The Lymphedema Evaluation in Gynecological cancer Study (LEGS): design of a prospective, longitudinal, cohort study

Running head: LEGS study protocol

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ABSTRACT

Background: The Lymphoedema Evaluation in Gynecological cancer Study (LEGS) was a longitudinal, observational, cohort study prospectively evaluating the incidence and risk factors of lower-limb lymphedema after treatment for gynecological cancer. Here we describe the study protocol and characteristics of the sample.

Methods: Women with a newly diagnosed gynecological cancer between June 1, 2008 and February 28, 2011, aged 18 years or older, and treated at one of six hospitals in Queensland, Australia, were eligible. Lymphedema was assessed by circumference measurements, bioimpedance spectroscopy, and self-reported swelling. LEGS incorporated a cohort of patients requiring surgery for benign gynecological conditions for comparison purposes. Data were collected prior to surgery and at regular intervals thereafter up to 2-years post-diagnosis.

Results: 546 women participated (408 cancer, 138 benign), with a 24-month retention rate of 78%. Clinical and treatment characteristics of participants were similar to the Queensland gynecological cancer population, except for a higher proportion of early-stage cervical cancers recruited to LEGS compared with Queensland proportions (89% versus 55%, respectively).

Discussion: Few imbalances were observed between participants with complete and incomplete follow-up data. The prospective design and collection of objective and patient-reported outcome data will allow comprehensive assessment of incidence and risk factors of lower-limb lymphedema.

Keywords: cohort; gynecological cancer; longitudinal; lymphedema; observational; prospective.
INTRODUCTION

The lymphatic vascular system complements the venous and arterial vessel systems in the body. It drains and transports fluids, proteins and immune-competent cells (lymphocytes). Defects in the lymphatic system can lead to primary (congenital) lymphoedema or secondary (acquired) lymphoedema. It has been estimated that one in 30 people worldwide develop LE [1], highlighting the magnitude of this condition. Primary lymphoedema accounts for 10% of all lymphoedema patients [1]. Secondary lymphoedema (LE) is most recognizably associated with parasite infection in developing countries, and following treatment for cancer in developed countries. Secondary LE after cancer is thought to be caused through removal of lymph nodes and damage to lymph vessels during treatment (surgery, radiotherapy) resulting in reduced flow or stasis of lymph fluid.

Secondary cancer-related LE poses a significant burden for cancer survivors. LE is an independent predictor of decreased quality of life, affecting psychological wellbeing, body image, pain, sexual wellbeing, energy, physical mobility, financial wellbeing [2-9] and potentially survival [10]. Given increasing cancer incidence and survival rates [11, 12], the incidence of secondary LE is also expected to increase. For women with breast cancer, a large body of evidence, including high quality, prospectively designed population-based cohort studies, demonstrate that about 20% will develop secondary upper-limb LE, with the majority of cases presenting within 24 months post-diagnosis [13]. Strong evidence (i.e., includes at least two prospective cohort studies) has been found for extensive surgery and being overweight or obese as risk factors for breast cancer-related LE [13]. In contrast, estimates of LE risk following gynecological cancer are crude and imprecise. While it seems likely that lower-limb LE following gynecological cancer is at least as common as upper-limb...
secondary LE following breast cancer [14], individual studies report wide variation in the incidence of between 1% and 72% [15-37]. Furthermore, there is a paucity of literature on risk factors among gynecological cancer survivors with only specific aspects of the treatment (i.e., extensive surgery, number of lymph nodes removed, surgical wound infection) thought, but yet to be confirmed, to contribute [38].

Current work investigating lower-limb LE following gynecological cancer is restricted by self-report LE assessment, retrospective study design and/or limited follow-up period (maximum follow-up period is six months post-surgery [39, 40]). Lessons learnt from the breast cancer-related LE setting clearly demonstrate that to improve understanding of secondary LE, longitudinal, cohort studies with prospective and comprehensive LE assessment (including self-report and objective measures) and follow-up of at least 24 months post-diagnosis are needed. The Lymphedema Evaluation in Gynecological cancer Study (LEGS) is unique in Australia and indeed worldwide in its aim to establish the incidence and prevalence of LE in a prospective study of women pre- to 24 months post-surgery for gynecological cancer. The purpose of this paper is to provide a detailed report of the LEGS study protocol, to describe the characteristics of the sample and to evaluate sample generalizability to the wider gynecological cancer cohort.

METHODS

Study design

The prospective, longitudinal LEGS cohort study was designed to evaluate the prevalence, incidence and risk factors of lower-limb LE after diagnosis and treatment for gynecological cancer. In parallel, a cohort of patients undergoing surgery for benign gynecological diseases
was also recruited to assess the impact of surgery for causes other than cancer on lower-limb LE. In 2009, LEGS received scientific support and approval from the Australian and New Zealand Gynecological Oncology Group (ANZGOG 0901).

Eligibility criteria

Women with newly diagnosed gynecological cancer (International Classification of Diseases Codes C51-C58) between June 1, 2008 and February 28, 2011, aged 18 years or older, and treated at one of six hospitals in Queensland, Australia, were eligible for enrolment. Cancer treatment for gynecological cancer in Queensland is largely centralized with all gynecological oncologists working together within the Queensland Centre for Gynecological Cancer (QCGC) including both public and private hospitals. The QCGC represents virtually all gynecological cancer patients in Queensland, with some small percentage difference due to death certificate-only notifications. Patients were considered eligible to participate if they were not pregnant, were able to provide informed consent and were likely to return to the hospital for follow-up care. Patients with a pacemaker, allergies against adhesive electrodes or extensive internal metal plates were ineligible for bioimpedance spectroscopy (BIS) measurement, but if they met the eligibility criteria otherwise, were still offered to participate in all other components of the study.

Recruitment process

Following ethical approval from hospital Human Research Ethics Committees (approval numbers: 2008000211, 2007/168, 200842, 1189A/P, 08/16, 10/14, 10/10/RPAH/28), medical staff at the surgical gynecological oncology departments recruited patients, which involved undertaking initial screening to confirm eligibility, discussion of study, and
informed consent. This typically occurred when patients were admitted to hospital for pre-
surgical assessment. Once consent and eligibility were established, research staff conducted
all further procedures.

Assessment schedule
A baseline assessment taking approximately 30-40 minutes per participant was typically
performed during the consented patient’s pre-admission clinic, the week prior to surgery.
Subsequent assessments for cancer patients were coordinated with their usual schedule of
hospital follow-up visits up to two years post-surgery. The number of follow-up visits
differed for each hospital but could be as regular as once every three months. Patients with
benign diagnoses were assessed pre-operatively, at the six-week follow-up visit and were
called in for at least one subsequent assessment. Follow-up study visits were held at the
treating hospital.

Data collection
Standardized data collection protocols were used to collect data via clinical assessment, self-
administered questionnaire, and clinical records. Research staffs involved with data
collection had tertiary qualifications in a health-related discipline and were trained in the
objective assessment of lymphedema, including BIS and circumference methods, by an
accredited physiotherapist with specialist skills in lymphedema assessment and treatment
(HRH). A reliability study was conducted to assess the intra- and inter-rated consistency for
BIS and circumference assessments between staff. Inter-tester reliability was found to be
high with interclass coefficients of 0.93 (0.66, 0.98) to 0.99 (0.96, 1.00) for circumference
and BIS measurements, respectively. Bland Altman analysis also demonstrated that the
mean difference and limits of agreement between our highly trained study personnel for measures of lymphedema ranged between 0.01 (-0.08, 0.10) and 0.04 (-0.03, 0.10) for BIS and 0.01 (-2.91, 2.94) and 0.58 (-1.25, 0.90) for circumferences.

Clinical assessment

*Bioimpedance spectroscopy (BIS)* (ImpediMed SFB7) electrodes were placed on hands and feet at anatomical locations optimized for the measurement of limb impedance [41] including: middle of styloid process of right and left arm; distal end of third metacarpal on the right and left hand; lateral malleolus of the fibula on the right and left leg; and distant end of the third metatarsal on the right and left foot. Measurements were taken for each limb, according to standard ImpediMed protocol. BIS data were analyzed and checked for quality using Bioimp v4.15.0 (ImpediMed).

*Circumference measurements* followed the standard measurement protocol available from the Australasian Lymphology Association [42] (measuring every 10 centimeters from the heel working proximally). The standard method involves the use of a measuring board and a set-square to mark the limb medially and laterally every 10 centimeters from the heel. The patient lies down with the leg slightly abducted and resting on the measuring board with the sole of the foot flat against the end of the board and the dorsal surface of the foot aligned and facing upward. The other leg was supported at the hip during measurement to avoid rotation of the pelvis during marking of the limb [43].

Clinical assessments also included measurement of height and weight using a standardized tape measure and a calibrated scale and documented in SI units.
Self-administered questionnaire

*Self-reported swelling.* At every data collection session, women were asked to answer ‘yes’, ‘no’ or ‘unsure’ to the question, ‘Have you experienced swelling in both legs?’ with a ‘yes’ response being used to indicate the presence of self-reported leg swelling. The same question was asked for each of the following regions: right leg only, left leg only, between legs (vulva), lower abdomen, or pelvic region. Anatomical sites were condensed into three regions of swelling: legs, vulva, and abdomen/pelvis.

*Lower-limb symptoms.* Women were asked to report on a five-point scale for severity, within the last week, including ‘none’, ‘mild’, ‘moderate’, ‘severe’ and ‘extreme’ the presence of 14 lower-limb symptoms that have been found to be associated with upper-limb LE following breast cancer [44]. The 14 patient self-reported lower-limb symptoms included: pain, pain when you performed any specific activity, tingling (pins and needles), weakness, stiffness, poor range of movement, numbness, tightness, ache, heaviness, reddish skin coloring, tenderness, thickened/hardened skin, hot areas on your skin.

*Secondary outcomes.* Additionally, at baseline as well as all subsequent data collection sessions, patients completed standardized questionnaires on quality of life (Functional Assessment of Cancer Therapy-General, FACT-G [45]), body image (Body Image Scale [46]), anxiety and depression (Hospital Anxiety and Depression Scale, HADS [47]), and physical activity (Active Australia Survey [48]), as well as questions on financial impact of LE. Standardized questionnaires pertaining to health services use [49], as well as the EuroQol
Group (EQ-5D-3L [50]) standardized questionnaire, were included at the six-week questionnaire and thereafter.

At the pre-operative (baseline) visit only, participants were asked to complete questions on demographics and behavioral characteristics (e.g., smoking status, alcohol consumption).

Case Report Forms

*Pre-surgical assessment.* Relevant information was collected at the patients’ pre-operative visit, including menstrual status, medical conditions (e.g., past history of cancer, cardiac conditions, diabetes and auto-immune diseases), baseline medications (i.e., that could have an effect on the patient’s fluid balance), and overall quality of life (single item). Weight, height, BIS and circumference measurements were also taken.

*Follow-up assessments* collected information on the following; menstrual status, adverse events (e.g., seroma, wound infection, lymphedema), concomitant medications, and overall quality of life. Leg measurements (BIS and circumferences) were also taken, and women were asked if they had received any treatment for LE since their last visit and, if so, by whom.

*Treatment data* abstracted from participant’s clinical file at the two year final follow-up visit included type of surgery performed, number of lymph nodes dissected and number positive, histopathology, adjuvant treatments and patient status (living tumor free, living with the tumor, progressive disease, and death).
Clinical diagnosis and referral to services. As the study itself did not provide treatment to patients who developed LE, women were referred back to their General Practitioner for further assessment and treatment if any of the following were recorded: ≥5% increase in leg circumference measurements when compared with pre-surgical measurements in two consecutive visits; or ≥5% increase in leg circumference measurements when compared with pre-surgical measurements plus significant patient-reported leg symptoms. Participants were also advised to visit their General Practitioner if they were concerned or noticed swelling between study visits.

Sample size calculations and power

A priori sample size calculations were based on the primary outcome, incidence of lower-limb LE. Assuming an incidence of at least 20% of patients with LE within the malignant group (82 out of 408 patients), power is 100% to be able to detect as statistically significant with 95% confidence intervals around estimates of LE incidence in the range of ±7%. Higher incidence rates of LE generally will increase statistical power (i.e., provide narrower confidence intervals).

Data management

Participants were assigned a unique anonymous number which was used to track their progress through the study and to match their Case Report Forms, written forms and electronic files. Data from Case Report Forms and questionnaires were entered into a password protected database. A comprehensive validation check program was used to verify the data (e.g., identifying values outside the possible range) and discrepancy reports were generated accordingly for resolution by the investigator. Data were stored in locked
offices or password-protected computer files, accessible only by study staff. Data verification on a 10% random sample of participant questionnaires was performed and compared with original data entry files. The error rate between the files was <2% and the original therefore retained.

Statistical analysis

Information from up to 10 data collection points was available, however follow-up schedules across the six hospitals varied as did assessments for malignant and benign diagnoses, and were thus grouped into four phases: Time 1 = baseline; Time 2 = 6 weeks to 3 months; Time 3 = 6 to 12 months; Time 4 = 15 to 24 months post-surgery.

Of particular interest for this manuscript were recruitment and retention rates, characteristics of our sample and sample generalizability. Recruitment rates were calculated by the number of consenting and participating women divided by the number of eligible women approached to participate. Retention rates equaled the number of participants who completed follow-up testing divided by the number of participants who completed baseline testing. Baseline participant characteristics were described using mean and standard deviation (SD) for normally-distributed, continuous characteristics; median, minimum and maximum for non-parametric data; and proportions for categorical characteristics. The clinical and treatment characteristics of LEGS participants were compared with the population of women treated for gynecological cancer in Queensland in 2009. The comparison data were made available from the QCGC; this is the largest gynecological cancer service in Australia and houses a population-based registry of Queensland gynecological cancer patients. A priori absolute differences between groups of >10% were
considered relevant. Characteristics for participants with complete (i.e., four phases) and incomplete (i.e., fewer than four phases) follow-up data were also compared using Chi-squared tests to explore the sampling distributions. Statistical significance of \( P<0.05 \) (Fisher’s Exact Test used where available, otherwise Pearson Chi-Squared used) for all personal, treatment and disease characteristics between participants with complete versus incomplete follow-up data were considered relevant. When there was an overall statistically significant difference between groups, post-hoc analyses using standardized residuals (converted to a z-score, \( \pm 1.96 \)) were performed to investigate which category differed between the groups.

**RESULTS**

Recruitment and retention

Of the 2,121 potentially eligible participants, 65\% (n=1,385) were excluded due to not meeting the inclusion criteria and 9\% (n=190) declined to participate (see Figure 1). Of the 546 women who remained eligible and gave informed consent, 408 were diagnosed with malignant disease and 138 with benign disease. All women had baseline measurements taken pre-surgery (i.e., prior to their first surgery). The study retention rates at Times 2, 3 and 4 were 84\% (86\% malignant; 80\% benign), 84\% (84\% malignant, 85\% benign), and 78\% (78\% malignant; 77\% benign), respectively.

Examples of benign conditions among participants included: benign ovarian cysts or tumors, endometrial hyperplasia with or without atypia, adenomyosis, uterine fibroids as well as vulval intraepithelial neoplasia (VIN) III.
Generalizability

On the whole, characteristics of the participants of LEGS and the wider gynecological cancer population were comparable (Table 1). A higher proportion of stage I cervical cancer cases were involved in the LEGS study compared with Queensland proportions (89.2% versus 55.0%, respectively); likely because only those women with early-stage cervical cancer are referred to the surgical gynecological oncology department, which is where participants were recruited from. Subsequently, a greater proportion of LEGS cervical cancer participants underwent surgery (95% versus 52%, respectively), and fewer received chemotherapy (24% versus 48%, respectively), external beam radiotherapy (27% versus 52%, respectively), or brachytherapy (8% versus 30%, respectively) compared with the Queensland population of cervical cancer patients.

Baseline characteristics

Women who were deemed eligible following baseline assessment and who participated in at least one follow-up data collection session will contribute to further analyses, including 138 women with benign disease, 235 endometrial, 114 ovarian, 37 cervical, 22 vulvar/vaginal cancer cases (see Table 2).

Participants with complete follow-up data versus incomplete follow-up data

Participants with complete follow-up data (i.e., data available for all four phases) were compared with participants with incomplete follow-up data (i.e., data available for less than four phases) for malignant (n = 249 versus 159, respectively) and benign (n = 84 versus 54, respectively) disease separately (see Table 3).
**Malignant disease.** Many demographic, general health, clinical and treatment characteristics were similar for the women in this study with and without complete follow-up data, including age, menstrual status, histological type, surgery, lymph node dissection, radiotherapy and relapse status. Women with incomplete follow-up data had more missing demographic (education, child status, health insurance, household income) and general health (smoking status) data. The group of participants with incomplete follow-data were more likely to be past drinkers (16% versus 6%, respectively), diagnosed with stage III disease (28% versus 16%, respectively) and to have received chemotherapy (48% versus 36%, respectively) compared with the group of participants with complete follow-up data. They were also less likely to be married or in a de facto relationship (42% versus 65%, respectively), born in Australia (52% versus 74%, respectively), classified as obese (23% versus 34%, respectively), diagnosed with endometrial cancer (47% versus 65%, respectively), and to be alive at the end of the study period (82% versus 96%, respectively) compared with those with complete follow-up data.

**Benign disease.** Demographic, general health, clinical and treatment characteristics were similar for the women in this study with and without complete follow-up data. Those with incomplete follow-up data were missing more demographic (child status, health insurance, household income, country of birth) and general health (drinking status) information than those with complete follow-up data. Those with incomplete follow-up data were more likely to have undergone midline incisional surgery (35% versus 24%, respectively) and less likely to have a laparoscopy (46% versus 69%, respectively) compared with those with complete follow-up data. No further differences were noted.
DISCUSSION

Findings presented here clearly demonstrate the successful recruitment of women into LEGS with a sample size adequate to statistically meet the primary objectives of the study. Retention rate for LEGS was high, with the majority of participants followed for up to two years following surgery (the maximum in the literature is to six months [39, 40]). The length of follow-up will allow us to capture delayed development of the lymphedema, as has been documented in the breast cancer setting. Further, the LEGS sample is generally representative of the wider Queensland gynecological cancer population and therefore upcoming results are likely to be generalizable to this broader group.

The LEGS study represents a landmark, high quality, cohort study, unique in Australia, able to provide prospective evaluation of the onset, incidence and risk factors of lower-limb lymphedema after treatment for gynecological cancer up to two years following diagnosis of gynecological cancer. Similar studies are currently underway in the United States (ClinicalTrials.gov Identifiers: NCT00956670, NCT01406769). Like LEGS, they are recruiting women undergoing surgery for gynecological cancer and prospectively investigating the incidence of lower-limb LE via multiple methods up to 24 months post-operatively. Unlike LEGS, exclusion criteria are placed on stage of disease (endometrial stage I-II; cervical stage I-IIA), ovarian cancer is not included, and BIS measurements are only taken on women diagnosed with vulvar cancer. Despite these differences there will be sufficient comparable data to allow estimation of similarities and differences in risk factors for LE.

A notable strength of LEGS is the thorough assessment of LE, including objective and self-report assessment. The objective methods of assessment include the measure typically used
in clinical practice (i.e., circumferences), as well as the most sensitive method of assessment capable of diagnosing the condition before it presents clinically (BIS). In addition, lymphedema detected during routine clinical follow-up and participant self-report of swelling and associated symptoms has been assessed. This comprehensive assessment of the primary outcome will allow for a detailed investigation on how best to measure and define LE in its early stages and throughout its progression, with the time-course of transitioning from stage 0 through to stage IV lymphedema currently unknown. This is exactly the type of information necessary to identify the pros and cons of the various lymphedema diagnostic methods. We will use this information to guide future clinical practice with respect to the most optimal lymphedema diagnostic tool.

LEGS also involved measurement of a wide range of personal, diagnostic, treatment and behavioral characteristics, which in turn will enable us to properly explore potential LE risk factors, and to describe the relationship between LE, quality of life, financial burden and survival. Further, by recruiting benign cases in parallel with women with malignant disease, we will be able to distinguish between LE developed as a consequence of surgery alone versus surgery plus additional treatment. LEGS took place within the QCGC, the largest clinical and treatment unit of its kind in the Southern Hemisphere. As such, there is great potential for its findings to identify risk reduction strategies and inform lymphedema prevention guidelines and survivorship care practices.

A few shortcomings of LEGS should be noted. Statistical power may be low among cancer subgroups, limiting our ability, for example, to identify cancer-specific risk factors. Due to recruitment through the surgical gynecological oncology department lower participation
rates among women with higher stage cervical cancer assigned to chemo-radiation treatment may underestimate the true rates of LE present in the gynecological cancer population, or overestimate it if surgery is the main driver. Nonetheless, the recruitment and retention rates of the generalizable sample of LEGS make it clear that we will confirm LE prevalence and incidence following gynecological cancer, and identify risk factors for its development (including measurement of risk factors not previously assessed in the upper-limb setting), as well as potential prevention and treatment strategies. The proposed alternative models for diagnosing LE will allow us to compare their reliability and sensitivity, which in turn will be valuable for future clinical care, as using the most sensitive measure will promote early diagnosis and referral to treatment. Finally, the comprehensive assessment of the primary outcome, LE, alongside the assessment of other important physical and psychosocial outcomes, has set the scene for advancing our understanding of gynecological cancer survivorship in a way that will be able to influence the lives of women diagnosed with gynecological cancer, as well as public health burden from the disease.
List of abbreviations

BIS, bioimpedance spectroscopy; EQ-5D-3L, EuroQol Group, 5 dimensions, 3 level version questionnaire; FACT-G, Functional Assessment of Cancer Therapy-General; HADS, Hospital Anxiety and Depression Scale; LE, lymphedema; LEGS, Lymphedema Evaluation in Gynecological cancer Study; QCGC, Queensland Centre for Gynecological Cancer; SD, standard deviation.

Competing interests

Author LCW provides consultancy services to ImpediMed Ltd. ImpediMed had no input into the design or execution of this study or in the preparation of this manuscript.

Authors’ contributions

TD substantially contributed to analysis and interpretation of data, and drafting the article. MJ, SH and AO provided substantial contributions to conception and design of the study. HRH and LCW provided substantial contributions to acquisition of data. All authors of this paper have directly participated in its drafting and have read and approved the final version submitted.

Acknowledgements

The authors would like to thank the study manager, Fiona Menzies, the study coordinators Stacey Goodwin, Linda Rogers, Kerry Millgate, Anne Hughes, Samantha Gray, David Hickey and Kate Russell. We thank Jannah Baker for assistance with analysis and clinicians who made this research possible.
**Funding**

This work was supported by Cancer Australia (Grant 519711) and the Cancer Council Queensland (Grant 1026659). SCH is supported by a Cancer Council Queensland Senior Research Fellowship and MJ is supported by a Career Development Award from the National Health and Medical Research Council (1045247). The funding bodies did not have any input into the design, collection, analysis, interpretation of data or in the writing of the manuscript and the decision to submit the manuscript for publication.
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Figure 1. Flow Chart of Participant Recruitment and Retention

* Borderline cases were reviewed and seven (n=7) were reclassified as malignant.
| Characteristic          | QCGCa | LEGSb |
|------------------------|-------|-------|
|                        | All   | Endometrial | Cervical | Vulvar/Vaginal N (%) | All   | Endometrial | Cervical | Vulvar/Vaginal N (%) |
| Number of cases        | 806 (100) | 380 (47) | 241 (30) | 132 (16) | 53 (6) | 408 (100) | 235 (58) | 114 (28) | 37 (9) | 22 (5) |
| Age at diagnosis, years |       |       |       |         |       |       |       |       |        |
| Mean (SD)              | 61 (14.3) | 64 (11.6) | 63 (13.9) | 50 (15.5) | 62 (16.5) | 60 (11.4) | 62 (10.1) | 60 (11.1) | 48 (12.0) | 57 (12.3) |
| Surgery                |       |       |       |         |       |       |       |       |        |
| No evidence            | 114 (14) | 20 (5) | 21 (9) | 64 (48) | 9 (17) | 8 (2.0) | 3 (1.3) | 3 (2.6) | 2 (5.4) | 0 (0.0) |
| Yes                    | 692 (86) | 360 (95) | 220 (91) | 68 (52) | 44 (83) | 400 (98.0) | 232 (98.7) | 111 (97.4) | 35 (94.6) | 22 (100.0) |
| Stage                  |       |       |       |         |       |       |       |       |        |
| I                      | 436 (54) | 278 (73) | 57 (24) | 72 (55) | 29 (54) | 241 (59.1) | 165 (70.2) | 28 (24.6) | 33 (89.2) | 15 (68.2) |
| II                     | 100 (12) | 31 (8) | 26 (11) | 35 (27) | 8 (15) | 41 (10.0) | 26 (11.1) | 14 (12.3) | 1 (2.7) | 0 (0.0) |
| III                    | 185 (23) | 37 (10) | 121 (50) | 17 (13) | 10 (19) | 84 (20.6) | 27 (11.5) | 54 (47.4) | 1 (2.7) | 3 (13.6) |
| IV                     | 53 (7) | 23 (6) | 20 (8) | 8 (6) | 2 (4) | 27 (6.6) | 13 (5.5) | 14 (12.3) | 0 (0.0) | 0 (0.0) |
| Missing                | 32 (4) | 11 (3) | 17 (7) | 0 (0) | 4 (8) | 15 (3.7) | 4 (1.7) | 4 (3.5) | 2 (5.4) | 4 (18.2) |
| Chemotherapy           |       |       |       |         |       |       |       |       |        |
| No evidence            | 453 (56) | 299 (79) | 44 (18) | 69 (52) | 41 (77) | 241 (59.1) | 175 (74.5) | 19 (16.7) | 28 (75.7) | 19 (86.4) |
| Yes                    | 353 (44) | 81 (21) | 197 (82) | 63 (48) | 12 (23) | 167 (40.9) | 60 (25.5) | 95 (83.3) | 9 (24.3) | 3 (13.6) |
| Radiotherapy (EBRT)    |       |       |       |         |       |       |       |       |        |
| to whole pelvis        |       |       |       |         |       |       |       |       |        |
| No evidence            | 653 (81) | 316 (83) | 240 (99) | 63 (48) | 34 (64) | 324 (79.4) | 171 (72.8) | 111 (97.4) | 27 (73.0) | 15 (68.2) |
| Yes                    | 153 (19) | 64 (17) | 1 (1) | 69 (52) | 19 (36) | 84 (20.6) | 64 (27.2) | 3 (2.6) | 10 (27.0) | 7 (31.8) |
| Intracavity brachytherapy |       |       |       |         |       |       |       |       |        |
| No evidence            | 742 (92) | 361 (95) | 241(100) | 92 (70) | 48 (91) | 377 (92.5) | 207 (88.0) | 114 (100.0) | 34 (91.9) | 22 (100.0) |
| Yes                    | 64 (8) | 19 (5) | 0 (0) | 40 (30) | 5 (9) | 31 (7.5) | 28 (12.0) | 0 (0.0) | 3 (8.1) | 0 (0.0) |

a QCGC: Queensland Centre for Gynecological Cancer; women diagnosed in 2009; 8 patients had synchronous ovarian and endometrial cancer, they are counted in both groups; patients counted more than once if more than one treatment modality given.

b LEGS: Lymfedema Evaluation in Gynecological cancer Study; study participants were diagnosed between 2008 and 2011; one patient had synchronous endometrial and ovarian cancer and is counted as endometrial cancer.
### Table 2. Demographic, Clinical and Treatment Characteristics of LEGS Participants by Diagnosis

| Characteristic                  | Benign N (%) | Endometrial N (%) | Ovarian N (%) | Cervical N (%) | Vulvar/Vaginal N (%) |
|---------------------------------|--------------|------------------|--------------|---------------|---------------------|
| Number of cases                 | 138          | 235              | 114          | 37            | 22                  |
| Age at diagnosis, years         |              |                  |              |               |                     |
| Mean (SD)                       | 51 (11.9)    | 62 (10.1)        | 60 (11.1)    | 48 (12.0)     | 57 (12.3)           |
| Histological type               |              |                  |              |               |                     |
| Adenocarcinoma                  | -            | 176 (74.9)       | 36 (31.6)    | 4 (10.8)      | -                   |
| Squamous cell                   | -            | 1 (0.4)          | -            | 14 (37.8)     | 14 (63.6)           |
| Adenosquamous                   | -            | 1 (0.4)          | -            | -             | -                   |
| Serous carcinoma                | 4 (1.7)      | 38 (33.3)        | -            | -             | -                   |
| High-risk epithelial            | 14 (6.0)     | -                | -            | -             | -                   |
| Mesenchymal                     | 14 (6.0)     | -                | -            | -             | -                   |
| Epithelial, high grade serous   | -            | 12 (10.5)        | -            | -             | -                   |
| Epithelial, other               | -            | 8 (7.0)          | -            | -             | -                   |
| Non-epithelial                  | -            | 7 (6.1)          | -            | -             | -                   |
| Endometroid carcinoma           | 3 (1.3)      | -                | -            | -             | -                   |
| Other                           | -            | 4 (1.7)          | 4 (3.5)      | 2 (5.4)       | 2 (9.1)             |
| Benign                          | 124 (89.9)   | -                | -            | -             | 1 (4.5)             |
| Benign with prior diagnosis     | 4 (2.9)      | 18 (7.7)         | 4 (3.5)      | 17 (45.9)     | 5 (22.7)            |
| Borderline                      | 10 (7.2)     | -                | 5 (4.4)      | -             | -                   |
| Surgery                         |              |                  |              |               |                     |
| Midline incision                | 39 (28.3)    | 89 (37.9)        | 101 (88.6)   | 4 (10.8)      | 1 (4.5)             |
| Lower transverse                | 3 (2.2)      | 18 (7.7)         | 1 (0.9)      | 9 (24.3)      | 0 (0.0)             |
| Laparoscopy                     | 83 (60.1)    | 123 (52.3)       | 6 (5.3)      | 22 (59.5)     | 1 (4.5)             |
| Vulval/Vaginal-related          | 9 (6.5)      | 0 (0.0)          | 0 (0.0)      | 0 (0.0)       | 14 (63.6)           |
| Surgery abandoned               | 1 (0.7)      | 1 (0.4)          | 2 (1.8)      | 0 (0.0)       | 0 (0.0)             |
| Other                           | 3 (2.2)      | 1 (0.4)          | 2 (1.8)      | 0 (0.0)       | 6 (27.3)            |
| Missing                         | 0 (0.0)      | 3 (1.3)          | 2 (1.8)      | 2 (5.4)       | 0 (0.0)             |
| Lymph node dissection           |              |                  |              |               |                     |
| No                              | 138 (100)    | 128 (54.5)       | 71 (62.3)    | 11 (29.7)     | 17 (77.3)           |
| Yes                             | -            | 107 (45.5)       | 43 (37.7)    | 26 (70.3)     | 5 (22.7)            |
| Number of nodes removed         |              |                  |              |               |                     |
| Median (min, max)               | -            | 6.0 (0, 36)      | 5.5 (0, 32)  | 12.5 (0, 31)  | 4 (0, 21)           |
| Mean (SD)                       |              | 7.6 (8.0)        | 7.6 (7.8)    | 14.0 (7.9)    | 6.7 (6.5)           |
| Number of nodes metastatic      |              |                  |              |               |                     |
| Median (min, max)               | -            | 0 (0, 10)        | 0 (0, 9)     | 0 (0, 2)      | 0 (0, 3)            |
| Mean (SD)                       |              | 0.3 (1.1)        | 0.6 (1.6)    | 0.4 (0.7)     | 0.4 (0.8)           |
| Relapse during study period     |              |                  |              |               |                     |
| No know relapse                 | 131 (94.9)   | 200 (85.1)       | 74 (64.9)    | 33 (89.2)     | 16 (72.7)           |
| Yes                             | 7 (5.1)      | 35 (14.9)        | 40 (35.1)    | 4 (10.8)      | 6 (27.3)            |
| Relapse site*                   |              |                  |              |               |                     |
| Pelvic                          | 1 (14.4)     | 11 (31.4)        | 17 (42.5)    | 0 (0.0)       | 2 (33.3)            |
| Vault                           | 0 (0.0)      | 6 (17.1)         | 0 (0.0)      | 1 (25.0)      | 0 (0.0)             |
| Abdominal                       | 0 (0.0)      | 5 (14.3)         | 13 (32.5)    | 0 (0.0)       | 0 (0.0)             |
| Vulval/Vaginal                  | 0 (0.0)      | 0 (0.0)          | 0 (0.0)      | 0 (0.0)       | 3 (50.0)            |
| Distant                         | 0 (0.0)      | 5 (14.3)         | 10 (25.0)    | 1 (25.0)      | 0 (0.0)             |
| New primary*                    | 3 (42.8)     | 8 (22.9)         | 0 (0.0)      | 2 (50.0)      | 1 (16.7)            |
| Unknown                         | 3 (42.8)     | 0 (0.0)          | 0 (0.0)      | 0 (0.0)       | 0 (0.0)             |
| Status                          |              |                  |              |               |                     |
| Alive                           | 138 (100)    | 219 (93.2)       | 97 (85.1)    | 35 (94.6)     | 20 (90.9)           |
| Deceased                        | 0 (0.0)      | 16 (6.8)         | 17 (14.9)    | 2 (5.4)       | 2 (9.1)             |
| Characteristic          | Benign N (%) | Endometrial N (%) | Ovarian N (%) | Cervical N (%) | Vulvar/Vaginal N (%) |
|-------------------------|--------------|-------------------|---------------|----------------|----------------------|
| Cause of death          |              |                   |               |                |                      |
| Gynecological cancer    | -            | 12 (74.8)         | 15 (88.2)     | 2 (100)        | 2 (100)              |
| Unrelated morbidity     | -            | 1 (6.3)           | 1 (5.9)       | -              | -                    |
| Unknown                 | -            | 3 (18.8)          | 1 (5.9)       | -              | -                    |

* One endometrial patient had two relapse sites (pelvic and abdominal recurrence) and has been counted in both groups.

# New primary sites: breast (n=4), lung (n=2), colon (n=2), skin melanoma (n=2), face skin (n=2), ovarian with prior endometrial (n=1), pituitary (n=1).
### Table 3. Baseline Characteristics of LEGS Participants With Complete Follow-up Data (4 phases) Compared With Incomplete Follow-up Data (<4 phases)

| Characteristic                  | Malignant Complete | Benign Complete | Malignant Incomplete | Benign Incomplete |
|--------------------------------|--------------------|-----------------|----------------------|-------------------|
| Total patients                 | 249                | 84              | 159                  | 54                |

### Demographic characteristics

#### Age at diagnosis, years
- Mean (SD): Malignant: 60.5 (10.3), Benign: 59.0 (12.9)
- Median (minimum, maximum): Malignant: 60 (34, 85), Benign: 51 (28, 82)

#### Highest education
- Grade 12 or below: Malignant: 153 (61.5), Benign: 73 (29.3)
- Trade/University: Malignant: 7 (5.7), Benign: 9 (5.7)
- Other: Malignant: 9 (5.7), Benign: 3 (3.6)
- Missing: Malignant: 7 (2.8)%, Benign: 35 (22.1)%

#### Employment status
- Full-time/Part-time/casual: Malignant: 59 (23.7), Benign: 66 (26.5)
- Home duties: Malignant: 116 (46.5), Benign: 59 (22.0)
- Other: Malignant: 8 (3.2), Benign: 34 (22.1)%
- Missing: Malignant: 7 (2.8)%, Benign: 35 (22.1)%

#### Marital status
- Married/de facto: Malignant: 161 (64.7), Benign: 77 (32.6)
- Not married: Malignant: 77 (32.6), Benign: 58 (36.5)
- Missing: Malignant: 7 (2.7), Benign: 34 (21.4)%

#### Children in care
- None/never: Malignant: 185 (74.3), Benign: 77 (32.6)
- Age 0-14 years: Malignant: 19 (7.6), Benign: 11 (6.9)
- Age >14 years: Malignant: 37 (14.9), Benign: 17 (10.7)
- Missing: Malignant: 8 (3.2), Benign: 34 (21.4)%

#### Health insurance
- No: Malignant: 164 (65.9), Benign: 81 (32.5)
- Yes: Malignant: 29 (11.6), Benign: 39 (24.5)
- Missing: Malignant: 4 (1.6)%, Benign: 34 (21.4)%

#### Household income
- <$20,000: Malignant: 73 (29.3), Benign: 98 (39.4)
- $20,000 to $60,000: Malignant: 52 (20.8), Benign: 38 (33.9)
- $60,000+: Malignant: 26 (10.5), Benign: 48 (30.2)%
- Missing: Malignant: 3 (1.2)%, Benign: 33 (20.8)%

#### Birth country
- Australia: Malignant: 185 (74.3), Benign: 82 (51.6)%
- Other: Malignant: 61 (24.5), Benign: 44 (27.7)
- Missing: Malignant: 3 (1.2)%, Benign: 33 (20.8)%

### General health characteristics

#### Menstrual status
- Pre-menopausal: Malignant: 29 (11.6), Benign: 26 (16.4)
- Peri-menopausal: Malignant: 18 (7.2), Benign: 9 (5.7)
- Post-menopausal: Malignant: 202 (81.1), Benign: 124 (78.0)

#### Smoking status
- Never: Malignant: 153 (61.4), Benign: 63 (39.6)
- Past smoker: Malignant: 73 (29.3), Benign: 49 (30.8)
- Current smoker: Malignant: 19 (7.6), Benign: 13 (8.2)
- Missing: Malignant: 4 (1.6)%, Benign: 34 (21.4)%
| Characteristic                              | Malignant                            | Benign                             |
|--------------------------------------------|--------------------------------------|------------------------------------|
|                                            | Complete N (%) | Incomplete N (%) | Complete N (%) | Incomplete N (%) |
| Drinking status                            | *                     |                       | *                     |                       |
| Never                                      | 60 (24.1)          | 21 (13.2)             | 10 (11.9)            | 7 (13.0)              |
| Past                                       | 14 (5.6)           | 26 (16.4)             | 10 (11.9)            | 5 (9.3)               |
| Rarely                                     | 74 (29.7)          | 35 (22.0)             | 21 (25.0)            | 17 (31.5)             |
| Current                                    | 98 (39.4)          | 42 (26.4)             | 41 (48.8)            | 17 (31.5)             |
| Missing                                    | 3 (1.2)            | 35 (22.0)             | 2 (2.4)              | 8 (14.8)              |
| Body mass index                            | *                     |                       | *                     |                       |
| Under/normal weight                        | 122 (49.0)         | 88 (55.3)             | 51 (60.7)            | 33 (61.1)             |
| Overweight                                 | 41 (16.5)          | 33 (20.8)             | 12 (14.3)            | 12 (22.2)             |
| Obese                                      | 86 (34.5)          | 36 (22.6)             | 20 (23.8)            | 9 (16.7)              |
| Missing                                    | 0 (0.0)            | 2 (1.3)               | 1 (1.2)              | 0 (0.0)               |
| Clinical and treatment characteristics     | *                     |                       | *                     |                       |
| Tumour finding                             |                       |                       |                       |                       |
| Endometrial                                | 161 (64.7)         | 75 (47.2)             |                       |                       |
| Ovarian                                    | 60 (24.1)          | 53 (33.3)             |                       |                       |
| Cervical                                   | 16 (6.4)           | 21 (13.2)             |                       |                       |
| Vulvar/Vaginal                             | 12 (4.8)           | 10 (6.3)              |                       |                       |
| Histological type                          |                       |                       |                       |                       |
| Adenocarcinoma                             | 142 (57.0)         | 74 (46.5)             | -                    | -                    |
| Squamous cell                              | 13 (5.2)           | 16 (10.1)             | -                    | -                    |
| Adenosquamous                              | 1 (0.4)            | 0 (0.0)               | -                    | -                    |
| Serous carcinoma                           | 21 (8.4)           | 21 (13.2)             | -                    | -                    |
| High-risk epithelial                       | 10 (4.0)           | 4 (2.5)               | -                    | -                    |
| Mesenchymal                                | 8 (3.2)            | 6 (3.8)               | -                    | -                    |
| Epithelial, high grade serous             | 8 (3.2)            | 4 (2.5)               | -                    | -                    |
| Epithelial, other                          | 5 (2.0)            | 3 (1.9)               | -                    | -                    |
| Non-epithelial                             | 6 (2.4)            | 1 (0.6)               | -                    | -                    |
| Endometroid carcinoma                      | 2 (0.8)            | 1 (0.6)               | -                    | -                    |
| Other                                      | 6 (2.4)            | 6 (3.8)               | -                    | -                    |
| Benign                                     | 1 (0.4)            | 0 (0.0)               | 76 (90.5)            | 48 (88.9)             |
| Benign with prior diagnosis                | 22 (8.8)           | 22 (13.8)             | 3 (3.6)              | 1 (1.9)              |
| Borderline                                 | 4 (1.6)            | 1 (0.6)               | 5 (6.0)              | 5 (9.3)              |
| Stage                                      | *                     |                       | *                     |                       |
| I                                          | 162 (65.1)         | 79 (49.7)             |                       |                       |
| II                                         | 26 (10.4)          | 15 (9.4)              |                       |                       |
| III                                        | 40 (16.1)          | 44 (27.7)             |                       |                       |
| IV                                         | 13 (5.2)           | 14 (8.8)              |                       |                       |
| Missing                                    | 8 (3.2)            | 7 (4.4)               |                       |                       |
| Surgery                                    | *                     |                       | *                     |                       |
| Midline incision                           | 115 (46.2)         | 80 (50.3)             | 20 (23.8)            | 19 (35.2)             |
| Lower transverse                           | 15 (6.0)           | 13 (8.2)              | 1 (1.2)              | 2 (3.7)              |
| Laparoscopy                                | 100 (40.2)         | 52 (32.7)             | 58 (69.0)            | 25 (46.3)             |
| Vulvar/Vaginal-related                     | 9 (3.6)            | 5 (3.1)               | 5 (6.0)              | 4 (7.4)              |
| Surgery abandoned                          | 1 (0.4)            | 2 (1.3)               | 0 (0.0)              | 1 (1.9)              |
| Other                                      | 4 (1.6)            | 5 (3.1)               | 0 (0.0)              | 3 (5.6)              |
| Missing                                    | 5 (2.0)            | 2 (1.3)               | -                    | -                    |
| Lymph node dissection                      |                       |                       |                       |                       |
| No                                         | 133 (53.4)         | 94 (59.1)             | 84 (100)             | 54 (100)             |
| Yes                                        | 116 (46.6)         | 65 (40.9)             | -                    | -                    |
| Characteristic                        | Malignant Complete N (%) | Malignant Incomplete N (%) | Benign Complete N (%) | Benign Incomplete N (%) |
|--------------------------------------|---------------------------|----------------------------|-----------------------|-------------------------|
| Chemotherapy                         |                           |                            |                       |                         |
| No                                   | 157 (63.1)                | 77 (48.4)                  | -                     |                         |
| Yes                                  | 90 (36.1)                 | 77 (48.4)                  | -                     |                         |
| Missing                              | 2 (0.8)                   | 5 (3.1)                    | -                     |                         |
| Radiotherapy (EBRT) to whole pelvis  |                           |                            |                       |                         |
| No                                   | 7 (2.8)                   | 2 (1.3)                    | -                     |                         |
| Yes                                  | 50 (20.1)                 | 34 (21.4)                  | -                     |                         |
| Missing                              | 192 (77.1)                | 123 (77.4)                 | -                     |                         |
| Intracavity brachytherapy            |                           |                            |                       |                         |
| No                                   | 35 (14.1)                 | 22 (13.8)                  | -                     |                         |
| Yes – HDR                            | 17 (6.8)                  | 10 (6.3)                   | -                     |                         |
| Yes – LDR                            | 2 (0.8)                   | 1 (0.6)                    | -                     |                         |
| Yes – PDR                            | 0 (0.0)                   | 1 (0.6)                    | -                     |                         |
| Missing                              | 195 (78.3)                | 125 (78.6)                 | -                     |                         |
| Relapse during study period          |                           |                            |                       |                         |
| No know relapse                      | 205 (82.3)                | 118 (74.2)                 | 80 (95.2)             | 51 (94.4)               |
| Yes                                  | 44 (17.7)                 | 41 (25.8)                  | 4 (4.8)               | 3 (5.6)                 |
| Status                               |                           |                            |                       |                         |
| Alive                                | 240 (96.4)                | 131 (82.4)                 | 84 (100)              | 54 (100)                |
| Deceased                             | 9 (3.6)                   | 28 (17.6)                  | 0 (0.0)               | 0 (0.0)                 |

* P<0.05 between follow-up and baseline-only groups (Fisher’s Exact Test used where available else Pearson Chi-Square used).

# Chi-Square no longer statistically significant when the missing category is removed from the analysis.

- Standardized residual (converted to a z-score) greater than -1.96 (indicating the cell was under-represented in the actual sample compared to the expected frequency); values indicate a difference larger than expected by chance for a p-value of 0.05.

+ Standardized residual (converted to a z-score) greater than +1.96 (indicating the cell was over-represented in the actual sample compared to the expected frequency); values indicate a difference larger than expected by chance for a p-value of 0.05.