinical importance

Novel for our study is reporting differences in QoL related to a clinical important difference. Previous studies report differences in QoL by statistically significant levels or by ≥10 points differences as described by Osoba (227). In our study we compared QoL by a novel method for interpretation of the EORCT QLQ-C30 score, called *threshold for clinical importance*. These thresholds are developed systematically with the views of both patients and health care professionals and are validated for use on the EORCT QLQ-C30. They are based on external criteria reflecting the clinical importance of the problem, defined as any aspect of a health problem that makes it relevant for the clinical encounter. The thresholds for clinical importance may add a more clinically meaningful interpretation of scores (175). In terms of research, thresholds for clinical importance may aid in the interpretation of group-level data and allow calculations of prevalence rates. However, a limitation of these thresholds for clinical importance is limited statistical power following the loss of information by dichotomizing.

CONCLUSIONS

The conclusions of this thesis are as follows:

- PET/CT tends to be superior to CT/MRI for detection of lymph node metastases in endometrial cancer, particularly in detecting paraaortic lymph node metastases (Paper I).
- The improved ability of preoperative PET/CT to exclude paraaortic lymph node metastases may strengthen the argument for continued implementation of the SLN algorithm (Papers I and II).
- Applying the SLN algorithm for surgical staging in women with endometrial cancer is of no detriment regarding long term oncologic outcome (Paper II).
- SLN implementation is not associated with increased prevalence of LEL compared to hysterectomy alone but is associated with a significantly lower prevalence compared to patients undergoing LND (Paper III). The risk of LEL should therefore not be used as an argument against implementation of an SLN algorithm.
- The presence of lymphedema significantly impacts QoL (Paper III).
- Risk factors for developing LEL in addition to LND are high BMI and adjuvant chemotherapy.
- The prevalence of LEL might not be as high as previously reported, as underlying musculoskeletal disorders could mimic signs and symptoms of LEL.

FUTURE PERSPECTIVES

The introduction of advanced preoperative imaging with PET/CT, SLN biopsy and molecular classification are all part of precision medicine for endometrial cancer patients. The SLN algorithm has emerged as the gold standard for staging in women with endometrial cancer; however, we are still awaiting the results of ongoing prospective studies regarding oncologic outcome (223, 224). Another issue to be clarified is the significance of low volume disease, especially regarding the prognostic role of ITCs in patients otherwise stratified in low or intermediate risk groups. Future investigation should ensure an optimal clinical management of these patients regarding the use of adjuvant therapy.

The SLN algorithm allows the removal of fewer lymph nodes compared to LND. To further minimize removal of lymph nodes, work is being done to find tracers which can identify metastatic nodes. Mueller et al. performed a pilot study including 20 patients with endometrial or cervical cancer, using positron lymphography (PLG). During PLG, ^{18}F-FDG is injected *intracervically*, and transported via the lymph channels to the draining SLN. In the study, Muller and colleagues found three patients with lymph node metastasis, all three identified by PLG (228). SLN tracers capable of identifying patients with lymph node metastasis should be further investigated.

The development and validation of accessible surrogate markers for the four molecular subgroups has accelerated the understanding of tumor biology, opening opportunities for individualized treatment. The introduction of molecular sub-groups has been proven by Jamieson et al. in the Vancouver group to have a stronger prognostic impact than histopathological tumor characteristics, with an advantage of possibly being obtained by preoperative biopsies (229). The TCGA classification could lead to treatment de-escalation in patients with favorable factors such as POLE mutation, and to intensified treatment by adding adjuvant chemotherapy in the presence of unfavorable factors such as p53 mutation. In the presence of low volume lymph node metastases, information regarding the molecular subtypes might be supportive in decisions regarding adjuvant treatment. Currently, there is a lack of sufficient studies supporting molecular classification to alter the guidelines of adjuvant treatment, but molecular factors are being evaluated in multiple clinical trials, including PORTEC-4a (230), TAPER (231), and the TransPORTEC RAINBO study (232). The

introduction of the molecular classification of endometrial cancer also opens the opportunity for the use of personalized medicine such as immunotherapy.

Integrating knowledge from surgical staging and molecular classification may be used in coming years to determine the most appropriate adjuvant therapy in women with endometrial cancer. Preoperative molecular classification may also further de-escalate the need for surgical staging in certain patients. However, the knowledge regarding the molecular subgroups is still not sufficient for this purpose, as the exact risk of extrauterine disease for each molecular subgroup is currently unknown, and it remains to be determined if and how the knowledge of molecular subgroups may alter the type of *surgical staging for each of the molecular subgroups*. The EUGENIE study (Improving Endometrial cancer assessment by combining the new techniqUe of GENomic profiling with surgical Extra uterIne disEase assessment) aims to determine the association between molecular classification and disease stage with the hypothesis that each molecular subgroup has a specific pattern of spread. Hopefully, this pattern of spread can be utilized to guide the extent of surgical staging (233). The fact that molecular classification groups can be obtained on preoperative biopsies makes the information available for guiding surgical treatment planning, and makes the results from the EUGENIE study even more relevant. Future research should work towards integrating SLN status and molecular subtype to complement each other for better understanding and improved, personalized treatment.

Parallel to the development of the TCGA classification of endometrial cancers, there has also been a digital revolution in pathology, wherein digital models from the computer vision community have been used on digital histopathological slides combined with deep learning (DL) models (234). DL is a machine learning technique, teaching computers to learn by example, which has been utilized in several types of cancer (235). DL, is for instance, already in use for MSI prediction in colorectal cancer (236, 237) and for HRD prediction in breast cancer, showing that DL-based assessment has potential as a screening tool to discriminate molecular alterations in tissue slides (235). Exploiting DL to predict the four-class molecular endometrial cancer classification and to make correlates that could be interpreted by humans are yet to be explored. In the future, however, DL may offer opportunities in diagnosing and classifying endometrial cancers, for example by showing that further refining

of the endometrial cancer classification is possible by accurately combining histological and molecular data (234).

The available treatment options for patients with advanced or recurrent endometrial cancer have, so far, been limited. Recently, Eskander et al. published an RCT assessing the benefit of adding the PD1-inhibitor Pembrolizumab to standard treatment with chemotherapy (238). The addition of Pembrolizumab to standard chemotherapy followed by Pembrolizumab maintenance, resulted in a significantly longer PFS than with chemotherapy alone. These results were valid for both MMR deficient and MMR proficient tumors, with 70% and 46% risk reduction of progression or death, respectively. These data suggest that pembrolizumab be incorporated into first-line treatment of patients with advanced or recurrent endometrial cancer, and provide a strongly awaited treatment possibility for these groups of patients. However, approval of this treatment by the health authorities is still pending.

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PAPERS I – III AND APPENDICES

PAPER I

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Full length article

Initial experience with positron emission tomography/computed tomography in addition to computed tomography and magnetic resonance imaging in preoperative risk assessment of endometrial cancer patients

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ABSTRACT

Objective: Improved preoperative evaluation of lymph node status could potentially replace lymphadenectomy in women with endometrial cancer. PET/CT was routinely implemented in the preoperative workup of endometrial cancer at St Olav's University Hospital in 2016. Experience with PET/CT is limited, and there is no consensus about the use of PET/CT in the diagnostic workup of endometrial cancer. The aim of the study was to evaluate the diagnostic accuracy of PET/CT compared to standard CT/MRI in identifying lymph node metastases in endometrial cancer with histologically confirmed lymph node metastases as the standard of reference. We especially wanted to look at PET/CT as a supplement to the sentinel lymph node algorithm in the detection of paraaortic lymph nodes.

Study design: A retrospective study included all women undergoing surgery for endometrial cancer from January 2016 through July 2019 at St Olav's University Hospital. Clinical data, results of CT, MRI, and PET/CT, and histopathological results were analyzed.

Results: Among 185 patients included, 27 patients (15 %) had lymph node metastases. 17 (63 %) had pelvic lymph node metastases, one (4 %) had isolated paraaortic lymph node metastases, and 9 (33 %) had lymph node metastases in both the pelvis and the paraaortic region. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of PET/CT for the detection of lymph node metastases were 63 %, 98 %, 85 %, 94 %, and 93 %, respectively. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of CT/MRI were 41 %, 98 %, 73 %, 91 %, and 90 %, respectively (p = 0.07). For the 26 pelvic lymph node metastases, PET/CT had a sensitivity of 58 %, compared to 42 % for CT/MRI (p = 0.22). PET/CT detected all 10 paraaortic lymph node metastases, for a sensitivity of 100 %, compared to 50 % for CT/MRI (p = 0.06).

Conclusions: PET is superior to CT/MRI for detection of lymph node metastases in endometrial cancer, particularly in detecting paraaortic lymph node metastases. The ability of preoperative PET to exclude paraaortic lymph node metastases may strengthen the credibility of the sentinel lymph node algorithm.
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Introduction

Primary surgery for apparent early-stage endometrial cancer includes hysterectomy, bilateral salpingo-oophorectomy, and assessment of regional lymph node involvement. Lymph nodes are the most common site of extrauterine spread [1,2]. Detecting lymph node metastases in endometrial cancer is important for treatment and prognosis [3–6]. It is debated if paraaortic nodes should be removed, and whether comprehensive lymphadenectomy improves prognosis, at the cost of increased complications [3,4,7]. The sentinel lymph node (SLN) strategy has emerged as a compromise between comprehensive lymphadenectomy in high-risk patients and omittance of lymph node removal in low-risk patients, allowing sufficient lymph node assessment in patients of all risk categories [8].

Preoperative imaging provides important guidance in the choice of surgical procedure, especially as detection of suspicious paraaortic lymph nodes entails operation by laparotomy instead of minimally invasive surgery and SLN. Standard preoperative diagnostic tools in endometrial cancer are computed tomography (CT) and magnetic resonance imaging (MRI) [9–12]. The development of positron emission tomography (PET)/CT combines CT with radiolabeled ^{18}F-fluorodeoxyglucose (FDG), potentially allowing detection of small volume disease overlooked on CT and MRI. Since 2016, whole body FDG PET/CT has been included in the preoperative diagnostic workup of endometrial cancer in our hospital. However, experience and consensus about the use of PET/CT in the diagnostic workup of endometrial cancer are limited [9].

The aim of the present study was to evaluate the diagnostic accuracy of PET/CT compared to standard CT/MRI in identifying lymph node metastases in endometrial cancer, and particularly with regard to evaluation of the paraaortic region in candidates for SLN-mapping.

Materials and methods

Patient population

Patients with histologically confirmed endometrial cancer, operated in the period from 2016 through July 2019, were eligible to participate in a retrospective observational study. We compared the ability of preoperative PET/CT versus preoperative CT/MRI to detect lymph node metastases, with histologically confirmed lymph node metastases as the standard of reference. In our hospital, PET/CT was implemented as routine in 2016, and the sentinel lymph node (SLN) mapping algorithm has been used since 2012 [13].

Inclusion criteria were histologically confirmed endometrial cancer, preoperative CT of the thorax, abdomen, and pelvis, MRI of the pelvis, preoperative ^{18}F-FDG PET/CT, pelvic lymph node removal, and histologically confirmed presence of lymph nodes (Fig. 1).

In addition, patients operated between November 2012 through 2015 were included as a reference group, to determine if the addition of PET/CT had any influence on the performance and interpretation of CT/MRI. Patients in the reference group who had a PET/CT scan performed in the preoperative workup of endometrial cancer were excluded.

The patients were preoperatively classified into traditional risk categories, based on histopathological type and grade, and depth of myometrial infiltration assessed by preoperative imaging.

Preoperative imaging

The PET/CT procedure was performed according to the institutional standard with ^{18}F-FDG (4 M Bq/kg) injection following 6 h fasting. Blood glucose was controlled to be <10 nmol/l. PET/CT from the vertex to the middle femur was obtained 60 min after FDG injection. 3D image reconstruction was made using 256 × 256 matrix, 4 mm FWHM, Time Of Flight and Point Spread Function. All studies were performed on Siemens Biograph mCT. The images were assessed by experienced nuclear medicine physicians.

The classification of lymph nodes on PET/CT as imaging-suspicious was based on the presence of focally increased FDG uptake compared to the background uptake in blood and in the liver, and on the size, shape, symmetry and location of the lymph node. The classification of lymph nodes as imaging-suspicious on CT and MRI was based on size, shape and location. According to the clinical pathway for endometrial cancer, the preoperative assessment is completed within 36 days from the time of referral.

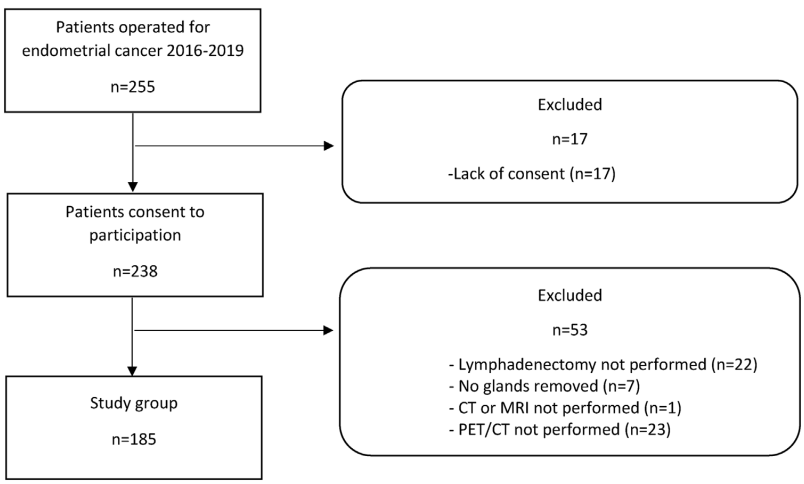

Fig. 1. Study population.

Surgical treatment

All patients underwent hysterectomy, bilateral salpingo-oophorectomy and pelvic lymph node removal. Patients with apparent early stage disease underwent robot-assisted laparoscopic operation with pelvic SLN mapping using indocyanine green fluorescence following the Memorial Sloan Kettering surgical algorithm [13,14]. Patients with uterine size >8 cm or imaging-suspicious lymph nodes cranial to the level of the inferior mesenteric artery had hysterectomy, bilateral salpingo-oophorectomy, and conventional lymph node removal (pelvic and eventually paraaortic) without SLN mapping by laparotomy.

Pelvic lymph node removal in addition to SLNs included removal of all imaging-suspicious lymph nodes, perioperative enlarged or fixed lymph nodes, or sampling of lymph nodes from the external iliac and obturator fossa. Some patients underwent additional paraaortic lymph node dissection, performed at the discretion of the surgeon, including imaging-suspicious lymph nodes, or sampling of lymph nodes below the inferior mesenteric artery.

Histopathological evaluation of lymph nodes

The surgical specimens underwent standard histopathological examination after formalin fixation and hematoxylin-eosin staining. For the patients undergoing SLN mapping, routine histology negative SLNs were further examined with ultrastaging, including additional sectioning and immunohistochemistry for cytokeratin. Lymph node metastases were categorized into macro-metastases (>2 mm) and micro-metastases (0.2–2 mm). Isolated tumor cells (<0.2 mm) were not defined as lymph node metastases and the isolated tumor cells category was diagnosed only when the tumor focus was visible in both the hematoxylin-eosin and the adjacent immunohistochemistry sections. The histopathological evaluation was performed by experienced gynecologic oncology pathologists.

Statistics

Patients characteristics were summarized using the median (range) for continuous variables and percentages for categorical variables. The result of the histological evaluation was set as standard of reference for statistical analyses of lymph node metastases. Differences in sensitivity and specificity between PET/CT and CT/MRI were examined using the McNemar exact test. Comparison of lymph node detection with CT/MRI between the study group and the reference group was performed with the Chi square test. For all analyses, p-values less than 0.05 were considered statistically significant. Statistical analyses were performed using International Business Machines Corporation (IBM) Statistical Package for the Social Science (SPSS), version 27.

Ethics

The study was approved by the Regional Committees for Medical and Health Research Ethics (REK midt 7193/2019).

Results

Patient population

A total of 255 patients underwent primary surgery due to endometrial cancer in the study period. Of the 238 patients who consented to participate, 185 fulfilled the inclusion criteria, constituting the study population (Fig. 1). Demographic and clinical characteristics are given in Table 1.

Table 1
Demographic and clinical characteristics (N = 185).

	Median	Range
Age (years)	69.0	39–88
Body mass index (kg/m^2)	28.1 *	16.6–53.7
Operation time (minutes)	109	65–312
Blood loss (milliliters)	50	0–1920
	N	**Percentage**
Histologic type		
Endometrioid	134	72.4
Serous	20	10.8
Clear cell	9	4.9
Carcinosarcoma	5	2.7
Mixed	8	4.3
Others	9	4.9
FIGO stage		
IA	96	51.9
IB	47	25.4
II	5	2.7
IIIA	8	4.3
IIIB		
IIIC	26	14.1
IV	3	1.6
Blood- or lymph vascular space invasion		
No	142	76.8
Yes	43	23.2
Postoperative chemotherapy		
No	115	62.2
Yes	70	37.8
Operation method		
Robotic with SLN	130	70.3
Robotic without SLN	2	1.1
Laparotomy	53	28.6

* Three missing body mass indexes.

In the study group, 132/185 (71 %) underwent robot-assisted laparoscopic surgery, and 53/185 (29 %) laparotomy. Pelvic lymph node removal with SLN mapping was performed in 130/132 (98 %) of the robot-assisted cases.

Of the 185 patients in the study group, 168 (91 %) had a PET positive uterine tumor. Of the 17 patients with PET negative uterine tumors, 14 had stage 1A, one stage 1B. Two patients had stage 3C due to lymph node spread, both had uterine stage 1A disease, one had PET negative while one had PET positive lymph node metastases.

Prevalence of metastatic disease

The overall metastatic rate was 19 % (35/185).

Prevalence of lymph node metastases

The lymph node metastatic rate was 15 % (27/185). Seventeen (63 %) had pelvic lymph node metastases, 1 (4%) had isolated paraaortic lymph node metastases, and 9 (33 %) had metastases in both regions.

Size of lymph node metastases

The median size of the lymph node metastases was 4.5 mm (0.20–80.0 mm). Fourteen out of 27 (52 %) were macro-metastases and 13/27 (48 %) micro-metastases. Additionally, isolated tumor cells (<0.2 mm) were detected in 12 patients (6%). The characteristics of the patients with lymph node metastases are given in Table 2.

Non-lymphatic metastases

Fifteen patients (8%) had non-lymphatic spread of disease. Eleven had spread of tumor to the ovary or the fallopian tube, the

Table 2
Characteristics of patients with lymph node metastases.

Case	Histology	Grade	Risk category*	Diameter of largest lymph node metastasis (mm)	Location	Metastatic lymph node(s) on PET/CT	Metastatic lymph node(s) on CT/MR	Metastatic lymph node in SLN or non-SLN
1	Endometrioid	1	Low	20	Pelvic	Pelvic	Pelvic	SLN
2	Endometrioid	1	Intermediate	0.3	Pelvic	Negative	Negative	SLN
3	Endometrioid	1	Intermediate	1.5	Pelvic	Negative	Negative	SLN
4	Endometrioid	1	Intermediate	4.5	Pelvic	Negative	Negative	SLN
5	Endometrioid	2	Low	0.6	Pelvic	Negative	Pelvic	SLN
6	Endometrioid	2	Intermediate	0.2	Pelvic	Negative	Negative	SLN
7	Endometrioid	2	Intermediate	0.5	Pelvic	Pelvic	Negative	SLN
8	Endometrioid	2	Intermediate	0.7	Paraaortic	Paraaortic	Negative	Non-SLN***
9	Endometrioid	2	Intermediate	9	Pelvic + paraaortic	Pelvic + paraaortic	Pelvic + paraaortic	Non-SLN***
10	Endometrioid	3	Intermediate	0.2	Pelvic	Negative	Negative	SLN
11	Endometrioid	3	Intermediate	0.3	Pelvic	Negative**	Negative	SLN
12	Endometrioid	3	Intermediate	12	Pelvic + paraaortic	Pelvic + paraaortic	Negative	Non-SLN***
13	Endometrioid	3	High	6	Pelvic + paraaortic	Pelvic + paraaortic	Negative	Non-SLN***
14	Endometrioid + serous	2	High	5	Pelvic	Pelvic	Pelvic	SLN
15	Endometrioid + serous	3	High	1.5	Pelvic	Pelvic	Pelvic	Non-SLN***
16	Serous		High	1	Pelvic	Pelvic	Pelvic	Non-SLN***
17	Serous		High	17	Pelvic + paraaortic	Paraaortic**	Negative	Non-SLN****
18	Serous		High	18	Pelvic + paraaortic	Pelvic + paraaortic	Negative	Non-SLN***
19	Serous		High	24	Pelvic + paraaortic	Pelvic + paraaortic	Pelvic + paraaortic	Non-SLN***
20	Serous		High	25	Pelvic + paraaortic	Pelvic + paraaortic	Pelvic + paraaortic	Non-SLN***
21	Clear cell		High	0.4	Pelvic	Negative	Negative	SLN
22	Clear cell		Inconclusive	42	Pelvic + paraaortic	Pelvic + paraaortic	Pelvic + paraaortic	Non-SLN***
23	Carcinosarcoma		High	0.9	Pelvic	Negative	Negative	SLN
24	Carcinosarcoma		High	2	Pelvic	Negative	Negative	SLN
25	Carcinosarcoma		High	18	Pelvic	Pelvic	Negative	Non-SLN***
26	Carcinosarcoma		High	29	Pelvic	Pelvic	Pelvic	Non-SLN***
27	Neuroendocrine		High	80	Pelvic + paraaortic	Pelvic + paraaortic	Pelvic + paraaortic	Non-SLN***

* Risk category: Based on histopathological type and grade, and depth of myometrial infiltration (assessed by preoperative imaging).
** Tumor PET negative.
*** Operated by laparotomy.
**** Converted to laparotomy.

remaining four patients to the omentum, lung/skeleton, small bowel serosa, or the pouch of Douglas. Preoperative detection of non-lymphatic metastases was 5/15 (33 %) with PET/CT compared to 4/15 (27 %) with CT/MRI.

Lymph node findings on pre-operative imaging

The sensitivity to detect metastatic nodes was higher for PET/CT than for CT/MRI. Lymph node metastases were detected in 17/27 (63 %) patients on PET/CT, compared to 11/27 (41 %) on CT/MRI (p = 0.07). The sensitivity, specificity, positive predictive value, negative predictive value, accuracy and likelihood ratios for PET/CT and CT/MRI are presented in Table 3. Of the 26 patients with pelvic lymph node metastases, these metastases were detected in 15 (58 %) on PET/CT, and in 11 (42 %) on CT/MRI (p = 0.22). Of the 10 patients with paraaortic lymph node metastases, these metastases were detected in 10 (100 %) on PET/CT, and 5 (50 %) on CT/MRI (p = 0.06) (Fig. 2). One patient had isolated paraaortic lymph node metastases which was detected on PET/CT, but not on CT/MRI.

Table 3
Preoperative detection of lymph node metastases on PET/CT and CT/MRI by histopathology in removed lymph nodes in the study group.

		Histopathology		Total
		Positive	Negative	
PET/CT	Positive	17	3	20
	Negative	10	155	165
CT/MRI	Positive	11	4	15
	Negative	16	154	170
	Total # (%)	**27 (15)**	**158 (85)**	**185**

PET/CT: Sensitivity 63.0 %. Positive predictive value 85.0 %. Specificity 98.1 %. Negative predictive value 93.9 %. Accuracy 93.0 %. Positive likelihood ratio 32.5, negative likelihood ratio 0.38.
CT/MRI: Sensitivity 40.7 %. Positive predictive value 73.3 %. Specificity 97.5 %. Negative predictive value 90.6 %. Accuracy 89.2 %. Positive likelihood ratio 16.1, negative likelihood ratio 0.61.

Size of lymph node metastases

The median size of metastases detected on PET/CT was 17.0 mm (0.5–80.0 mm) and on CT/MRI 20.0 mm (0.6–80.0 mm). Macro-metastases were more often detected on PET/CT: 13/14 (93 %), compared to CT/MRI: 8/14 (57 %), (p = 0.06). There was no difference in the detection of micro-metastases, 4/13 (31 %) on PET/CT versus 3/13 (23 %) on CT/MRI (p = 1.0).

The median size of lymph node metastases *not* detected was 0.5 mm (0.2–4.5 mm) for PET/CT and 1.2 mm (0.2–18.0 mm) for CT/MRI.

Among the 12 cases of isolated tumor cells in lymph nodes, all were CT/MRI negative, while one (8%) was PET positive.

Detection of lymph node metastases in different risk categories

The distribution of preoperative uterine risk categories was 39 % low-risk, 30 % intermediate-risk and 28 % high-risk. Six patients could not be categorized into a preoperative risk group due to insufficient preoperative histology. The presence of lymph node metastases in the different risk groups, and the detection rates for PET/CT and CT/MRI are shown in Table 4.

Detection in the SLN group

In the patients treated with the SLN algorithm, the sensitivity, specificity and accuracy for PET/CT was 29 %, 98 %, and 91 %, compared to 21 %, 98 %, and 90 % for CT/MRI.

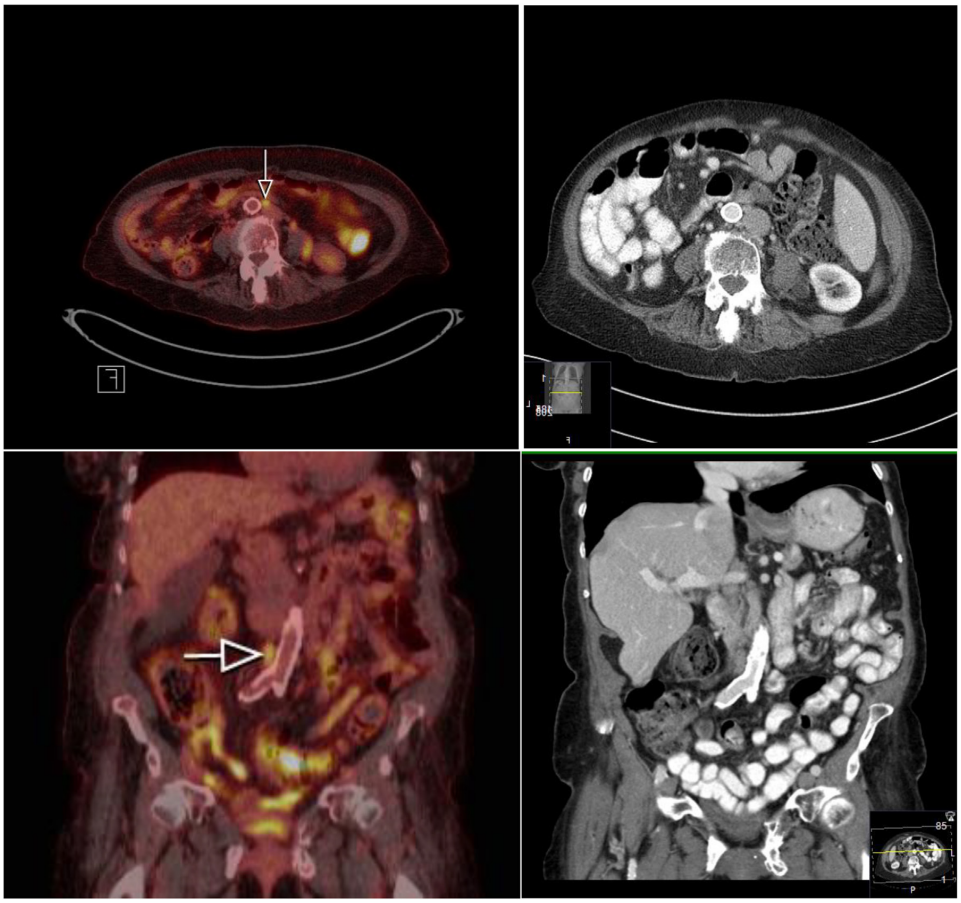

Fig. 2. PET/CT images (left) showing metastatic paraaortic lymph node overseen on CT (right). The pictures are published with the patient's consent.

Table 4
The distribution of risk categories, corresponding rates of lymph node (LN) metastases and detection by CT/MRI vs PET/CT.

Preoperative risk category	Number of patients (%)	Number with LN metastases (%)	Number of LN metastases detected on PET/CT (%)	Number of LN metastases detected on CT/MRI (%)
Low	73 (39)	2 (3)	1 (50)	2 (100)
Intermediate	55 (30)	10 (18)	4 (40)	1 (10)
High	51 (28)	14 (27)	11 (79)	7 (50)
Missing	6 (3)	1 (17)	1 (100)	1 (100)
Total	185	27		

Detection rate in the reference group

Lymph node metastases were detected in 36 of those 173 patients (21 %) operated before 2016 (reference group). There was no statistically significant difference in the detection of lymph node metastases on preoperative CT/MRI between the reference group and the study group; 20/36 (56 %) versus 11/27 (41 %), respectively (p = 0.244).

Discussion

The present study indicates a diagnostic value of PET/CT in the preoperative work-up of endometrial cancer patients, especially in detecting paraaortic lymph node metastases. Several studies have suggested a prognostic benefit of surgical removal of metastatic paraaortic lymph nodes [15–17]. In our study, all paraaortic

metastases were detected on PET/CT, but only half of them on CT/MRI. Most of the patients with paraaortic lymph node metastases also had pelvic lymph node metastases, but one patient had isolated paraaortic lymph node metastases, only detected on PET/CT.

We found a sensitivity of 63 % and a specificity of 98 % to detect lymph node metastases with PET/CT. Chang et al. found a similar sensitivity of 63 % and a specificity of 95 % in a meta-analysis of 243 endometrial cancer patients [18]. In a meta-analysis including 861 patients, Bollineni et al. found a sensitivity of 72 % and a specificity of 94 % [19].

The identification of metastatic lymph nodes on both CT and MRI is based on measurements of node size. A common threshold for considering a lymph node metastatic is 8–10 mm [11,20–25]. However, it is a challenge to differentiate metastatic lymph nodes from benign reactive nodes of similar size, and metastatic lymph nodes of normal size and enlarged reactive lymph nodes can be misclassified [23,25]. PET/CT provides functional data due to increased glucose metabolism in malignant cells, and therefore PET/CT is potentially able to detect smaller lymph node metastases than CT and MRI.

We found a relatively high rate of false negative lymph node metastases on PET/CT. Current PET/CT technology has low spatial resolution and can only detect lesions with a sufficient number of metabolically active malignant cells [9,18,26,27]. The mean value of spatial resolution in PET is 5 mm [21,23,28]. This limited spatial resolution makes the presence of metastases in small lymph nodes hardly detectable.

In our study, PET/CT detected 93 % of the macro-metastases and 31 % of the micro-metastases. In comparison, CT/MRI detected 57 % of the macro-metastases and 23 % of the micro-metastases. The median size of the lymph node metastases *not* detected on PET/CT was 0.5 mm, whereas the median size of the lymph node metastases not detected on CT/MRI was 0.9 mm. Kitajima et al. found a detection rate on PET/CT of only 12.5 % in metastatic lymph nodes measuring 4 mm or less, but 100 % when the lymph nodes were 10 mm or larger [21]. Budak et al. found a 0% detection rate for lymph node metastases 4 mm or less, but a 100 % detection rate for lymph node metastases 10 mm or larger [20].

The relatively high rate of false negative PET/CT results may partly be related to the SLN ultra-staging technique, which allows detection of micro-metastatic deposits too small for detection on PET/CT [29]. Most patients in our study underwent robot-assisted laparoscopic surgery with sentinel lymph node removal and ultra-staging. Tanaka et al. compared the combined diagnostic accuracy of FDG-PET/CT and sentinel lymph node biopsy in the prediction of pelvic lymph node metastases in endometrial cancer. They found that PET/CT had lower sensitivity for lymph node metastases compared to sentinel node biopsy (36.8 % versus 57.9 %), especially in patients with small metastatic lymph nodes [30]. However, the sensitivity was higher for PET/CT than for sentinel node biopsy in lymph node metastases ≥5 mm (62.5 % versus 37.5 %). The limited sensitivity of PET/CT in detection of metastatic lymph nodes in low-/intermediate-risk patients in our study emphasizes the importance of SLN in endometrial cancer patients.

The omittance of paraaortic nodes in SLN algorithms is a potential limitation. Taskin et al. recently evaluated the complementary role of PET/CT in the sentinel lymph node algorithm in high-risk patients. In their study of 38 patients, two out of 10 patients with lymph node metastases had isolated paraaortic metastases diagnosed only on PET/CT [31].

Limitations of our study include the retrospective study design and few patients with lymph node metastases. Further, evaluation of PET/CT and CT/MRI was performed unblinded by the radiologists. To address this, we investigated the detection of lymph node metastases by CT/MRI before and after PET/CT was introduced, and did not find improved CT/MRI detection after the introduction of PET/CT.

In our study we have performed PET only in combination with CT (PET/CT) and used ^{18}F-FDG as tracer. Studies on PET/MRI and use of other tracers have shown various results and should be further explored [10,32–39].

Conclusion

In conclusion, PET/CT was superior to CT and MRI in the detection of lymph node metastases in endometrial cancer. PET/CT has a diagnostic value, in particular in detecting paraaortic lymph node spread in endometrial cancer patients that are candidates for minimal access surgery with SLN mapping. It is reasonable to continue performing PET/CT in the preoperative evaluation of patients with endometrial cancer.

Declaration of Competing Interest

The authors report no declarations of interest.

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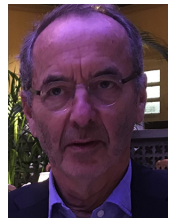

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PAPER II

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Full length article

"Long-term outcome in endometrial cancer patients after robot-assisted laparoscopic surgery with sentinel lymph node mapping"

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ABSTRACT

Objective: Sentinel Lymph Node (SLN) mapping is increasingly used as an alternative to lymphadenectomy in endometrial cancer. There is, however, limited data regarding the clinical outcome and survival after SLN mapping. The aim of the study was to determine long-term outcome data in endometrial cancer patients undergoing robot-assisted laparoscopic surgery and SLN mapping.

Study design: Retrospective cohort study of 108 patients with primary endometrial cancer who underwent robot-assisted laparoscopic surgery and sentinel lymph node mapping using the Memorial Sloan Kettering Cancer Center (MSKCC) algorithm with near-infrared fluorescence detection of indocyanine green for endometrial cancer, from November 20th 2012 to January 1st 2016 at St. Olav's Hospital in Norway. The primary endpoint was recurrence-free survival. Secondary endpoints were overall survival and treatment complications.

Results: Among 108 patients operated in accordance with the SLN algorithm, 17 (16%) had lymph node metastases. Adjuvant chemotherapy was administered on indication endometrial cancer to 36 (33%) of the patients. After a median follow up of 75 months (range 61–98), five (4.6%) patients had recurrence, and three patients had died from the disease. Four of the patients who had recurrence had lymph node metastasis at diagnosis. The 5-year recurrence-free survival was 95.4% (95% CI, 91.5 – 99.3). The 5-year disease-specific survival was 97.2% (95% CI, 94.1 – 100.3). The 5-year overall survival was 92.6% (95% CI, 87.7 – 97.5). Peripheral neuropathy after chemotherapy was the most common complication (9.3%), followed by lower limb lymphedema (2%) and postoperative hernia (2%).

Conclusion: The present study demonstrated excellent oncologic outcome and low long-term treatment complication rate in patients treated according to the SLN algorithm more than five years after diagnosis.

Introduction

Endometrial cancer is the most common gynecological malignancy, accounting for 828 new cases in Norway in 2019 (1). The majority of patients are diagnosed with localized disease, with five-year survival rates of over 95%. However, with regional or distant spread, the survival rates are 69% and 17%, respectively (2).

Lymph nodes are the most common site of extrauterine spread, and lymph node metastasis is a significant prognostic factor in apparently early stage disease (3). The regional lymph node metastatic status has an important prognostic role, while the therapeutic effect of lymph node removal is uncertain (4,5). Thus, it has been debated whether comprehensive lymphadenectomy improves prognosis and if paraaortic lymph nodes should be removed in addition to pelvic nodes (4–6). The sentinel lymph node (SLN) strategy is a compromise between comprehensive lymphadenectomy in high-risk patients and omittance of lymph node removal in low risk patients, allowing sufficient lymph node assessment in patients of all risk categories. Less extensive lymph node removal and surgical trauma are advantages of the SLN approach, which may lead to fewer late effects (7).

Since 2012, the preferred surgical procedure for apparently early stage endometrial cancer at our institution, has been robot-assisted laparoscopic hysterectomy with bilateral salpingo-oophorectomy and SLN mapping using the Memorial Sloan Kettering Cancer Center

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(MSKCC) algorithm with near-infrared (NIR) fluorescence detection of indocyanine green (ICG) (8). In 2016, results from the initial three-year experience in our institution were published, showing an SLN detection rate of 96% and lymph node metastatic rate of 16% overall, 9% in low-risk patients (9). Due to the relative paucity of long-term follow-up data, our aim for this study was to report long-term outcome data in this cohort (10).

Material and methods

Patient population

We included consecutive endometrial cancer patients who underwent robot-assisted laparoscopic surgery with SLN mapping using the MSKCC algorithm with NIR fluorescence detection of ICG from November 2012 through December 2015, at St. Olav's Hospital, Norway. Patients operated by laparotomy or without SLN mapping were excluded. The primary endpoint was recurrence-free survival. Secondary endpoints included overall survival and long-term complications. Information on outcome and complications were collected from the patients' electronic records. Follow-up data were registered from the date of primary surgery through December 2020.

All the surgical procedures were performed by one of three collaborating surgeons, the surgical team had SLN experience from 35 pilot procedures using blue dye.

Categorization of lymph node metastases

The lymph node pathology data were categorized into macro-metastases (tumor clusters $\geq$ 2.0 mm), micro-metastases (tumor clusters between 0.2 and 2.0 mm), and isolated tumor cells (ITCs) (single tumor cells or small tumor clusters $\leq$ 0.2 mm). Cytokeratin-positive cells in immunohistochemistry sections not confirmed in corresponding hematoxylin-eosin (HE) sections, were considered node-negative. Mode of detection, whether the lymph node metastases were detected by routine only or additional immuno-histology, was also recorded.

Adjuvant treatment

The indications for adjuvant chemotherapy were lymph node metastases, non-endometrioid or grade 3 endometrioid histology, and grade 2 endometrioid histology in combination with deep myometrial invasion.

Statistics

Patient characteristics were analyzed using the median (range) for continuous variables and percentages for categorical variables. Recurrence-free survival (RFS) was defined as the time from surgery to the time of recurrence. Disease specific survival (DSS) was defined as the time from surgery to the time of death from disease. RFS, DSS and overall survival (OS) were evaluated within the first 5 years after surgery, and survival curves were estimated with the Kaplan-Meier method. Patients who died were censored at the time of death.

Statistical analyses were performed using International Business Machines Corporation (IBM) Statistical Package for the Social Science (SPSS), version 27.

Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK midt 7193/2019).

Results

Patient population

Out of 219 potential participants, 108 patients were included in the study (Fig. 1). Median follow-up was 75 months (range 61 – 98). The median age was 66.5 years (Table 1). The most frequent histological diagnosis was endometrioid adenocarcinoma, most patients were in FIGO stages IA, IB and IIIC, and 17 patients (16%) had lymph node metastasis at the time of diagnosis (Table 1). SLN detection rate was 96% (78% bilateral). The distribution by anatomic location was: external iliac 51%, obturator 38%, common iliac 9%, parametrial 0.7%, para-aortic 0.6% and presacral 0.4%.

Sixteen of 17 patients had SLN metastasis. Thirty-six (33%) patients received adjuvant chemotherapy with paclitaxel and carboplatin (Supplementary table 1). Additionally, one patient received chemotherapy due to synchronous ovarian cancer. Adjuvant chemotherapy was administered to 14 (82%) of the 17 patients with lymph node metastasis. There was deviation from protocol of unknown reason for one patient with lymph node metastasis, and one patient refused chemotherapy. Adjuvant radiotherapy was not used.

Long-term oncologic outcome

The 5-year recurrence-free survival was 95.4% (95% CI, 91.5 – 99.3), and the 5-year disease-specific survival was 97.2% (95% CI, 94.1 – 100.3) (Fig. 2). The overall survival was 92.6% (95% CI, 87.7 – 97.5), based on three deaths among the five patients with recurrent endometrial cancer and five deaths due to causes other than endometrial cancer. At observation cut-off, recurrence had occurred in five patients (4.6%) (Table 2). Four had stage IIIC disease at diagnosis, while the fifth had low risk stage IA disease, however with positive abdominal cytology (Table 3). The recurrence pattern was unilocal in two patients, pelvic bone and vagina, respectively. The remaining three patients had multilocal recurrence including paraaortic lymph nodes. However, isolated paraaortic node recurrence was not observed. Median time to recurrence was 19 months (range 9 – 39 months).

Eighty-eight of the patients (81%) had stage I disease. Adjuvant chemotherapy was administered to 21 (24%) of these patients. Among the patients with stage I disease the 5-year recurrence-free survival was 98.9% (95% CI, 95.7 – 101.1) and the 5-year disease-specific survival was 100%.

Two patients with lymph node metastases detected on immunohistochemical ultrastaging had adjuvant chemotherapy, one of those relapsed. Adjuvant chemotherapy was also administered to the one patient with ITC. She did not relapse.

Late effects

Lower limb lymphedema after surgery was registered in 2 patients. They underwent bilateral SLN mapping with removal of four and six lymph nodes, respectively. The first patient was obese and had diabetes mellitus with diabetic leg ulcers preoperatively. She did not have lymph node metastases. The second patient without preoperative risk factors, had a micrometastasis detected by ultrastaging.

Postoperative trocar hernia was registered in 2 patients. Vaginal cuff dehiscence was observed 10 months after surgery in 1 patient. Neuropathy due to chemotherapy was noted in 10 patients, 3 were grade 1 and 7 were grade 2 according to the Common Terminology Criteria for Adverse Events (CTCAE).

Discussion

We found that more than five years after primary treatment for endometrial cancer using the SLN algorithm, recurrence-free survival and overall survival were excellent. In addition, long-term treatment

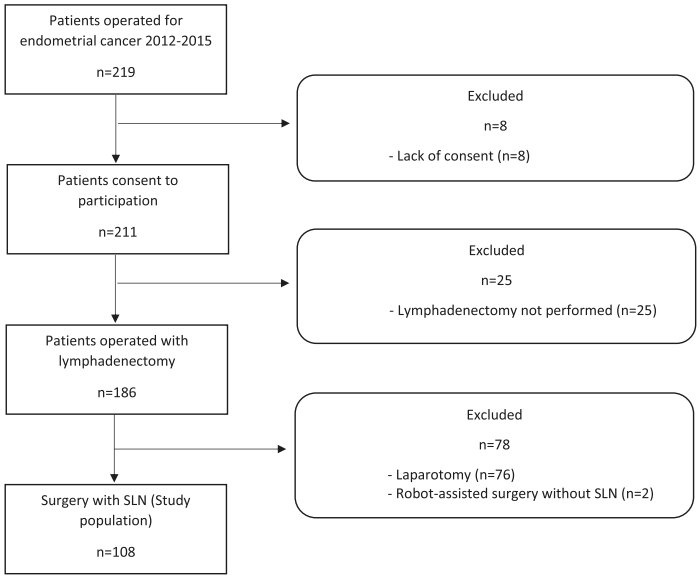

Fig. 1. Study population.

Table 1
Demographic and clinical characteristics (N = 108).

	Median	Range
Age (years)	66.5	35–91
Body mass index (kg/m^2)	27.7 *	17.9–49.6
	N	**Percentage**
Histologic type		
Endometrioid	89	82
Serous	12	11
Clear cell	4	4
Carcinosarcoma	2	2
Mucinous	1	1
FIGO stage		
IA	48	44
IB	40	37
II	1	1
IIIA	2	2
IIIC	17	16
Myometrial invasion		
< 50 %	60	56
≥ 50 %	48	44
Cervical stroma invasion		
No	105	97
Yes	3	3
Blood or lymph vascular space invasion		
No	88	81
Yes	20	19
Postoperative chemotherapy		
No	71	66
Yes	37	34
Peritoneal cytology		
Negative	103	95
Positive	2	2
Not sampled	3	3

* One missing body mass index

complications were rare.

We found a recurrence rate of 4.6% and 5-year disease-specific survival rate of 97.2%, which is in line with results in other studies (11–14). In a systematic review, Bogani et al. reported a 3-year recurrence rate of 4.3% in 853 endometrial cancer patients undergoing SLN mapping. In comparison with conventional lymphadenectomy, the recurrence rate was nonsignificantly lower with SLN mapping (4.3% vs. 7.3%, p = 0.63) (11). Eriksson et al. investigated low risk endometrial cancer patients with endometrioid carcinoma and limited myometrial invasion and found similar 3-year disease-free survival (DFS) for patients treated with the SLN algorithm compared to patients having lymphadenectomy (LND), 94.9% and 96.8%, respectively (p = 0.35) (12). Buda et al. compared the oncologic outcome for patients with apparently early stage endometrial cancer and found a 3-year DFS of 90.4% in the SLN group compared to 89.6% in the LND group (p = 0.433), with a median follow-up of 30 months (range 3 – 75) in the SLN group and 34 months (range 1 – 294) in the LND group (13). In a retrospective analysis of high-risk early stage endometrial cancer, Buda et al. found a recurrence rate after SLN of 9.1% compared to 8.6% after LND (p = 0.86), with a median follow-up time of 20 months (range 5 – 80) in the SLN group and 16 months (range 6 – 88) in the LND group (14). Kogan et al. evaluated the added value of SLN mapping by comparing long-term oncologic outcome after SLN followed by complete pelvic LND (SLN cohort) and complete pelvic LND alone (LND cohort). They found a RFS of 95% in the SLN cohort, similar to 95.4% in our study, and 90% in the LND cohort (15). Their study did not include patients treated exclusively with SLN, and is thus unable to address the safety of omitting rescue LND after SLN mapping. In an American cancer database study, Garzon et al. reported an overall survival in the SLN only group of 90.9%, compared to 92.6% in our study (16). Garzon et al. did not report RFS, DSS or complication data, and their median follow up time was 34.5 (IQR 22.1 – 48.2) months, significantly shorter than our own.

Increased detection of lymph node metastases is associated with increased use of adjuvant therapy (17). Ultrastaging with ultra-sectioning and immune-histochemical (IHC) staining for cytokeratin provides increased detection of low volume lymph node metastases (micrometastases and ITCs) and potential upstaging to stage IIIC disease, especially in low-risk patients (17,18). In our material, four patients with lymph node metastases were detected only by ultrastaging.

The FIRES and FILM trials found low volume nodal disease accounting for > 50% of positive SLNs in endometrial cancer (19,20). Studies in cervix and breast cancers have not demonstrated any benefit of adjuvant chemotherapy in patients with ITC only, and the prognostic significance of detection of low volume disease in endometrial cancer is

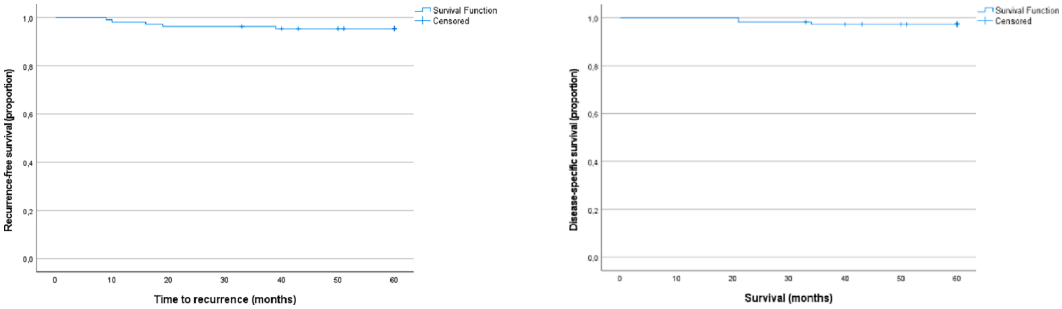

Fig. 2. Kaplan-Meier curves showing recurrence-free survival (left) and disease-specific survival (right) first 5 years after surgery.

Table 2
Clinical and tumor characteristics of the patients with relapsed disease.

Case	Histology	Myometrial invasion	FIGO stage	Preoperative risk category	Adjuvant treatment	Postoperative risk category	Location of first recurrence	Age	Time from surgery to recurrence (months)	Lymph node metastases (location)	Status
1	Endometrioid grade 2	<50 %	IA	Low	None	Low	Multilocal: Omental cake, paraaortic lymph nodes, pleural fluid, ascites, gastrohepatic ligament	74	39	None	Alive with disease
2	Endometrioid grade 3	>50%	IIIC1	Intermediate	Paclitaxel / Carboplatin	High	Pelvic bone	75	9	Pelvis: left side (macromet)	Dead from disease
3	Endometrioid grade 3	>50 %	IIIC1	High	Refused	High	Paraaortic lymph nodes + right ovary	36	10	Pelvis; left side (macromet)	Alive with disease
4	Serous	<50 %	IIIC1	High	Paclitaxel / Carboplatin	High	Paraaortic lymph nodes + vaginal	77	16	Pelvis; left side (micromet)	Dead from disease
5	Serous	>50 %	IIIC1	High	Paclitaxel / Carboplatin	High	Vagina	65	19	Pelvis bilateral (micromet)	Dead from disease

Table 3
The distribution of risk categories, corresponding rates of lymph node metastases and recurrent disease.

Risk category	Number of patients (%)	Number with lymph node metastases (%)	Number with recurrent disease (% of total number of patients in risk category)
Low	45 (42%)	4 (9%)	1 (2%)
Intermediate	35 (32%)	4 (11%)	0 (0%)
High	28 (26%)	9 (32%)	4 (14%)
Total	108 (100%)	17 (16%)	5 (4.6%)

debated (21,22). Bogani et al. found that patients with low volume disease undergoing adjuvant treatment had oncologic outcome similar to patients with negative nodes (23). However, Backes et al. found that patients with exclusively ITCs in SLNs may not have the same benefit from adjuvant therapy compared to patients with macrometastases (24), suggesting that adjuvant treatment should be tailored to uterine and molecular factors rather than based solely on the presence of ITCs (25). In a *meta*-analysis, Gómez-Hadalgo et al. found that the presence of micrometastases or ITCs combined, implied increased risk of recurrence, even in patients who had received adjuvant chemotherapy (26). It is therefore essential to clarify the role of low-volume metastases, especially in patients with otherwise low-risk disease, when adjuvant therapy is often omitted.

The patients in our study received uniform treatment, and none received adjuvant radiotherapy. Due to the lack of survival benefit, adjuvant radiotherapy is often omitted in most endometrial cancer patients in the Nordic countries (27–30). Matei et al. demonstrated no benefit of adding adjuvant radiotherapy to chemotherapy in stage III and IVA endometrial cancer patients (31). In the PORTEC-3 study, however, adjuvant chemotherapy was shown to improve failure-free survival, especially in patients with stage III disease (32).

One concern has been the potential risk of undetected paraaortic lymph node metastases, as the SLN algorithm results in fewer patients having paraaortic lymph node removal – in our material only two patients. Isolated paraaortic lymph node metastases are rare, 3% in endometrial cancer patients with limited myometrial invasion (33). Three of our patients had multifocal relapse including paraaortic nodes, but no isolated paraaortic relapse was observed. In a study investigating the importance of thoroughness of pelvic lymphadenectomy in intermediate and high-risk endometrial cancer patients, Kim et al. demonstrated that the rate of isolated paraaortic lymph node metastases decreased as the number of negative pelvic nodes removed increased (34). This result suggests that the risk of overlooking isolated paraaortic lymph node metastases may be lower following SLN mapping, because pelvic lymph node metastases tend to be more frequently detected with this strategy.

The immediate postoperative complications in our material have

been previously described (9). Significant postoperative complications occurred in five patients (4.6%), two with intraabdominal bleeding on the first postoperative day, one with right iliac fossa trocar incision bleeding, one with abscess in the supraumbilical trocar incision, and finally one patient who developed adductor paralysis due to left obturator nerve injury.

Lymphedema is the most common long-term complication after surgery for endometrial cancer, reported to occur in 27.6 – 41.5% of the patients (35–37). Lower limb lymphedema reduces quality of life, daily function and body image (38). Lymphadenectomy per se, the number of lymph nodes removed, radiotherapy and overweight are associated with increased risk of lymphedema (37,39). The occurrence of lower extremity lymphedema in our study was low, reflecting a significant advantage of the SLN strategy. Our results add to previous studies strongly indicating that removing SLNs results in lower incidence of lower extremity lymphedema and less severe post-operative complications compared to LND (7,40). The most common long-term complication in our study was persistent neuropathy following chemotherapy.

The strength of our study is the long observational time, with a minimum follow-up of 5 years, and a median follow-up of 75 months (range 61 – 98). None of the patients recurred later than 39 months after surgery. The weakness of the study is the retrospective design and the relatively small number of cases. However, since the surgical procedures comprised a significant part of the learning process for the surgeons, it is reasonable to expect similarly good results in a “high volume practice”.

Conclusion

The study supports the finding that SLN mapping is an effective and safe approach in the treatment of patients with endometrial cancer, and non-inferior to traditional lymphadenectomy regarding oncologic outcome. The prognostic value of increased detection of low volume nodal disease and tailoring of adjuvant treatment as a result of ultra-staging, is unclear and further studies are required.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary results

The diagnosis of lymph node metastasis was made by routine HE histology in thirteen patients and by ultrastaging with immunohistochemical detection of cytokeratin in 4 patients. Among the seventeen patients with lymph node metastases, 11 (65%) had macrometastases, five (29%) micrometastases, and one patient (6%) had isolated tumor cells (ITCs). Of the four patients with metastatic disease detected with ultrastaging, one had macrometastasis, two had micrometastasis and one had ITC. The lymph node metastasis rates according to prognostic risk group were 9% for low, 11% for intermediate, and 32% for high risk, respectively. Immediate (within 3 weeks) complications were encountered in 4.6% of the patients. Of the six patients with low volume disease, defined as micrometastases or ITCs, 2 (33%) were preoperatively low-risk, one (17%) was intermediate-risk and three (50%) were high-risk. All 17 patients had lymph node metastases in the pelvis, one had also paraaortic lymph node metastases.

Supplementary tables

Supplementary table S1: Patients receiving chemotherapy (N=37).

Stage	#	Histology
1A	8	5 serous
		2 endometrioid grade 2
		1 synchronous ovarian cancer stage 1C
1B	13	7 endometrioid
		- 3 grade 2
		- 4 grade 3
		2 serous
		1 carcinosarcoma
		3 clear cell
3A	2	1 carcinosarcoma
		1 endometrioid grade 1
3C	14	5 serous
		9 endometrioid
		- 2 grade 1
		- 3 grade 2
		- 4 grade 3
Refused:		
Stage 1A	1	Endometrioid grade 2
Stage 3C	1	Endometrioid grade 3

Supplementary table S2: Distribution of lymph node metastasis category and preoperative risk category.

	Macrometastasis	Micrometastasis	ITC	Total
Low risk	2	1	1	4
Intermediate risk	3	1	0	4
High risk	6	3	0	9
Total	11	5	1	17

Supplementary table S3: Distribution of patients with lymph node metastases and detection vs preoperative risk category.

	Routine HE	Ultrastaging	Total
Low risk	3	1	4
Intermediate risk	2	2	4
High risk	8	1	9
Total	13	4	17

PAPER III

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Self-reported lower extremity lymphedema and quality of life after surgical staging of endometrial carcinoma: A population based cross-sectional study

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HIGHLIGHTS

- Lymphedema is more prevalent after lymphadenectomy compared to sentinel lymph node biopsy.
- Adding sentinel lymph node to hysterectomy does not increase the prevalence of lymphedema.
- Lower extremity lymphedema is associated with lower quality of life.
- Questionnaires may not distinguish symptoms of lymphedema from musculoskeletal complaints.

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ABSTRACT

Objectives. Sentinel lymph node biopsy (SLN) has replaced lymphadenectomy in staging of endometrial carcinoma. The aims of the study were to explore the prevalence of self-reported lymphedema (LEL), identify factors associated with LEL, compare quality of life (QoL) scores using thresholds of clinical importance, and assess correlation between different questionnaires.

Methods. Women who underwent staging for endometrial carcinoma from 2006 to 2021 were invited to complete the Lower Extremity Lymphedema Screening Questionnaire (LELSQ), EORTC QLQ-C30, QLQ-EN24 and EQ-5D-5L.

Results. Of 2156 invited survivors, 61% participated in the study, whereof 1127 were evaluable by LELSQ. The LEL prevalence was 51%, 36% and 40% after lymphadenectomy, SLN and hysterectomy, respectively ($p < 0.001$). Higher BMI, undergoing lymphadenectomy and receiving adjuvant chemotherapy were associated with LEL; odds ratios 1.07 (95% CI 1.05–1.09), 1.42 (95% CI 1.03–1.97) and 1.43 (95% CI 1.08–1.89) respectively. QoL was lower for women with LEL compared to those without. In women *with* musculoskeletal complaints the prevalence of LEL was 59%, 50% and 53% after lymphadenectomy, SLN and hysterectomy ($p = 0.115$), respectively, compared to 39%, 17% and 18% ($p < 0.001$) in women *without* musculoskeletal complaints. Spearman's correlation was moderate to strong between the questionnaires.

Conclusion. SLN implementation is not associated with increased LEL prevalence compared to hysterectomy alone, but is associated with a significantly lower prevalence compared to lymphadenectomy. LEL is associated with lower QoL. Our study demonstrates moderate to strong correlation between self-reported LEL and QoL

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scores. Available questionnaires may not distinguish between symptoms caused by LEL and musculoskeletal disease.

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1. Introduction

Most women diagnosed with endometrial carcinoma present at an early stage, carrying good prognosis [1]. Recommended treatment for assumed early-stage endometrial carcinoma is minimally invasive hysterectomy, bilateral salpingo-oophorectomy with or without nodal assessment [2]. Lower extremity lymphedema (LEL) is a long-term complication after several cancer treatments, including endometrial carcinoma [3]. Replacing lymphadenectomy (LND) with a sentinel lymph node algorithm (SLN), has showed a reduction in risk of developing LEL [4,5]. Other risk factors for LEL are older age, increased body mass index (BMI) and adjuvant chemo-radiation therapy [6–8]. There is no gold standard for measuring or reporting LEL. Several methods exist, including patient-reported outcome measures (PROMs). LEL prevalence is reported from three to 70% using various measuring tools [4,6,8–10].

Previous studies have demonstrated reduced Quality of Life (QoL) in women with LEL [7,8,11,12]. The European Organisation for Research and Treatment of Cancer (EORTC) QoL group has recently established thresholds for clinical importance of absolute scores in order to better interpret differences in scores from individual patients at a single point in time [13]. Comparison of QoL applying these thresholds for clinically important changes has not previously been reported for endometrial carcinoma survivors.

The primary aim of this study is to explore the post-operative prevalence of self-reported LEL in endometrial carcinoma survivors stratified by nodal assessment, and to identify risk factors associated with the development of LEL. Secondary aims are to compare QoL scores using thresholds of clinical importance, and assess correlation between PROMs tools.

2. Materials and methods

This study was approved by Regional Committees for Medical and Health Research Ethics in South East and Central Norway (References 149,597 and 7193/2019). All women provided informed consent. Data were handled in accordance with relevant ethical regulations.

This multicenter, population-based cross-sectional study included women treated for assumed early-stage endometrial carcinoma from 2006 to 2021 at Oslo University Hospital (OUH) and 2012 to 2021 at St. Olav's Hospital. Both hospitals are tertiary referral centers for gynecologic cancers, covering 66% of the Norwegian population and were selected as they represent the only regions where the SLN approach was implemented during the study period (Supplemental Fig. 1). Both institutions use the Memorial Sloan Kettering Cancer Centre (MSKCC) SLN algorithm [14]. Nodal assessment was defined as *hysterectomy* if no nodal assessment was performed, as *SLN* if the MSKCC SLN algorithm was adhered to and as *lymphadenectomy (LND)* if pelvic LND with or without para-aortic LND was performed. The cohorts were mutually exclusive.

A power calculation was performed prior to study start. With a two-sided significance level of 5% and a power of 90%, 227 patients were needed in each group to detect a 15% difference in prevalence of lower extremity lymphedema between cohorts. This absolute difference was based on the expected LEL prevalence of 35% in the SLN and hysterectomy cohorts and 50% in the lymphadenectomy cohort based on previous studies. This was less than the number of potential respondents (2156 women) and allows adjusting for several potential confounding variables in this observational design setting.

2.1. Patient-reported outcome measures

A mixed-mode survey design was used to optimize participation rate (Fig. 1). The survey included questions regarding demographics, comorbidities and the LELSQ. In order to evaluate QoL by a cancer-specific, diagnosis-specific and generic PROMs tool; EORTC QLQ-C30, EORTC QLQ-EN24 and EQ-5D-5L were selected [15–17].

2.2. LELSQ

LELSQ is a validated questionnaire consisting of 13 graded questions. At least seven questions must be answered to be evaluable [18]. Self-reported LEL was defined as scoring ≥5 points out of 52 possible points on LELSQ or being diagnosed with LEL by health care professionals. Only women with newly developed LEL after surgery were included, i.e. patients with a diagnosis of LEL prior to surgery were not included in this analysis. LELSQ was chosen in order to compare results with previously published studies [7,8,18–20]. Our group has translated and tested LELSQ in a Norwegian population [21].

2.3. EQ-5D-5L

EQ-5D-5 L^{17} measures health status in five domains, using five levels in each domain. The EQ-5D-5L answer-set is transformed into a QoL-index from 0 to 1, using the EQ-5D-5L scoring manual [22]. We used the British value set [23] in this study and denoted the index as Quality Adjusted Life Year weight (QALYw). EQ-5D-5L also includes a visual analog scale (VAS) ranging from 0 ("the worst health you can imagine") to 100 ("the best health you can imagine"), where death is not included on the scale.

2.4. EORTC QLQ-C30 and EORTC QLQ-EN24

EORTC QLQ-C30 [24] and EORTC QLQ-EN24 [16] are developed to evaluate QoL in cancer patients. QLQ-C30 consists of 30 items structured into a global health status/QoL scale, five functional scales, three symptom scales, and six single items. QLQ-EN24 consists of 24 endometrial carcinoma-specific items structured into ten symptom scales and three functional scales. All questions are graded; "none", "a little", "quite a bit" or "very much". The scoring of the QLQ-C30 and QLQ-EN24 were performed according to scoring manual of the EORTC QoL group [15]. Thresholds of clinical importance was defined according to the EORTC QoL Group where scale scores of EORTC QLQ-C30 were dichotomized into categories over or under the thresholds of clinical importance [13].

Demographics, comorbidities, tumor- and treatment-related factors were extracted from electronic medical records. A modified version of the Self-Administered Comorbidity Questionnaire [25] adding "deep venous thrombosis", was used to collect self-reported comorbidities at survey [26]. *Musculoskeletal complaints* was defined as arthritis and/or back pain and/or rheumatoid arthritis. Follow-up time was defined as months from surgery to first invitation to survey.

2.5. Statistical analysis

Descriptive statistics were provided for baseline variables. Categorical variables were presented as frequencies and proportions, continuous variables as mean with standard deviation (SD) or median with

Fig. 1. Flow chart showing timeline for participation recruitment.
A mixed-mode survey design was used to optimize participation rate. The first mailing included study information and an invitation to participate in an online survey. Invited women were informed that a paper version of the questionnaire would be mailed to non-responders after electronic reminders. Non-responders were reminded by text messages containing direct links to the online survey two and four weeks later. Finally, a paper version with a pre-paid envelope was distributed to non-responders one month after the final text message.

interquartile range (IQR). Comparison of cohorts stratified by nodal assessment (hysterectomy, SLN and LND) or LEL status (negative/positive) was performed by chi2 test, *t*-test or ANOVA and Mann-Whitney or Kruskal-Wallis tests, as appropriate.

Logistic regression analysis was used to investigate associations of baseline covariates with self-reported LEL. Variables included in the multivariable model were BMI at surgery, nodal assessment and adjuvant therapy. Nodal count and histology were omitted from the model due to their high correlation with nodal assessment and adjuvant treatment.

To further explore a potential relationship with musculoskeletal complaints and LEL, regression analysis was stratified by presence or absence of musculoskeletal complaints. In addition to investigating *type* of nodal assessment, we also considered the number of nodes removed. A log transformation was applied due to its non-linear relationship with LEL.

Relationship between the global health status/QoL scale and QALYw and VAS, and participants´ individual scores from LELSQ and the lymphedema domain in EORTC QLQ-EN24 were assessed by Spearman's correlation coefficient with 95% confidence interval (CI) calculated by bootstrap estimation. A correlation coefficient of 0.40–0.69 was considered as moderate, and > 0.70 as strong.

The significant level was set to $p < 0.05$. Stata/SE 17.0 was used for statistical analysis.

3. Results

Of 2156 invited survivors, 1226 (61%) responded to the survey (Fig. 2). Responders were younger, had shorter follow-up, lower BMI at surgery and received more adjuvant chemotherapy than non-responders (Supplement Table 1). Of responders, 90/1226 were not evaluable by LELSQ. Two patients underwent para-aortic LND alone and were excluded from further analysis. The remaining 1134 responders were stratified according to nodal assessment; 35% underwent LND, 34% SLN and 31% hysterectomy (Supplemental Table 2). The SLN-cohort was older at surgery and younger at survey. There was no significant difference in BMI between cohorts. SLN mapping was bilateral in 80% and unilateral in 15% of women.

Regarding self-reported comorbidities at time of survey, no statistically significant differences were observed between cohorts (data not shown).

Median number of lymph nodes removed was 21 (IQR 14–28) and three (IQR 2–5) in the LND and SLN cohorts, respectively. More patients in the LND cohort received adjuvant therapy. No significant difference in recurrence was detected when comparing LND and SLN cohorts; 8% and 5% respectively ($p = 0.18$).

3.1. Lymphedema

The LELSQ was evaluable for 1127 women, where the overall LEL-prevalence was 42%. For the LND- SLN- and hysterectomy cohorts the prevalence was 51%, 36% and 40% respectively ($p < 0.001$) (Table 1).

Mean age at survey was 71.2 years, not differing between groups. LEL-positive women had longer follow-up; 70 vs 62 months ($p = 0.006$), higher BMI; 29.9 vs 27.6 ($p < 0.001$), and were more frequently diagnosed with hypertension at surgery; 42% vs 34% ($p = 0.005$) than LEL-negative women. For self-reported comorbidities at survey; hypertension, ulcer/stomach disease, anemia/blood disease, depression, arthritis, back pain, rheumatoid arthritis, deep venous thrombosis/pulmonary embolism and "other disease/health complaint" were more common in the LEL-positive group. There was no difference between groups regarding FIGO stage. In the LEL-positive group, a median of four lymph nodes (IQR 0–19) were removed, compared to three (IQR 0–10) in the LEL-negative group ($p < 0.005$). Women with self-reported LEL more often received adjuvant chemotherapy. Eight of 1127 (<1%) patients received adjuvant radiotherapy, three in the LEL-negative group and five in the LEL-positive group.

When exploring associations of LEL, adjusting for relevant variables in the multivariate model; BMI at surgery (per one unit increase), LND (hysterectomy as reference) and adjuvant chemotherapy remained significantly associated with LEL; OR 1.07 (95% CI 1.05–1.09), OR 1.42 (95% CI 1.03–1.97), and OR 1.43 (95% CI 1.08–1.89) respectively (Table 2).

Musculoskeletal complaints were reported by 637 (56%) of responders (Table 1), of which 98% reported that musculoskeletal problems affected activities of daily living (data not shown). Women who self-reported musculoskeletal complaints were older and had higher BMI (data not shown).

When stratifying by musculoskeletal complaints (Fig. 3); for women *with* musculoskeletal complaints, the prevalence of self-reported LEL *did not* differ between nodal assessment cohorts; 59%, 50% and 53% after LND, SLN and hysterectomy, respectively ($p = 0.115$). For women *without* musculoskeletal complaints the prevalence of self-reported LEL *did* differ between nodal assessment cohorts; 39%, 17%, 18% for LND, SLN and hysterectomy, respectively ($p < 0.001$). The prevalence of self-reported LEL was significantly lower for women *without* musculoskeletal complaints when compared to women *with* musculoskeletal complaints in the corresponding nodal assessment cohort; 39% vs 59%, 17% vs 50% and 18% vs 53% for LND, SLN and hysterectomy, respectively ($p < 0.001$) (Fig. 3).

Further, for women with musculoskeletal complaints, BMI and adjuvant chemotherapy were significantly associated with scoring positive for LEL, while type of nodal assessment was not (Table 2). For women

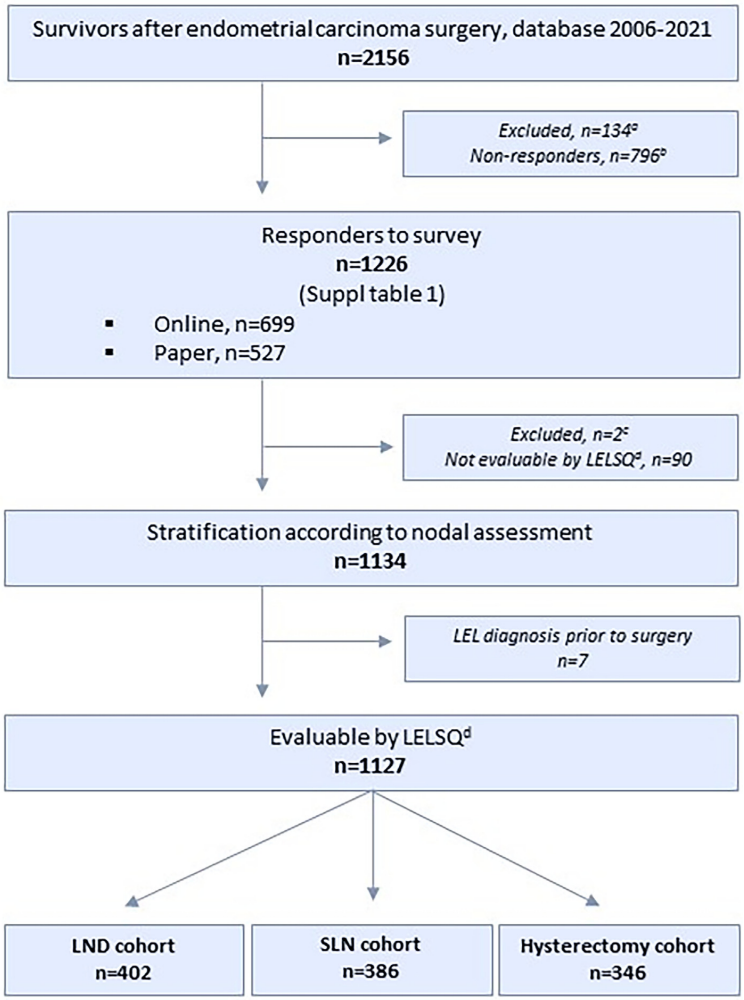

Fig. 2. Consort flow chart showing study recruitment.
(LEL = Lower extremity lymphedema, LELSQ = Lower Extremity Lymphedema Screening Questionnaire, LND = Lymphadenectomy, SLN = Sentinel lymph node biopsy, PALND=Para-aortic lymphadenectomy).

without musculoskeletal complaints, BMI and LND were significantly associated with scoring positive for LEL (Table 2).

In further analysis, using the log of number of nodes removed, there was a positive association with LEL (OR 1.24, 95% CI 1.08–1.42). BMI and adjuvant chemotherapy remained significant in this model (Supplement Table 3).

3.2. Quality of life

Women with LEL had significant more problems compared to women without LEL, in all domains of QLQ-C30 (Table 3). The proportion of patients with LEL over or under the threshold for clinical importance for functional and symptoms scales, ranged from 6% (appetite loss) to 74% (physical functioning).

Median QALYw and VAS scores were 0.94 and 80 for LEL-negative women, and 0.81 and 65 for LEL-positive women ($p < 0.001$) (Supplemental Table 4).

Compared to LEL negative women, LEL-positive women scored significantly lower in all domains of EORTC QLQ-C30 and EORTC QLQ-EN24, except sexual enjoyment and sexual interest (Supplemental Table 2).

The relationship between participants' LELSQ scores and EORTC QLQ-EN24 lymphedema domain scores was strong; Spearman's correlation coefficient 0.83 (95% CI 0.81–0.85). The relationship between EORTC QLQ-C30 global health status/QoL scale, and QALYw and VAS were moderate; 0.67 (95% CI 0.63–0.71) and 0.79 (95% CI 0.76–0.81) (Supplemental Table 4).

4. Discussion

4.1. Principal findings

In this unselected population, 42% of women scored positive for LEL after surgical staging for endometrial carcinoma. Prevalence of LEL was

Table 1
Clinicopathological characteristics according to self-reported lower extremity lymphedema (LEL).

Demographic characteristics	Evaluable by LELSQ[a]	LEL negative	LEL positive	
	$n = 1127$	$n = 651$ (58%)	$n = 476$ (42%)	p-value
Age at surgery (years), mean (SD)	64.5 (9.4)	64.4 (9.0)	64.6 (9.9)	$p = 0.790$
Follow-up time (months), median (interquartile)	71 (39–122)	62 (29–107)	70 (38.5–122.5)	$p = 0.006$
Age at survey (years), mean (SD)	71.2 (9.2)	70.8 (8.9)	71.7 (9.2)	$p = 0.124$
BMI at surgery (m/kg^2), mean (SD) $n = 1092$	28.6 (6.2)	27.6 (5.8)	29.9 (6.6)	$p < 0.001$
Self-reported BMI at survey (m/kg^2), $n = 1099$	28.0 (5.7)	27.1 (5.2)	29.4 (6.1)	$p < 0.001$
Comorbidities at surgery				
Hypertension $n = 1127$	421 (37%)	221 (34%)	200 (42%)	$p = 0.005$
Diabetes mellitus $n = 1127$	110 (10%)	61 (9%)	49 (10%)	$p = 0.432$
COPD $n = 1127$	26 (2%)	12 (2%)	14 (3%)	$p = 0.220$
Coronary artery disease $n = 1127$	31 (3%)	18 (3%)	13 (3%)	$p = 0.985$
Previous deep venous thrombosis or Pulmonary Embolism $n = 1127$	32 (3%)	15 (2%)	17 (4%)	$p = 0.202$
Dementia or cognitive impairment $n = 1127$	1 (<1%)	1 (<1%)	0	$p = 0.394$
Cerebrovascular disease or Transitory Ischemic Attack $n = 1121$	30 (3%)	17 (3%)	13 (3%)	$p = 0.874$
Self-reported comorbidities at survey				
Self-reported hypertension $n = 1069$	469 (41%)	245 (38%)	224 (47%)	$p = 0.001$
Self-reported ulcer/stomach disease $n = 1016$	21 (2%)	7 (1%)	14 (3%)	$p = 0.016$
Self-reported anemia or other blood disease $n = 1013$	35 (3%)	11 (2%)	24 (5%)	$p = 0.001$
Self-reported depression $n = 1015$	150 (13%)	66 (10%)	84 (18%)	$p < 0.001$
Self-reported arthritis[b] $n = 1048$	445 (39%)	190 (29%)	255 (54%)	$p < 0.001$
Self-reported back pain $n = 1042$	431 (38%)	189 (29%)	242 (51%)	$p < 0.001$
Self-reported rheumatoid arthritis $n = 1007$	69 (6%)	20 (3%)	49 (10%)	$p < 0.001$
Self-reported deep venous thrombosis/pulmonary embolism $n = 1018$	64 (6%)	28 (4%)	36 (7%)	$p = 0.010$
Other disease/health complaint[c] $n = 896$	343 (30%)	159 (24%)	184 (38%)	$p < 0.001$
Muscle/skeletal complaints combined (arthritis/back pain/rheumatoid arthritis)[d] $n = 1078$	637 (56%)	292 (45%)	345 (72%)	$p < 0.001$
Self-reported heart disease $n = 1026$	129 (13%)	71 (11%)	58 (12%)	$p = 0.357$
Self-reported lung disease $n = 1015$	102 (9%)	52 (8%)	50 (10%)	$p = 0.099$
Self-reported diabetes mellitus $n = 1030$	154 (14%)	85 (13%)	69 (14%)	$p = 0.389$
Self-reported renal disease $n = 1008$	22 (2%)	10 (2%)	12 (3%)	$p = 0.194$
Self-reported liver disease $n = 1009$	4 (<1%)	2 (<1%)	2 (<1%)	$p = 0.709$
Self-reported cancer (other than endometrial) $n = 1034$	242 (22%)	142 (22%)	100 (21%)	$p = 0.909$
Final stage (FIGO 2009)				$p = 0.246$
I	953 (84%)	563 (86%)	390 (82%)	
II	49 (4%)	25 (4%)	24 (5%)	
III (A + B)	28 (2%)	14 (2%)	14 (3%)	
III C	88 (8%)	43 (7%)	45 (9%)	
IV	9 (<1%)	6 (1%)	3 (<1%)	
Final histology				p = 0.001
Endometrioid	865 (76%)	523 (80%)	342 (72%)	
Non-endometrioid	262 (23%)	128 (20%)	134 (28%)	
Nodal assessment				p < 0.001
Hysterectomy	344 (31%)	208 (32%)	136 (29%)	
SLN algorithm	385 (34%)	246 (38%)	139 (29%)	
LND	398 (35%)	197 (30%)	201 (42%)	
Nodes removed				
Median (interquartile), $n = 1122$	3 (0–15)	3 (0−10)	4 (0–19)	p = 0.005
Adjuvant therapy				p = 0.006
None	727 (65%)	442 (68%)	285 (60%)	
Chemotherapy only	384 (34%)	199 (31%)	185 (39%)	
Radiotherapy w/wo chemo	8 (<1%)	3 (<1%)	5 (1%)	
Unknown/missing	8 (<1%)	7 (1%)	1 (<1%)	
Recurrence				$p = 0.169$
No	1054 (94%)	615 (94%)	439 (92%)	
Yes	65 (6%)	30 (5%)	34 (7%)	
Unknown/missing	9 (<1%)	6 (1%)	3 (<1%)	

[a] Lower Extremity Lymphedema Screening Questionnaires.
[b] Osteoarthritis or degenerative arthritis.
[c] Other disease/health complaint is not further specified.
[d] Minimum one of the three complaints.

higher in women after LND than after SLN or hysterectomy, and similar for the SLN- and hysterectomy-cohorts. Other independent risk factors for LEL were increasing BMI and adjuvant chemotherapy. In women who self-reported musculoskeletal complaints, nodal assessment did not influence self-reported LEL.

Women with LEL reported lower QoL in all domains of EORTC QLQ-C30 assessed by a novel threshold for clinical importance, not previously assessed for endometrial carcinoma survivors. The correlations between EORTC QLQ-C30 global health status/QoL scale and QALYw and VAS by EQ-5D-5L, and the correlation between LELSQ and the EORTC QLQ-EN24 lymphedema domain were all moderate to strong.

5. Results in the context of what is known

5.1. Adding a SLN algorithm to hysterectomy alone does not increase prevalence of LEL

The higher prevalence of LEL in women after LND compared to SLN or hysterectomy alone are in line with previous studies [7,8]. Our findings of similar prevalence of LEL after SLN and hysterectomy alone are not previously reported in large studies. Unlike previous studies, women with failed mapping undergoing uni- or bilateral side-specific LND are included in the SLN-cohort as per intention-

Table 2
Multivariable logistic regression analysis for scoring positive for lower extremity lymphedema, also stratified by musculoskeletal complaints, $n = 1122$.

Characteristics	Total	Musculoskeletal complaints	No musculoskeletal complaints
	OR (95% CI)	OR (95% CI)	OR (95% CI)
BMI at surgery (kg/m^2)[a]	1.07 (1.05–1.09)	1.06 (1.03–1.09)	1.05 (1.01–1.09)
LND[b,c]	1.42 (1.03–1.97)	1.15 (0.74–1.78)	2.64 (1.47–4.75)
SLN[b,d]	0.75 (0.54–1.03)	0.73 (0.48–1.12)	0.82 (0.44–1.53)
Chemotherapy[e]	1.43 (1.08–1.89)	1.49 (1.02–2.15)	1.18 (0.70–1.96)

OR = odds ratio, CI = confidence interval.
[a] One unit increase.
[b] Hysterectomy as reference.
[c] LND = Pelvic +/− para-aortic lymphadenectomy.
[d] SLN = Sentinel Lymph Node Biopsy.
[e] No adjuvant therapy as reference.

to-treat, irrespective of number of nodes removed [7,8,10]. The reported prevalence of LEL after surgery and adjuvant chemotherapy in this mainly radiotherapy-naïve population is in line with previously published findings, indicating that receipt of *any* adjuvant therapy may negatively influence development of LEL. Forsse et al. described an increased lymphedema score after adjuvant chemotherapy compared to nodal staging without chemotherapy [12]. This differs from our findings where both LND and adjuvant chemotherapy where associated with LEL. Despite chemotherapy being more commonly administered in the SLN cohort compared to hysterectomy, this does not seem to increase LEL prevalence for the SLN cohort.

5.2. Musculoskeletal complaints may mimic LEL symptoms

To our knowledge, no previous studies have reported the prevalence of musculoskeletal disease in endometrial carcinoma survivors and its potential influence on scoring positive for LEL. In our study, the prevalence of underlying musculoskeletal complaints is in line with the general population of elderly females in Norway (50%) [27]. Questions used to capture LEL in the LELSQ are similar to symptoms commonly reported by patients with musculoskeletal disease such as pain, stiffness and swelling.{Miller, 1990 #348} Due to overlapping symptoms of musculoskeletal complaints and LEL, the LELSQ may be unable to differentiate between these conditions.

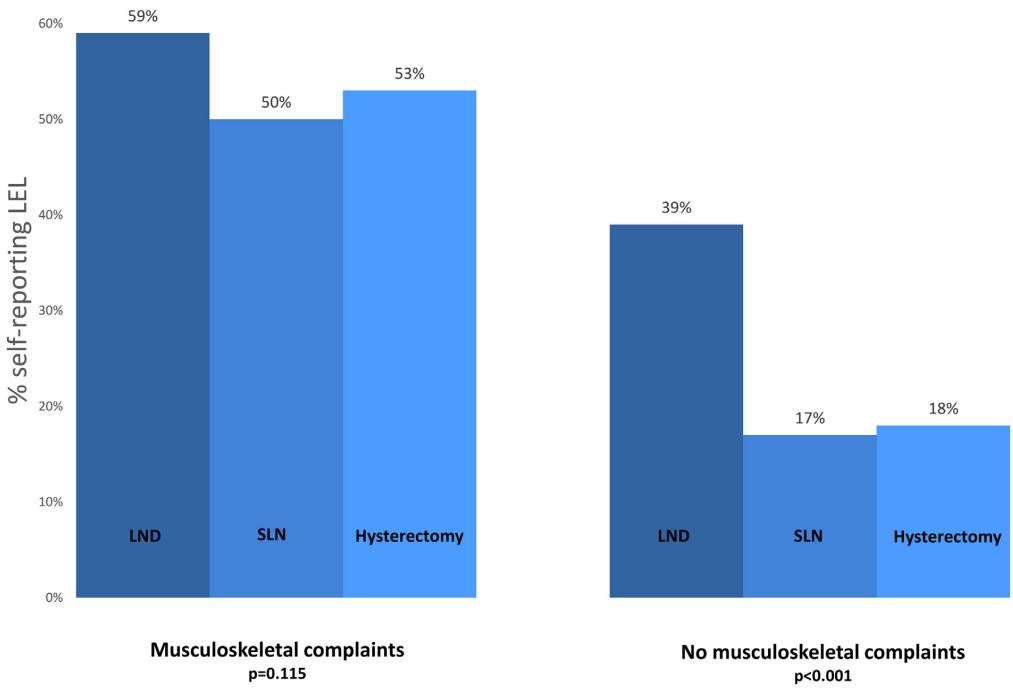

Fig. 3. Bar chart showing the prevalence of LEL stratified by musculoskeletal complaints.
For women *with* musculoskeletal complaints the prevalence of self-reported LEL *did not* differ between nodal assessment cohorts. For women *without* musculoskeletal complaints the prevalence of self-reported LEL *did* differ between nodal assessment cohorts.
The prevalence of self-reported LEL was significantly lower for women *without* musculoskeletal complaints when compared to women *with* musculoskeletal complaints in the corresponding nodal assessment cohort ($p < 0.001$).
(LEL = Lower extremity lymphedema, LND = Lymphadenectomy, SLN = Sentinel lymph node biopsy).

Table 3
Quality of Life measured by EORTC QLQ-C30 reported as the % of women under or over the threshold for clinical importance determined by the EORTC QoL group.

	LEL negative n = 651 (58%)	LEL positive n = 476 (42%)	p-value
Functional scale	% of women under threshold determined by EORTC Quality of Life group		
Physical functioning $n = 1095$	34%	74%	$p < 0.001$
Role functioning $n = 1109$	7%	28%	$p < 0.001$
Emotional Functioning n = 1092	13%	33%	$p < 0.001$
Cognitive function $n = 1004$	15%	34%	$p < 0.001$
Social function $n = 1107$	8%	27%	$p < 0.001$
Symptom scale	% of women over threshold determined by EORTC QoL group		
Fatigue $n = 1102$	18%	50%	$p < 0.001$
Nausea and vomiting $n = 1110$	10%	25%	$p < 0.001$
Pain $n = 1100$	27%	69%	$p < 0.001$
Dyspnea $n = 1117$	30%	57%	$p < 0.001$
Sleep disturbance n = 1117	17%	37%	$p < 0.001$
Appetite loss $n = 1116$	3%	6%	$p < 0.002$
Constipation $n = 661$	8%	18%	$p < 0.001$
Diarrhea $n = 1111$	28%	44%	$p < 0.001$
Financial difficulties $n = 1108$	7%	20%	$p < 0.001$

P-values describe the statistical differences between LEL positive and negative women.

This hypothesis is supported by our finding that type of nodal assessment (LND, SLN or hysterectomy alone) was *not* associated with scoring positive for LEL in women *with* self-reported musculoskeletal complaints (Fig. 3). It is also supported by the finding of significant differences in prevalence of women scoring positive for LEL after hysterectomy and SLN in women with and without self-reported musculoskeletal disease. In our study, 17% and 18% of women *without* musculoskeletal complaints scored positive for LEL after SLN or hysterectomy. This prevalence is lower than for those with musculoskeletal disease where 50% and 53% scored positive for LEL after SLN and hysterectomy respectively. This is also lower than previously published results from cross-sectional studies in an American population; 27% after SLN[8] and 36% after hysterectomy [7].

5.3. QoL is lower in women with LEL according to a novel threshold for clinical importance

Previous studies report differences in QoL by statistically significant levels [8] or by ≥10 points difference as described by Osoba [7]. We compared QoL by a novel method for interpretation of the EORTC QLQ-C30 score; *threshold for clinical importance*. We believe this method adds a more clinically meaningful interpretation of scores.

5.4. EQ-5D-5L and EORTC QLQ-C30 can be considered comparable for QoL evaluation

Comparing EORTC QLQ-C30 scores to EQ-5D-5L in endometrial carcinoma survivors has not previously been reported. As demonstrated in our study, nodal assessment is correlated to development of LEL with subsequent detriment to QoL. Based on our results, QALYw and VAS as per EQ-5D-5L can be considered comparable to EORTC QLQ-C30 when reporting QoL. We demonstrated a strong correlation between participants' individual LELSQ scores and EORTC QLQ-EN24 lymphedema specific domain scores.

6. Clinical implications

Patients with endometrial carcinoma scheduled for staging surgery should be counselled regarding increasing BMI as a possibly modifiable risk factor for LEL. The potential risk of LEL after SLN biopsy should not be used to argue against implementation of an SLN algorithm, even in assumed low-risk patients, as similar prevalence of self-reported LEL are seen in women after hysterectomy alone and SLN. The risk of LEL is associated with each additional lymph node removed, highlighting the importance of successful *bilateral* SLN mapping, thus limiting nodal removal to only sentinel lymph nodes in contrast to multiple nodes removed for lymphadenectomy.

Adjuvant chemotherapy was significantly associated with LEL and should be limited to women who will truly benefit from it. This can be achieved by further developing individual treatment algorithms incorporating predictive and prognostic biomarkers, molecular classification, and alternative targeted therapies.

7. Research implications

In our study, women who scored positive for LEL more often self-report musculoskeletal complaints, possibly reflecting overlapping risk factors for development of LEL and musculoskeletal disorders such as increasing BMI and age, as well as overlapping symptoms. This relationship has not been described previously and should be investigated further. As cross-sectional studies are hypothesis generating, we hypothesizes that the PROMs used in this study may not be able to capture LEL alone, but actually capture musculoskeletal complaints as well. Questionnaires for LEL are commonly developed based on questionnaires intended for breast cancer survivors [18,28]. Musculoskeletal complaints may not overlap with symptoms and risk factors for upper extremity lymphedema. Creation and validation of PROMs capturing LEL should address this.

8. Strengths and limitations

This is a large population-based study regarding self-reported LEL and QoL in endometrial carcinoma survivors. Importantly, this study had a robust response rate and was performed in a public health care system with an unselected patient population.

The retrospective design is a limitation with its inherent biases. Although the non-randomized study design may be a limitation, nodal assessment groups were equally represented in this study, and responders did not vary greatly from non-responders regarding known characteristics. Some non-responders may be too frail to respond to the questionnaire, and thus not be represented in the LEL and QoL data. This limitation could lead to a general overestimation of QoL in EC survivors. The shorter follow-up of the SLN cohort may be considered a weakness. The median follow-up for all cohorts is however more than two years after initial therapy, which is the time-period when LEL commonly develops [6].

Clinical examination and objective measurements would strengthen the results. This was not feasible for this large population, but is planned in a future intervention study for a selected group of women. Overall, the results from our study are robust, and we await the results from ENDO3 with its randomized, prospective design, for comparison [29].

9. Conclusions

Our study confirms that risk factors associated with self-reported post-operative LEL are higher BMI, receiving adjuvant chemotherapy and undergoing LND. LEL is associated with lower QoL. The addition of a SLN algorithm to hysterectomy alone does not increase the risk of LEL, and should not be used as an argument against implementation of SLN in this patient population.

Interestingly, the prevalence of LEL may not be as high as previously reported in endometrial carcinoma survivors, as underlying musculoskeletal disorders could mimic LEL signs and symptoms. This relationship should be further explored.

Author contributions

All authors revised and agreed on the final version to be submitted.

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Tweetable statement

Women with lymphedema after endometrial carcinoma surgery report reduced quality of life, however musculoskeletal complaints may mimic lymphedema symptoms cautioning interpretation of results from PROMs.

Declaration of Competing Interest

Ane Gerda Z Eriksson reports receiving speakers' fees from Intuitive surgical and GSK. Other authors report no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2023.05.070.

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Supplemental table 1: Alive patients. Non-responders vs responders

Characteristics	**Whole-cohort**	**Non-responders**	**Responders**	**p-value**
	n=2022	n=796 (39%)	n=1226 (61%)	
Age at surgery (years), mean (SD)	65.6 (10.4)	66.6 (11.7)	64.9(9.5)	p=0.001
Follow-up (months), median (interquartile)	69 (32-123)	74 (33-131)	66 (32-114)	p=0.003
Age at survey (years), mean (SD)	72.5 (10.5)	74.0 (12.1)	71.6 (9.3)	p<0.001
BMI at surgery (m/kg^2), mean (SD)	28.8 (6.5)	29.4 (6.9)	28.5 (6.2)	p=0.002
Comorbidities at surgery				
Hypertension	804 (40%)	348 (44%)	456 (37%)	p=0.004
Diabetes mellitus	231 (11%)	116 (14%)	115 (9%)	p=0.001
COPD	60 (3%)	34 (4%)	26 (2%)	p=0.005
Coronary artery disease	83 (4%)	48 (6%)	35 (3%)	p<0.001
Dementia or cognitive impairment	8 (<1%)	7 (1%)	1 (<1%)	p=0.005
Cerebrovascular disease or Transitory Ischemic Attack	73 (4%)	41 (5%)	32 (3%)	p=0.003
Previous deep venous thrombosis or pulmonary embolism	55 (3%)	19 (2%)	36 (3%)	p=0.463
Nodal assessment n= 2018				p=0.066
LND[a]	708 (35%)	274 (34%)	434 (35%)	
SLN[b] algorithm	643 (32%)	235 (29%)	408 (33%)	
Hysterectomy	667 (33%)	285 (36%)	382 (31%)	
Final stage				
I	1701 (84%)	670 (84%)	1031 (84%)	p=0.870
II	85 (4%)	31 (4%)	54 (4%)	
III (A+B)	55 (3%)	23 (3%)	32 (3%)	
III C	167 (8%)	68 (8%)	99 (8%)	
IV	14 (<1%)	4 (<1%)	10 (<1%)	
Final histology				
Endometrioid	1586 (78%)	646 (81%)	940 (77%)	p=0.017
Non-endometrioid	436 (22%)	150 (19%)	286 (23%)	
Adjuvant therapy				
None	1338 (66%)	553 (69%)	785 (64%)	

Chemo only	654 (32%)	230 (29%)	424 (35%)	p=0.050
Radiotherapy w/wo chemo	16 (<1%)	8 (1%)	8 (<1%)	
Unknown	15 (<1%)	5(<1%)	9 (<1%)	
Modality				
Robotic	895 (44%)	319 (40%)	576 (47%)	p=0.006
Laparoscopic	450 (22%)	184 (23%)	266 (22%)	
Laparotomy	674 (33%)	293 (37%)	381 (31%)	
Vaginal	3 (<1%)	0	3 (<1%)	
Recurrence				p=0.067
No	1888 (93%)	739 (93%)	1149 (94%)	
Yes	124 (6%)	56 (7%)	68 (6%)	
Unknown	10 (<1%)	1 (<1%)	9 (<1%)	
Status				p=0.427
No evidence of disease	1961 (97%)	769 (97%)	1192 (97%)	
Alive with recurrence	61 (3%)	27 (3%)	34 (3%)	

[a] LND= Pelvic +/- paraaortic lymphadenectomy
[b] SLN= Sentinel Lymph Node Biopsy

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Supplemental table 2: Clinicopathological characteristics of responders according to nodal assessment

Demographic characteristics	**Whole cohort** n=1134	**LND[a]** n=402 (35%)	**SLN[b]** n=386 (34%)	**Hysterectomy** n=346 (31%)	**p-value**
Age at surgery (years), mean (SD)	64.5 (9.4)	63.7 (8.3)	66.2 (9.4)	63.6 (10.4)	p<0.001
Follow-up (months), median (IQR)	66 (32-113)	97 (65-143)	31 (19-47)	81 (43-134)	p<0.001
Age at survey (years), mean (SD) n=1134	71.2 (9.2)	72.5 (7.8)	69.7 (9.5)	71.3 (10.2)	p<0.001
BMI at surgery (m/kg^2), mean (SD) n=1128	28.6 (6.2)	28.1 (5.7)	29.1 (6.2)	28.6 (6.8)	p=0.092
Final stage (FIGO 2009)					p<0.001 [c,d]

I	960 (85%)	295 (73%)	333 (86%)	332 (96%)	
II	49 (4%)	29 (7%)	14 (4%)	6 (2%)	
III (A + B)	28 (2%)	16 (4%)	6 (2%)	6 (2%)	
III C	88 (8%)	55 (14%)	33 (9%)	0	
IV	9 (1%)	7 (2%)	0	2 (<1%)	
Final histology					p<0.001[c]
G1 Endometrioid	511 (45%)	110 (27%)	141 (37%)	260 (73%)	p=0.017[d]
G2 Endometrioid	245 (22%)	93 (23%)	89 (23%)	63 (18%)	
G3 Endometrioid	116 (10%)	55 (14%)	54 (14%)	6 (2%)	
Clear cell	42 (4%)	25 (6%)	16 (4%)	1 (<1%)	
Serous	115 (10%)	68 (17%)	38 (10%)	9 (3%)	
Carcinosarcoma	50 (4%)	27 (7%)	20 (5%)	3 (1%)	
Other	56 (5%)	24 (6%)	28 (7%)	4 (1%)	
Modality					p<0.001
Robotic	541 (48%)	61 (15%)	381 (99%)	99 (29%)	
Laparocopic	242 (21%)	58 (14%)	0	184 (53%)	
Laparotomy	349 (31%)	283 (70%)	5 (1%)	61 (18%)	
Vaginal	2 (<1%)	0	0	2 (<1%)	
Mapping					
Bilateral mapping	N/A	N/A	309 (80%)	N/A	
Unilateral mapping	N/A	N/A	57 (15%)	N/A	
No mapping	N/A	N/A	20 (5%)	N/A	
Nodes removed					
Median (IQR), n=1127	3 (0-16)	21 (14-28)	3 (2-5)	N/A	p<0.001
Adjuvant therapy					p<0.001
None	733 (65%)	184 (46%)	232 (60%)	317 (92%)	
Chemotherapy only	385 (34%)	211 (52%)	149 (39%)	25 (7%)	
Radiotherapy w/wo chemo	8 (<1%)	5 (1%)	2 (<1%)	1 (<1%)	
Unknown/missing	8 (<1%)	2 (<1%)	3 (<1%)	3 (<1%)	
Recurrence					p=0.034[c]
No	1060 (93%)	365 (91%)	362 (94%)	333 (96%)	p=0.177[d]
Yes	65 (6%)	34 (8%)	20 (5%)	11 (3%)	p=0.315[e]
Missing	9 (<1%)	3 (<1%)	4 (1%)	2 (<1%)	
Evaluable by LELSQ[f]	1127 (99%)	398 (99%)	385 (100%)	344 (99%)	

Self-reported LEL, n =1127					p<0.001[c]
Negative	651 (58%)	197 (49%)	246 (64%)	208 (60%)	p=0.340[e]
Positive	476 (42%)	201 (51%)	139 (36%)	136 (40%)	

[a] LND= Pelvic +/- paraaortic lymphadenectomy
[b] SLN= Sentinel Lymph Node Biopsy
[c] Chi2 comparing all three groups
[d] Chi2 comparing LND and SLN
[e] Chi2 comparing SLN and hysterectomy
[f] defined as ≥7 questions answered

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Supplemental Table 3: Quality of life measured by EORTC QLQ-C30 and EORTC QLQ-EN24 stratified by lymphedema status.

	Evaluable by LELSQ	**LEL negative**	**LEL positive**	
	n=1127	n=651 (58%)	n=476 (42%)	p-value
EORTC QLQ-C30				
Global health status				
Mean (SD) n=1097	71.3 (21.2)	78.6 (18.9)	61.5 (20.2)	p<0.001
Functional scales[a]				
Physical functioning n=1095				
Mean (SD)	77.3 (21.9)	85.4 (17.8)	66.0 (22.2)	p<0.001
Clinical importance[c]		34 %	74 %	p<0.001
Role functioning n=1109				
Mean (SD)	80.2 (26.2)	88.2 (20.1)	69.0 (28.8)	p<0.001
Clinical importance[c]		7 %	28 %	p<0.001
Emotional Functioning n=1092				
Mean (SD)	84.7 (20.2)	89.3 (16.7)	78.4 (22.6)	p<0.001
Clinical importance[c]		13 %	33 %	p<0.001
Cognitive function n=1004				
Mean (SD)	83.7 (20.5)	88.3 (16.9)	77.3 (23.0)	p<0.001
Clinical importance[c]		15 %	34 %	p<0.001
Social function n=1107				
Mean (SD)	80.8 (24.8)	88.4 (19.4)	70.2 (27.5)	p<0.001
Clinical importance[c]		8 %	27 %	p<0.001
Symptom scales [b]				
Fatigue n=1102				
Mean (SD)	31.7 (25.7)	23.0 (22.0)	43.6 (25.7)	p<0.001
Clinical importance[c]		18 %	50 %	p<0.001
Nausea and vomiting n=1110				
Mean (SD)	3.7 (9.8)	2.1 (6.9)	6.0 (12.4)	p<0.001
Clinical importance[c]		10 %	25 %	p<0.001
Pain n=1100				
Mean (SD)	25.9 (27.5)	15.5 (21.6)	40.1 (23.4)	p<0.001
Clinical importance[c]		27 %	69 %	p<0.001
Dyspnea n=1117				
Mean (SD)	18.7 (25.7)	12.2 (20.6)	27.7 (29.1)	p<0.001

Clinical importance[c]		30 %	57 %	p<0.001
Sleep disturbance n=1117				
Mean (SD)	31.1 (32.3)	24.0 (29.2)	40.8 (33.9)	p<0.001
Clinical importance[c]		17%	37%	p<0.001
Appetite loss n=1116				
Mean (SD)	7.3 (18.7)	4.8 (15.8)	10.7 (21.5)	p<0.001
Clinical importance[c]		3 %	6 %	p<0.002
Constipation n=661				
Mean (SD)	16.3 (26.0)	11.6 (22.2)	23.2 (29.4)	p<0.001
Clinical importance[c]		8 %	18 %	p<0.001
Diarrhea n=1111				
Mean (SD)	14.7 (22.9)	11.6 (21.0)	19.1 (24.7)	p<0.001
Clinical importance[c]		28 %	44 %	p<0.001
Financial difficulties n=1108				
Mean (SD)	5.7 (16.9)	3.1 (12.1)	9.1 (21.2)	p<0.001
Clinical importance[c]		7 %	20 %	p<0.001
EORTC QLQ-EN24				
Symptom scale [b]				
Lymphedema n=1105				
Mean (SD)	17.6 (23.9)	3.8 (8.9)	36.9 (24.7)	p<0.001
Urological symtoms n=1095				
Mean (SD)	20.9 (21.8)	14.8 (17.6)	29.3 (24.1)	p<0.001
Gastrointestinal symptoms n=1095				
Mean (SD)	17.7 (17.8)	12.6 (14.6)	24.8 (19.3)	p<0.001
Poor body image n=1097				
Mean (SD)	14.1 (24.2)	8.9 (18.6)	21.2 (28.8)	p<0.001
Sexual/vaginal problems [d] n=279				
Mean (SD)	27.2 (26.0)	24.9 (24.4)	31.4 (28.3)	p=0.046
Pain in back and pelvis n=1103				
Mean (SD)	25.8 (30.5)	16.6 (25.0)	38.3 (32.9)	p<0.001
Tingling/numbness n=1110				
Mean (SD)	28.5 (32.8)	16.9 (26.1)	44.5 (34.5)	p<0.001
Muscular pain n=1115				
Mean (SD)	35.4 (33.2)	23.0 (28.4)	52.4 (31.9)	p<0.001

Hair loss n=1104				
Mean (SD)	14.9 (27.2)	10.7 (23.6)	20.7 (30.7)	p<0.001
Taste change n=1118				
Mean (SD)	6.2 (17.7)	3.6 (13.5)	9.8 (21.7)	p<0.001
Function scale [b]				
Sexual interest n=1105				
Mean (SD)	16.6 (22.1)	17.0 (22.0)	16.0 (22.3)	p=0.495
Sexual activity n=1105				
Mean (SD)	12.9 (21.0)	14.4 (21.5)	10.6 (20.2)	p<0.001
Sexual enjoyment [d] n=285				
Mean (SD)	58.4 (27.6)	59.0 (28.0)	57.2 (27.1)	p=0.596

[a] Higher functional scores indicate better functional well-being
[b] Higher symptom scores indicate worse symptoms
[c] % of patients over or under threshold by EORTC Quality of Life group
[d] For the domains sexual/vaginal problems and sexual enjoyment, one must have scores ≥2 points on the domain sexual activity

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Supplemental table 4: Multivariate logistic regression for scoring positive for lower extremity lymphedema for log transformation of number of lymph nodes removed, n= 1122

Characteristics	**Total** **OR (CI 95%)**
BMI at surgery[a]	1.06 (1.03 - 1.09)
Number of lymph nodes[b]	1.24 (1.08 – 1.42)
Chemotherapy[c]	1.47 (1.09 – 1.98)

8 OR = odds ratio, CI = confidence interval

9

10 [a] One unit increase

11 [b] Log transformation of number of lymph nodes removed by each lymph node

12 [c] No adjuvant therapy as reference

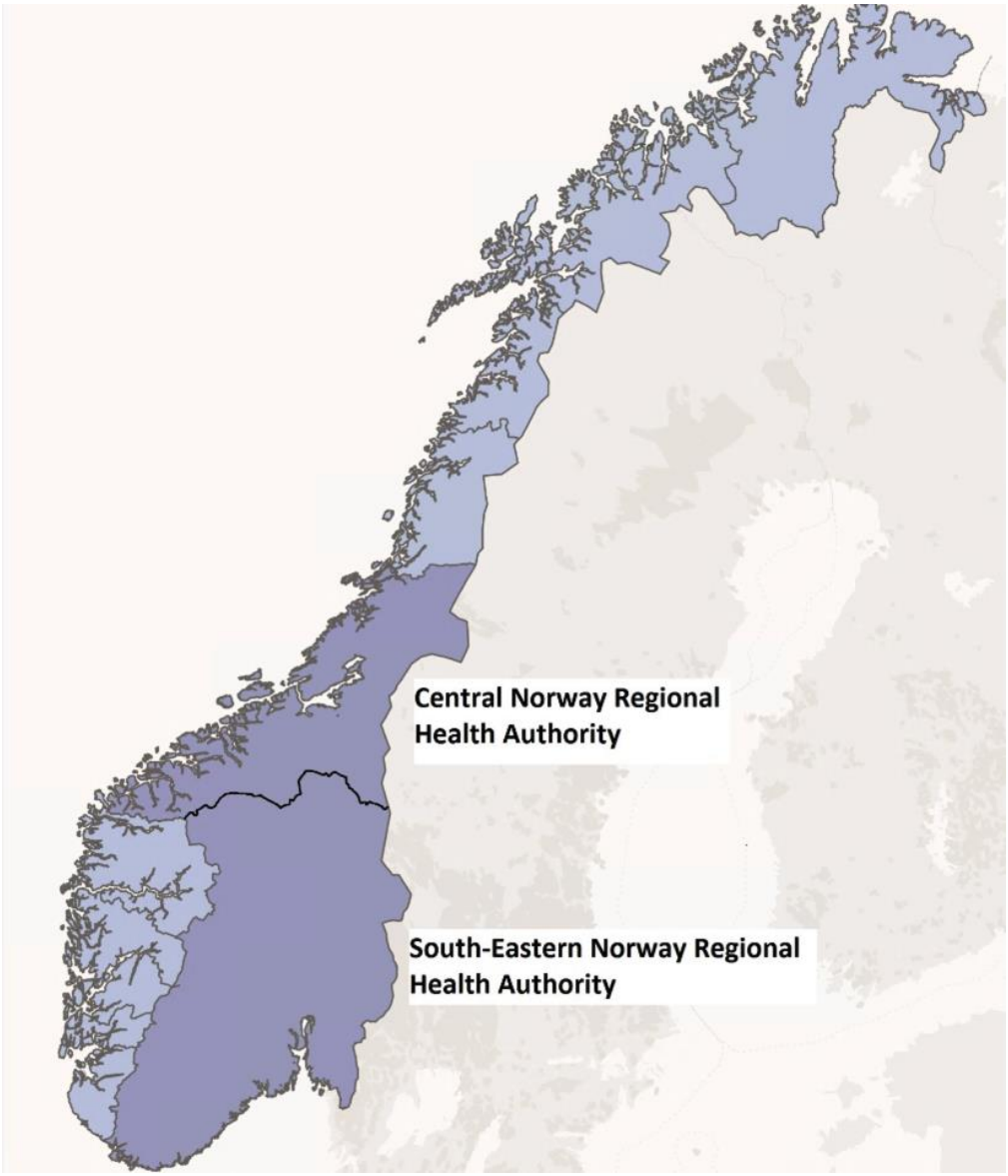
13

14

Supplemental table 5: QALYw and VAS scores according to lower extremity lymphedema (LEL)

	All evaluable by LELSQ	**LEL negative**	**LEL positive**	
EQ-5D-5L	n=1127	n=651 (58%)	n=476 (42%)	p-value
QALYw, median (interquartile) n=1070	0.88 (0.79-1)	0.94 (0.86-1)	0.81 (0.69-0.88)	p<0.001
Mean (SD)	0.84 (0.17)	0.90 (0.13)	0.76 (0.19)	p<0.001
VAS score, median (interquartile) n=1066	75 (60-87)	80 (70-90)	65 (50-75)	p<0.001
Mean (SD)	70.5 (20.1)	77.5 (17.4)	61.0 (19.7)	p<0.001

Global health scale/QoL scale (mean and standard deviation) is reported in supplement table 2.



Supplemental figure 1: Map showing the four Regional Health Authorities in Norway, highlighting the areas covering the study population.

APPENDIX

ID-nummer

I den første delen av spørreskjemaet ønsker vi bakgrunnsinformasjon om deg, din helse og lymfødem generelt. Lymfødem er hevelse som kan oppstå overalt i kroppen. Hevelsen oppstår når lymfevæsken ikke renner tilbake til lymfesystemet fordi lymfesystemet er blokkert eller skadet.
Det er viktig at du svarer så godt du kan, det finnes ingen riktige eller feil svar. Det er viktig at alle spørsmål besvares.

Vennligst kryss av for din sivilstand

- ☐ Gift/samboer/partner
- ☐ Separert/skilt
- ☐ Enslig
- ☐ Enke
- ☐ Annet

Hvilken utdanning er den høyeste du har fullført?

- ☐ Minst 4-års utdanning fra universitet eller høyskole
- ☐ 1-3 års utdanning fra universitet eller høyskole
- ☐ Videregående skole, altså 10-12 års skolegang
- ☐ Grunnskole

Hva er/var ditt yrke?

- ☐ Administrativ leder eller politiker (for eksempel politiker, toppleder, administrativ/merkantil leder, leder i hotell, restaurant, varehandel mm)
- ☐ Akademisk yrke (for eksempel realister, sivilingeniør, medisinske yrker, undervisningsyrker, rådgivere innen økonomi, administrasjon og salg, IKT-rådgivere, juridiske, samfunnsvitenskapelige og humanistiske yrker)
- ☐ Høyskoleyrke (for eksempel ingeniører, helserelaterte yrker, medarbeider innen økonomi, administrasjon og salg, yrker innen kultur/idrett, IKT-teknikere)
- ☐ Kontor- og kundeserviceyrke (kontormedarbeider, kundeserviceyrker, økonomi- og logistikkmedarbeidere, postbud, arkiv- og personalkontormedarbeidere)
- ☐ Salgs-, service- og omsorgsyrker (yrke innen personlig tjenesteyting, salgsyrke, pleie- og omsorgsarbeider, sikkerhetsarbeid)
- ☐ Jordbruk, skogbruk og fiske
- ☐ Håndverker og lignende (for eksempel byggarbeid, metall- og maskinarbeid, presisjonsarbeid, kunsthåndverk, grafiske arbeid, elektrikere, andre håndverkspregete yrker)
- ☐ Prosess- og maskinoperatører, transportarbeidere mv.
- ☐ Renholdere, hjelpearbeidere, kjøkkenassistent, renovasjons- og gjennvinningsarbeider
- ☐ Militære yrker (ikke sivile stillinger i forsvaret)

Hvilket alternativ beskriver best din arbeidssituasjon før du fikk livmorkreft?

- ☐ I fullt arbeid
- ☐ Deltidsarbeid
- ☐ Arbeidssøker
- ☐ Alderspensjonist
- ☐ Sykmeldt
- ☐ Uføretrygdet
- ☐ Permittert
- ☐ Hjemmeværende
- ☐ Arbeidsavklaring
- ☐ Annet, vennligst beskriv her

……..

Hvis du var sykemeldt, ufør eller permittert, i hvilken grad (%) var du sykemeldt/ufør/på arbeidsavklaring/permittert?

☐ 0 ☐ 10 ☐ 20 ☐ 30 ☐ 40 ☐ 50 ☐ 60 ☐ 70 ☐ 80 ☐ 90 ☐ 100

Hvis du jobbet deltid, i hvilken grad (%) jobbet du?

☐ 0 ☐ 10 ☐ 20 ☐ 30 ☐ 40 ☐ 50 ☐ 60 ☐ 70 ☐ 80 ☐ 90 ☐ 100

Førte kreftsykdommen eller følgetilstander etter behandling til endring i arbeidssituasjon?

Med dette spørsmålet mener vi all type endring i arbeidssituasjon: sykemelding, pensjonering før planlagt, uførhet o.l.

- ☐ Ja
- ☐ Nei
- ☐ Arbeidssituasjonen min har endret seg, men det har ikke noe med kreftsykdommen/følgetilstander å gjøre

Hvis følgetilstander etter behandlingen har ført til at du jobber mindre, har lymfødem ført til at du jobber mindre enn du kunne ha gjort?

- ☐ Ja
- ☐ Nei, det er andre grunner til at jeg jobber mindre

Hvilket alternativ beskriver din nåværende arbeidssituasjon?

- ☐ I fullt arbeid
- ☐ Deltidsarbeid
- ☐ Arbeidssøker
- ☐ Alderspensjonist
- ☐ Sykmeldt
- ☐ Uføretrygdet
- ☐ Permittert
- ☐ Hjemmeværende
- ☐ Arbeidsavklaring
- ☐ Annet

Hvis du er sykemeldt eller ufør, hvilken grad er du sykemeldt/ufør?

☐ 0 ☐ 10 ☐ 20 ☐ 30 ☐ 40 ☐ 50 ☐ 60 ☐ 70 ☐ 80 ☐ 90 ☐ 100

Nedenfor er en liste over vanlige sykdommer/helseplager. Vennligst fyll ut om du har noen av plagene. Dersom du krysser JA, vennligst kryss av om du mottar behandling for den og om den begrenser deg i aktiviteter. Dersom du har andre sykdommer/helseplager enn de som er listet opp her, vennligst fyll dem ut under.

	Har du denne sykdommen/ tilstanden?		**Mottar du behandling for denne sykdommen/ tilstanden?**		**Begrenser denne sykdommen/ tilstanden deg i dine aktiviteter?**	
	Nei	**Ja**	**Nei**	**Ja**	**Nei**	**Ja**
Hjertesykdom	☐	☐	☐	☐	☐	☐
Høyt blodtrykk	☐	☐	☐	☐	☐	☐
Lungesykdom	☐	☐	☐	☐	☐	☐
Diabetes/sukkersyke	☐	☐	☐	☐	☐	☐
Magesår	☐	☐	☐	☐	☐	☐
Nyresykdom	☐	☐	☐	☐	☐	☐
Leversykdom	☐	☐	☐	☐	☐	☐
Lav blodprosent eller annen blodsykdom	☐	☐	☐	☐	☐	☐
Har du/har du hatt kreft? (se bort fra livmorkreft)	☐	☐	☐	☐	☐	☐
Depresjon	☐	☐	☐	☐	☐	☐
Slitasjegikt	☐	☐	☐	☐	☐	☐
Ryggsmerter	☐	☐	☐	☐	☐	☐
Leddgikt	☐	☐	☐	☐	☐	☐
Blodpropp i ben/bekken eller lunger	☐	☐	☐	☐	☐	☐
Annet (spesifiser under)	☐	☐	☐	☐	☐	☐

Vennligst skriv andre sykdommer/helseplager du har her

.....

Har du brukt hormontilskudd mot overgangsplager etter at du ble operert for livmorkreft?
☐ Ja, tabletter eller plaster ☐ Ja, tabletter eller salve i skjeden ☐ Nei

Hvis du har brukt hormontilskudd, i hvor mange år har du brukt hormontilskudd? .....

Vennligst skriv inn navnet på preparatet hvis du husker det ....

Hvor høy er du? .....

Hvor mye veier du?.....

Røyker du?
☐ Nei, jeg har aldri røkt
☐ Nei, jeg har røkt tidligere
☐ Ja, jeg røyker av og til nå (ikke daglig)
☐ Ja, jeg røyker daglig nå

Tenk på det siste året; hvor mange ganger per uke spiser du disse matvarene:
(Sett ett kryss pr linje)

	Mindre enn 1 gang	1-3 ganger	4-6 ganger	7 eller mer
Frukt/bær	☐	☐	☐	☐
Grønnsaker	☐	☐	☐	☐
Rødt, rent kjøtt (storfe, svin, lam, vilt)	☐	☐	☐	☐
Hvitt, rent kjøtt (kylling, kalkun	☐	☐	☐	☐
Kjøttdeig, pølser eller lignende	☐	☐	☐	☐
Mager, ren fisk (for eksempel torsk, sei)	☐	☐	☐	☐
Fet fisk (for eksempel laks, ørret, sild, makrell som pålegg/middag)	☐	☐	☐	☐

Omtrent hvor ofte har du i løpet av de siste 12 måneder drukket alkohol? (Ikke regn med lettøl)

- ☐ Jeg har aldri drukket alkohol
- ☐ Ikke drukket alkohol siste 12 måneder
- ☐ 1 gang i måneden eller sjeldnere
- ☐ 2-4 ganger per måned
- ☐ 2-3 ganger per uke
- ☐ 4 eller flere ganger per uke
- ☐ Daglig

Hvor ofte driver du med mosjon? (Ta et gjennomsnitt)

Med mosjon mener vi at du f. eks går tur, går på ski, sykler, svømmer eller driver trening/idrett

- ☐ Aldri
- ☐ Sjeldnere enn en gang i uka
- ☐ En gang i uka
- ☐ 2-3 ganger i uka
- ☐ Omtrent hver dag

Hvor hardt mosjonerer du? (Ta et gjennomsnitt)

- ☐ Tar det rolig uten å bli andpusten eller svett
- ☐ Tar det så hardt at jeg blir andpusten eller svett
- ☐ Tar meg nesten helt ut

Hvor lenge holder du på hver gang? (Ta et gjennomsnitt)

- ☐ Mindre enn 15 minutter
- ☐ 15-29 minutter
- ☐ 30-60 minutter
- ☐ Mer enn 60 minutter

Har du husdyr?

- ☐ Nei
- ☐ Hund
- ☐ Katt
- ☐ Annet husdyr

Hvis du har husdyr, har du hatt husdyr hele tiden siden du ble operert for livmorkreft?

- ☐ Ja
- ☐ Nei

Hvis du har hatt husdyr siden før du ble operert, i hvor mange år har du hatt husdyr? ……

Hvis du ikke har husdyr nå, har du på noe tidspunkt, i tiden etter at du ble operert for livmorkreft, hatt husdyr?

- ☐ Ja
- ☐ Nei

Hvis du fikk husdyr etter at du ble operert, i hvor mange år har du hatt husdyr etter at du ble operert for livmorkreft?..........

Har en lege, sykepleier eller annet helsepersonell noen gang fortalt deg at du har fått tilbakefall av livmorkreft?

- ☐ Nei
- ☐ Ja
- ☐ Vet ikke

Hvis ja, når? .....

De neste spørsmålene er om lymfødem i underkroppen, det vil si nedenfor navlen.

Før du ble operert, fikk du informasjon fra fysioterapeut, sykepleier, lege eller annet helsepersonell om at operasjonen du skulle gjennomgå som behandling for livmorkreft kunne føre til lymfødem i underkroppen?

☐ Nei ☐ Ja ☐ Vet ikke

Har lege, sykepleier eller annet helsepersonell noen gang sagt til deg at du har lymfødem i underkroppen?

☐ Nei ☐ Ja ☐ Vet ikke

Hvis ja, når fikk du beskjed for første gang at du har lymfødem i underkroppen?

☐ Før operasjonen din for livmorkreft
☐ Innen to år etter operasjonen din for livmorkreft
☐ Mer enn to år etter operasjonen din for livmorkreft
☐ Vet ikke

Hvis du har hatt lymfødem, har du noen gang gjort noe av følgende for å håndtere lymfødem i underkroppen?

	Nei	Ja	Hvis du svarte ja på ett eller flere, gjør du fortsatt følgende? Nei	Ja
Brukt støttestrømper/ kompresjonsstrømper	☐	☐	☐	☐
Brukt bandasje	☐	☐	☐	☐
Gjennomført øvelser/trening, slik som tå-hev øvelse	☐	☐	☐	☐
Mottatt manuell lymfedrenasje (massajse) av fysioterapeut	☐	☐	☐	☐
Annet, vennligst spesifiser: …….	☐	☐	☐	☐

Den andre delen av skjemaet omhandler lymfødem. Noen av spørsmålene vil oppleves som like, det er med vilje. Det er viktig at du svarer så godt du kan, det finnes ingen riktige eller feil svar. Det er viktig at alle spørsmål besvares.

Følgende spørsmål gjelder dine opplevelser av bevegelse, aktivitet og søvn de siste fire ukene:

	Ja	Nei
Har du begrenset bevegelse i hoften?	☐	☐
Har du begrenset bevegelse i kneet?	☐	☐
Har du begrenset bevegelse i ankelen?	☐	☐
Har du begrenset bevegelse i foten?	☐	☐
Har du begrenset bevegelse i tærne?	☐	☐
Føles foten eller benet svakt?	☐	☐

Følgende spørsmål gjelder symptomer som du kanskje har opplevd i foten, leggen, hoften, lysken eller nedre del av kroppen de siste fire ukene:

	Ja	Nei
Har du opplevd ømhet?	☐	☐
Har du opplevd hevelse?	☐	☐
Har du opplevd hevelse med pitting? (Pitting er når man presser fingeren mot huden og det blir værende en liten grop i huden etter at trykket er over)	☐	☐
Har du opplevd rødme?	☐	☐
Har du hatt blemmer?	☐	☐
Har du opplevd at huden føles stram?	☐	☐
Har du opplevd at området føles varmt?	☐	☐
Har du opplevd tyngdefornemmelse?	☐	☐
Har du opplevd nummenhet?	☐	☐
Har du opplevd stivhet?	☐	☐
Har du opplevd verkende smerte?	☐	☐
Har du opplevd hevelse rundt hoften?	☐	☐
Har du opplevd hevelse i lysken/kjønnsleppene/vulva?	☐	☐
Har du opplevd lommer med væske?	☐	☐

Underkroppen

Følgende utsagn handler om symptomer du kan oppleve på enten begge sider av kroppen (høyre eller venstre) eller bare på en side.

For hvert utsagn, vennligst kryss av det som best beskriver hvordan du i gjennomsnitt har følt deg de siste fire ukene. Du skal beskrive den siden av kroppen som har mest symptomer hvis du har plager fra begge sider.

	Ikke i det hele tatt	Litt	Noe	Ganske mye	Veldig mye
Huden på benet mitt føles stram	☐	☐	☐	☐	☐
Huden over ankelen min føles stram	☐	☐	☐	☐	☐
Benet føles tungt	☐	☐	☐	☐	☐
Jeg har smerte eller ubehag i benet	☐	☐	☐	☐	☐
Benet mitt er tydelig mindre når jeg står opp om morgenen enn senere på dagen	☐	☐	☐	☐	☐
Jeg har hevelse i foten	☐	☐	☐	☐	☐
Jeg har hevelse rundt ankelen	☐	☐	☐	☐	☐
Jeg har hevelse i leggen, inkl kneet	☐	☐	☐	☐	☐
Jeg har hevelse i låret	☐	☐	☐	☐	☐
Jeg har hevelse i baken	☐	☐	☐	☐	☐
Jeg har hevelse rundt hoften	☐	☐	☐	☐	☐
Jeg har hevelse rundt midjen (lavere enn navlen)	☐	☐	☐	☐	☐
Jeg har hevelse i underlivet	☐	☐	☐	☐	☐

Den siste delen av skjemaet omhandler OGSÅ forhold vedrørende deg og din helse. Selv om noen av spørsmålene oppleves som gjentagelse av tidligere stilte spørsmål er det viktig at du besvarer alle spørsmål etter beste evne.

EORTC QLQ-C30

Vi er interessert i forhold vedrørende deg og din helse. Vær vennlig å besvare hvert spørsmål ved å sette et kryss i ruten som best beskriver din tilstand. Det er ingen «riktige» eller «gale» svar.

	1 Ikke i det hele tatt	2 Litt	3 En del	4 Svært mye
Har du problemer med å utføre anstrengende aktiviteter, slik som å bære en tung handlekurv eller en koffert?	☐	☐	☐	☐
Har du problemer med å gå en lang tur?	☐	☐	☐	☐
Har du problemer med å gå en kort tur utendørs?	☐	☐	☐	☐
Er du nødt til å ligge til sengs eller sitte i en stol i løpet av dagen?	☐	☐	☐	☐
Trenger du hjelp til å spise, kle på deg, vaske deg eller gå på toalettet?	☐	☐	☐	☐

I løpet av den siste uken:	1 Ikke i det hele tatt	2 Litt	3 En del	4 Svært mye
Har du hatt redusert evne til å arbeide eller utføre andre daglige aktiviteter?	☐	☐	☐	☐
Har du hatt redusert evne til å utføre dine hobbyer eller andre fritidsaktiviteter?	☐	☐	☐	☐
Har du vært tung i pusten?	☐	☐	☐	☐
Har du hatt smerter?	☐	☐	☐	☐
Har du hatt behov for å hvile?	☐	☐	☐	☐
Har du hatt søvnproblemer?	☐	☐	☐	☐
Har du følt deg slapp?	☐	☐	☐	☐
Har du hatt dårlig matlyst?	☐	☐	☐	☐
Har du vært kvalm?	☐	☐	☐	☐
Har du kastet opp?	☐	☐	☐	☐

I løpet av den siste uken:	1 Ikke i det hele tatt	2 Litt	3 En del	4 Svært mye
Har du hatt løs mage?	☐	☐	☐	☐
Har du hatt treg mage?	☐	☐	☐	☐
Har du følt deg trett?	☐	☐	☐	☐
Har smerter påvirket dine daglige aktiviteter?	☐	☐	☐	☐
Har du hatt problemer med å konsentrere deg, f. Eks. med å lese en avis eller se på tv?	☐	☐	☐	☐
Har du følt deg anspent?	☐	☐	☐	☐
Har du vært engstelig?	☐	☐	☐	☐
Har du følt deg irritabel?	☐	☐	☐	☐
Har du følt deg deprimert?	☐	☐	☐	☐
Har du hatt problemer med å huske ting?	☐	☐	☐	☐
Har din fysiske tilstand eller medisinske behandling påvirket ditt familieliv?	☐	☐	☐	☐
Har din fysiske tilstand eller medisinske behandling påvirket dine sosiale aktiviteter?	☐	☐	☐	☐
Har din fysiske tilstand eller medisinske behandling gitt deg økonomiske problemer?	☐	☐	☐	☐

Som svar på de neste spørsmålene, sett kryss i den ruten for det tallet fra 1 til 7 som best beskriver din tilstand.

Hvordan vil du vurdere helsen din den siste uken?

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

Svært dårlig — Helt utmerket

Hvordan har livskvaliteten din vært i løpet av den siste uken?

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

Svært dårlig — Helt utmerket

EORTC-QLQ EN24

En del pasienter opplever av og til at de har noen av følgende symptomer eller problemer. Vær vennlig å angi i hvilken grad du har hatt disse symptomene eller problemene i løpet av den siste uka.

I løpet av den siste uken:	1 Ikke i det hele tatt	2 Litt	3 En del	4 Svært mye
Har du hatt hevelser i ett eller begge ben?	☐	☐	☐	☐
Har du følt deg tung i ett eller begge ben?	☐	☐	☐	☐
Har du hatt smerter i korsryggen og/eller i bekkenet?	☐	☐	☐	☐
Når du følte trang til å urinere (tisse), var du nødt til å skynde deg på toalettet?	☐	☐	☐	☐
Har du vært nødt til å urinere (tisse) ofte?	☐	☐	☐	☐
Har du hatt ufrivillig vannlating (lekkasje)?	☐	☐	☐	☐
Har du hatt smerter eller svie ved vannlatingen?	☐	☐	☐	☐
Når du følte trang til å ha avføring, var du nødt til å skynde deg på toalettet?	☐	☐	☐	☐
Har du hatt lekkasje av avføring?	☐	☐	☐	☐
Har du vært plaget med luftavgang (flatulens)?	☐	☐	☐	☐
Har du hatt magesmerter?	☐	☐	☐	☐
Har du følt deg oppblåst i magen?	☐	☐	☐	☐
Har du kjent stikninger eller nummenhet i hender eller føtter?	☐	☐	☐	☐
Har du hatt verking eller smerter i muskler eller ledd?	☐	☐	☐	☐
Har du mistet håret?	☐	☐	☐	☐
Har mat og drikke smakt annerledes enn vanlig?	☐	☐	☐	☐
Har du følt deg mindre fysisk tiltrekkende på grunn av sykdommen eller behandlingen?	☐	☐	☐	☐
Har du følt deg mindre kvinnelig på grunn av sykdommen eller behandlingen?	☐	☐	☐	☐

I løpet av de siste fire ukene:	1 Ikke i det hele tatt	2 Litt	3 En del	4 Svært mye
I hvilken grad har du vært interessert i seksualitet?	☐	☐	☐	☐
Har du vært seksuelt aktiv?	☐	☐	☐	☐

Dette spørsmålet skal du bare svare på hvis du har vært seksuelt aktiv i løpet av de siste fire ukene:	1 Ikke i det hele tatt	2 Litt	3 En del	4 Svært mye
Kjentes skjeden tørr når du var seksuelt aktiv?	☐	☐	☐	☐
Har skjeden kjentes kort/stram?	☐	☐	☐	☐
Har du opplevd smerter under samleie/sex?	☐	☐	☐	☐
I hvilken grad har du hatt glede av sex?	☐	☐	☐	☐

Spørreskjema om helse

Norsk versjon, for Norge

(Norwegian version for Norway)

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Under hver overskrift ber vi deg krysse av den ENE boksen som best beskriver helsen din I DAG.

GANGE

Jeg har ingen problemer med å gå omkring ❑
Jeg har litt problemer med å gå omkring ❑
Jeg har middels store problemer med å gå omkring ❑
Jeg har store problemer med å gå omkring ❑
Jeg er ute av stand til å gå omkring ❑

PERSONLIG STELL

Jeg har ingen problemer med å vaske meg eller kle meg ❑
Jeg har litt problemer med å vaske meg eller kle meg ❑
Jeg har middels store problemer med å vaske meg eller kle meg ❑
Jeg har store problemer med å vaske meg eller kle meg ❑
Jeg er ute av stand til å vaske meg eller kle meg ❑

VANLIGE GJØREMÅL *(f.eks. arbeid, studier, husarbeid, familie- eller fritidsaktiviteter)*

Jeg har ingen problemer med å utføre mine vanlige gjøremål ❑
Jeg har litt problemer med å utføre mine vanlige gjøremål ❑
Jeg har middels store problemer med å utføre mine vanlige gjøremål ❑
Jeg har store problemer med å utføre mine vanlige gjøremål ❑
Jeg er ute av stand til å utføre mine vanlige gjøremål ❑

SMERTER/UBEHAG

Jeg har verken smerter eller ubehag ❑
Jeg har litt smerter eller ubehag ❑
Jeg har middels sterke smerter eller ubehag ❑
Jeg har sterke smerter eller ubehag ❑
Jeg har svært sterke smerter eller ubehag ❑

ANGST/DEPRESJON

Jeg er verken engstelig eller deprimert ❑
Jeg er litt engstelig eller deprimert ❑
Jeg er middels engstelig eller deprimert ❑
Jeg er svært engstelig eller deprimert ❑
Jeg er ekstremt engstelig eller deprimert ❑

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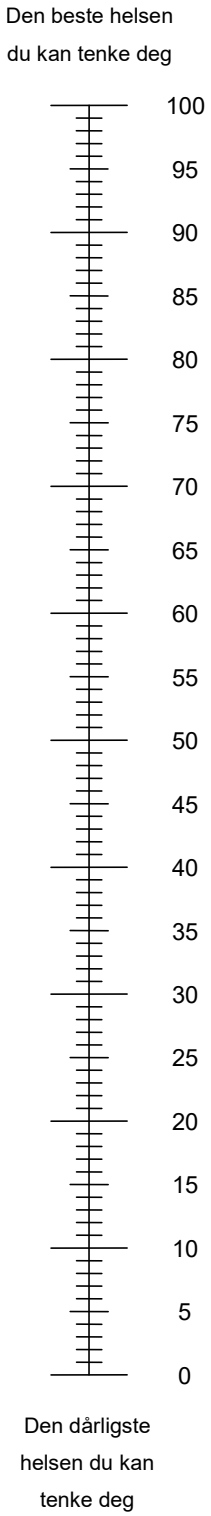
- Vi vil gjerne vite hvor god eller dårlig helsen din er I DAG.
- Denne skalaen er nummerert fra 0 til 100.
- 100 betyr den beste helsen du kan tenke deg.
  0 betyr den dårligste helsen du kan tenke deg.
- Sett en X på skalaen for å angi hvordan helsen din er I DAG.
- Skriv deretter tallet du merket av på skalaen
  inn i boksen nedenfor.

HELSEN DIN I DAG = ☐



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