Expression of L1CAM in curettage or high L1CAM level in preoperative blood samples predicts lymph node metastases and poor outcome in endometrial cancer patients

Ingvild L Tangen¹,², Reidun K Kopperud², Nicole CM Visser³, Anne C Staff⁴,⁵, Solveig Tingulstad⁶,⁷, Janusz Marcickiewicz⁸, Frédéric Amant⁹,¹⁰, Line Bjørge¹,², Johanna MA Pijnenborg¹¹, Helga B Salvesen¹,², Henrica MJ Werner¹,², Jone Trovik¹,²,¹² and Camilla Krakstad*,¹,²,¹²

¹Department of Gynaecology and Obstetrics, Haukeland University Hospital, 5053 Bergen, Norway; ²Centre for Cancer Biomarkers, Department of Clinical Science, University of Bergen, 5020 Bergen, Norway; ³Department of Pathology, Radboud University Medical Center, 6500 HB Nijmegen, The Netherlands; ⁴Department of Gynaecology, Oslo University Hospital, 0424 Oslo, Norway; ⁵Faculty of Medicine, University of Oslo, 0424 Oslo, Norway; ⁶Department of Gynaecology, St. Olav’s Hospital, 7006 Trondheim, Norway; ⁷Department of Laboratory Medicine, Children’s and Women’s Health (LBK), Norwegian University of Science and Technology (NTNU), 7491 Trondheim, Norway; ⁸Department of Obstetrics and Gynaecology, Halland’s Hospital Varberg, 43281 Varberg, Sweden; ⁹Department of Oncology and Gynaecologic Oncology, Leuven Cancer Institute, 3000 Leuven, Belgium; ¹⁰Center for Gynaecologic Oncology Amsterdam (CGOA), Netherlands Cancer Institute, 1006 BE Amsterdam, The Netherlands and ¹¹Department of Obstetrics and Gynaecology, Radboud University Medical Center, 6500 HB Nijmegen, The Netherlands

Background: Several studies have identified L1 cell adhesion molecule (L1CAM) as a strong prognostic marker in endometrial cancer. To further underline the clinical usefulness of this biomarker, we investigated L1CAM as a predictive marker for lymph node metastases and its prognostic impact in curettage specimens and preoperative plasma samples. In addition, we aimed to validate the prognostic value of L1CAM in hysterectomy specimen.

Methods: Immunohistochemical staining of L1CAM was performed for 795 hysterectomy and 1134 curettage specimen from endometrial cancer patients. The L1CAM level in preoperative blood samples from 372 patients was determined using ELISA.

Results: Expression of L1CAM in curettage specimen was significantly correlated to L1CAM level in corresponding hysterectomy specimen (P<0.001). Both in curettage and preoperative plasma samples L1CAM upregulation was significantly associated with features of aggressive disease and poor outcome (P<0.001). The L1CAM was an independent predictor of lymph node metastases, after correction for curettage histology, both in curettage specimen (P=0.002) and plasma samples (P=0.048). In the hysterectomy samples L1CAM was significantly associated with poor outcome (P<0.001).

Conclusions: We demonstrate that preoperative evaluation of L1CAM levels, both in curettage or plasma samples, predicts lymph node metastases and adds valuable information on patient prognosis.

*Correspondence: Professor C Krakstad; E-mail: camilla.krakstad@uib.no
¹²These authors contributed equally to this work.

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Endometrial cancer is the most common gynaecologic malignancy and the fourth most common cancer among women in industrialised countries (Torre et al, 2015). Although the prognosis is good, 15 to 20% of patients with presumed localised disease at diagnosis recur (Abeler and Kjorstad, 1991; Morrow et al, 1991). Identifying biomarkers that can select patient populations for optimal surgical and systemic treatment is important to improve outcome for these patients.

The diagnosis and treatment of endometrial cancer patients usually consists of a preoperative biopsy followed by imaging, surgery and adjuvant treatment depending on risk classification. A complete surgical staging of endometrial cancer patients involves both pelvic and para-aortic lymphadenectomy (Pecorelli, 2000). Worldwide, there are however a wide variation in lymphadenectomy in endometrial cancer, and selection criteria for lymphadenectomy are not uniformly standardised (Maggino et al, 1995, 1998). Metastases to the lymph nodes are known to be associated with poor prognosis, and although lymphadenectomy provides diagnostic information that can help in selecting optimal adjuvant treatment, its effect on survival is uncertain, and it is associated with increased complication rates (Benedetti Panici et al, 2008; Wright et al, 2012; Morice et al, 2016). Improved identification of high-risk patients preoperatively is therefore needed to tailor the primary surgical strategy.

L1 cell adhesion molecule (L1CAM) is a cell adhesion molecule of the immunoglobulin superfamily (Moos et al, 1988). It consists of an extracellular domain, a transmembrane region and a highly conserved cytoplasmic domain (Moos et al, 1988). The extracellular domain of L1CAM can be cleaved by the metalloproteases ADAM10 and ADAM17, resulting in a soluble form of L1CAM (Mechtersheimer et al, 2001; Maretzky et al, 2005). The L1CAM was initially identified in the nervous system and plays an important role in neurogenesis (Rathjen and Schachner, 1984; Moos et al, 1988; Schafer and Altevogt, 2010). Later, L1CAM has also been shown to be involved in almost every aspect of cancer progression including promoting cell proliferation, migration, invasion and metastases of cancer cells (Raveh et al, 2009; Schafer and Altevogt, 2010; Altevogt et al, 2016).

Expression of L1CAM has been investigated in several cancer types, and is associated with poor outcome (Fogel et al, 2003; Allory et al, 2005; Boo et al, 2007; Schroder et al, 2009; Tsichler et al, 2011; Tsutsumi et al, 2011; Wang et al, 2013; Hua et al, 2016). In endometrial cancer hysterectomy samples, L1CAM has been reported to be associated with aggressive disease characteristics including loss of hormone receptors and reduced survival (Huszar et al, 2010; Zeimet et al, 2013; Bosse et al, 2014; Dellingler et al, 2016; Geels et al, 2016; van der Putten et al, 2016; Komnoss et al, 2017). The L1CAM is a strong prognostic marker within the subgroup of stage I endometrioid endometrial cancer (Zeimet et al, 2013; van der Putten et al, 2016), and within the subgroup of advanced-stage endometrioid endometrial cancer (van der Putten et al, 2016) when evaluated postoperatively in hysterectomy samples. However, the expression of L1CAM in preoperative biopsies and its usefulness in preoperative prediction of lymph node metastases and outcome are not yet established. In addition, soluble L1CAM (sL1CAM) is suggested to be a valuable circulating biomarker in different cancers (Zander et al, 2011; Bondong et al, 2012). It has been detected in the culture medium from different cell lines including melanoma, breast and ovarian cancer (Beer et al, 1999; Gutwein et al, 2005; Li and Galileo, 2010), and also in serum and ascites of endometrial and ovarian cancer (Fogel et al, 2003; Wojciechowski et al, 2017), suggesting that the soluble form of L1CAM may also play a role in these cancers.

The primary objective of this study was to assess the value of L1CAM in preoperative samples (curettage and plasma samples) as a predictive marker for lymph node metastases and poor prognosis. In addition, we aimed to validate the prognostic value of L1CAM in hysterectomy samples.
staining and staining evaluation of ER and PR has previously been described (Trovik et al., 2013). Using the same scoring system as above, ER staining index \( \leq 3 \) and PR staining index 0 was defined as low expression/loss.

**Enzyme-linked immunosorbent assay (ELISA).** The EDTA-blood was obtained from 372 patients with endometrial cancer before primary surgery. The blood samples were centrifuged at 1600 g for 15 min and the plasma was stored at –80 °C until measurement of sL1CAM. The ELISA kits were bought from MyBioSource (Cat. No. MBS2033094, MyBioSource, San Diego, CA, USA) and the sandwich ELISA was performed according to the manufacturer’s instructions. Briefly, 100 μl plasma sample or standard was put into a 96-well microplate and incubated for 2 h at 37 °C. Then, 100 μl biotin-conjugated L1CAM-specific antibody was added and incubated for 1 h at 37 °C. After the well was washed three times with washing solution, 100 μl avidin conjugated to horseradish peroxidase (HRP) was added and incubated for 30 min at 37 °C. The wells were washed five times and 90 μl substrate solution was added before 20 min of incubation away from light followed by addition of 50 μl stop solution. The absorbance was measured in a microplate reader at the wavelength of 450 nm, and plasma concentration of sL1CAM calculated. For further statistical analysis the patients were grouped in four groups based on sL1CAM plasma level, and subsequently in high and low L1CAM based on similarities in survival (the three groups with lowest L1CAM level = low L1CAM level; the upper quartile = high L1CAM level) (Supplementary Figure 1). Plasma from healthy age-matched female blood donors (n = 32) was used as control group.

**Gene expression analysis.** The RNA was extracted from fresh frozen tissue from primary tumour from patients diagnosed with endometrial cancer. Hybridisation to Agilent (Santa Clara, CA, USA) Whole Human Genome Microarray 44k (Cat. No. G4112F) was done according to the manufacturer’s instructions. The arrays were scanned and normalised as previously described (Kraksstad et al., 2012).

**Statistical analyses.** Data were analysed using SPSS version 24 (SPSS Inc., Chicago, IL, USA). Probability of <0.05 was considered statistical significant, and all statistical tests were two sided. Associations between groups were analysed using the \( \chi^2 \) test for categorical variable and the Mann–Whitney \( U \)-test for continuous variables. Binary logistic regression was used to estimate odds ratios (ORs) for lymph node metastases. Univariate survival analysis was performed using the Kaplan–Meier (product-limit) method. Disease-specific survival was defined as time from surgery to death from endometrial cancer. Survival between groups was compared using the log-rank (Mantel–Cox) test. The Cox proportional hazard regression model was used to evaluate the prognostic impact of L1CAM adjusted for other prognostic parameters.

### RESULTS

**Expression of L1CAM in endometrial cancer curettage predicts lymph node metastases and poor outcome.** The protein expression of L1CAM was evaluated by IHC in curettage samples from 1134 patients. Low expression was defined as staining index 0–3 and was found in 88% (n = 1000) of the lesions, whereas 12% (n = 134) expressed high levels of L1CAM. High L1CAM expression in curettage specimen was significantly associated with high age, loss of ER and PR expression and high-risk curettage classification and also high FIGO stage, non-endometrioid histology and high grade in the hysterectomy specimen (all \( P < 0.001 \)) (Table 1). There was a highly significant correlation between L1CAM staining in curettage specimen and staining in the corresponding hysterectomy specimen (\( P < 0.001 \)) (Table 1). High expression of L1CAM in curettage specimen predicted poor disease-specific survival, both in the whole patient population (\( P < 0.001 \)) (Figure 1A) and within patients with low-risk curettage histology (\( P < 0.001 \)) (Figure 1B). Expression of L1CAM also showed independent prognostic impact in Cox survival analysis after correction for age, FIGO stage, histologic subtype and grade assessed in the hysterectomy specimens, with hazard ratio of 1.77 (95% CI 1.17–2.66, \( P = 0.006 \)) (Supplementary Table 1).

Interestingly, patients with high L1CAM expression in curettage specimen had significantly higher occurrence of lymph node metastases compared with patients with low expression of L1CAM, both in the whole patient population (33% vs 10% respectively,

**Table 1. Clinicopathological variables related to L1CAM status in curettage specimens for women operated for endometrial cancer**

| Variable | Low (0–3), n (%) | High (4–9), n (%) | P-value |
|----------|-----------------|------------------|---------|
| Age (years) | | | | |
| \( < 66 \) | 520 (95) | 30 (5) | <0.001 |
| \( \geq 66 \) | 480 (82) | 104 (18) | |
| Curettage histology | | | | |
| Low risk | 811 (95) | 40 (5) | <0.001 |
| High risk | 170 (64) | 94 (36) | |
| PR curettage | | | | |
| Positive | 795 (96) | 36 (4) | <0.001 |
| Negative | 191 (69) | 88 (31) | |
| ER-α curettage | | | | |
| Positive | 746 (95) | 43 (5) | <0.001 |
| Negative | 228 (72) | 89 (28) | |
| FIGO-09 stage | | | | |
| I–II | 872 (91) | 84 (9) | <0.001 |
| III–IV | 128 (72) | 50 (28) | |
| Histologic type | | | | |
| Endometrioid | 874 (96) | 36 (4) | <0.001 |
| Adenosquamous | 10 (91) | 1 (9) | |
| Clear cell | 29 (71) | 12 (29) | |
| Serous papillary | 39 (36) | 70 (64) | |
| Carcinosarcoma | 35 (76) | 11 (24) | |
| Undifferentiated/other | 13 (77) | 4 (23) | |
| Histologic grade | | | | |
| Grade 1/2 | 754 (97) | 21 (3) | <0.001 |
| Grade 3 | 120 (86) | 19 (14) | |
| Metastatic nodes | | | | |
| Negative | 657 (92) | 60 (8) | <0.001 |
| Positive | 77 (72) | 30 (28) | |
| Myometrial infiltration | | | | |
| <50% | 608 (92) | 51 (8) | <0.001 |
| \( \geq 50\% \) | 309 (84) | 60 (16) | |
| Ploidy | | | | |
| Diploid | 288 (94) | 17 (6) | <0.001 |
| Aneuploid | 49 (58) | 35 (42) | |
| L1CAM hysterectomy specimen | | | | |
| Low | 431 (96) | 16 (4) | <0.001 |
| High | 26 (36) | 46 (64) | |

Abbreviations: ER = oestrogen receptor, FIGO = Federation of Gynaecology and Obstetrics, L1CAM = L1 cell adhesion molecule, PR = progesterone receptor. Missing information on curettage histology classification for 19 patients, PR status in curettage for 24 patients, ER-α status in curettage for 28 patients, grade for 9 patients, metastatic nodes for 310 patients, myometrial infiltration for 106 patients, ploidy for 745 patients and L1CAM status in hysterectomy specimen for 615 patients.

* Curettage histological risk classification, low risk benign, hyperplasia or endometrioid grades 1–2) or high risk (non-endometrioid or endometrioid grade 3).

* Only endometrioid.
High expression of L1CAM in hysterectomy samples is significantly associated with poor survival in both the whole population (E) and the subgroup with stage 1 endometrioid endometrial cancer (F). *Curettage histological risk classification, low risk (benign, hyperplasia or endometrioid grades 1–2) or high risk (non-endometrioid or endometrioid grade 3). Number in brackets: number of patients in the group/number of events in the group.

P < 0.001, Table 1) and in the subgroup with low-risk histology classification (30% vs 9% respectively, P < 0.001, Supplementary Table 2). In a univariate model, curettage high-risk histology, combined loss of ER/PR (a marker previously shown to be a strong predictor of lymph node metastases in endometrial cancer patients; Trovik et al, 2013) and high expression of L1CAM all predicted presence of metastatic lymph nodes (Table 2). When adjusting for curettage histology and preoperative ER/PR loss in a multivariate model, high expression of L1CAM predicted lymph node metastases with adjusted OR 2.51 (95% CI 1.41–4.64, P = 0.002) (Table 2).

High sL1CAM level in preoperative blood samples is associated with lymph node metastases and poor survival in endometrial cancer patients. The level of sL1CAM was also investigated in preoperative plasma samples from 372 patients with endometrial cancer. The plasma level of sL1CAM was significantly higher in endometrial cancer patients compared with healthy controls (P = 0.001 (endometrial cancer patients: mean = 997 pg ml\(^{-1}\), s.e.m. = 27; healthy controls: mean = 684 pg ml\(^{-1}\), s.e.m. = 29)). There was a significant correlation between sL1CAM level in plasma evaluated by ELISA and L1CAM expression in both curettage specimen (P = 0.007) (Supplementary Figure 2A) and
There are several studies suggesting L1CAM as a promising biomarker in endometrial cancer, and its expression has earlier been shown to be associated with aggressive disease and poor survival, and inversely correlated with expression of ER and PR (Huszar et al, 2010; Zeimet et al, 2013; Bosse et al, 2014; Dellinger et al, 2016; Geels et al, 2016; van der Putten et al, 2016; Koomoss et al, 2017). Current data point to an added prognostic value of L1CAM, and integrating L1CAM status as part of the molecular classification of endometrial cancer can be useful. We here validate that L1CAM is a strong prognostic marker in hysterectomy samples when including all samples in this prospectively collected population-based series. In addition, within the subgroup of patients with FIGO stage 1 endometrioid endometrial cancer, L1CAM expression is a predictor of poor survival, although not as strong as shown in other studies (Zeimet et al, 2013; van der Putten et al, 2016). The usefulness of L1CAM as a prognostic marker within this subgroup was also questioned in a recent study including 388 patients where L1CAM failed to be a clinically relevant marker of poor prognosis in FIGO stage 1 endometrioid endometrial cancer (Smogeli et al, 2016). These differences could be explained by not only different scoring methods and cutoffs for L1CAM, but also differences in the patient cohort with regard to proportion of patients where lymphadenectomy is performed, as well as the use of adjuvant treatment.

In this study TMAs were used to determine the expression of L1CAM, and the staining index was used as scoring method with high expression defined as 4–9 and low expression defined as 0–3. Most other studies investigating the expression of L1CAM have used whole sections and a cutoff point of 10% (Zeimet et al, 2013; Bosse et al, 2014; Smogeli et al, 2016; van der Putten et al, 2016). The use of different scoring methods and cutoffs make the studies less comparable; however, the fact that different scoring methods identify L1CAM as a strong biomarker supports its robustness as biomarker in endometrial cancer. Although an interobserver κ-value of 0.76 was obtained for L1CAM in this study, a scoring method like the staining index where both intensity and area are taken into account may be more subjectively influenced compared with the method only considering the area. Before potential clinical implementation of L1CAM as biomarker in endometrial cancer, the optimal staining protocol, scoring method and cutoff will have to be determined and validated. In an investigational setting the use of TMAs is both time and cost effective, and the method has been shown to yield reproducible results compared with full sections (Konen et al, 1998; Fons et al, 2007). However, TMAs do not provide the same morphological information as full hysterectomy specimen (P = 0.015) (Supplementary Figure 2B) evaluated by IHC. High preoperative plasma levels of sL1CAM were significantly associated with high age, loss of ER and PR and high-risk histology in curettage, and also high FIGO stage and non-endometrioid histology in the hysterectomy specimen (Table 3). High sL1CAM plasma level predicted poor disease-specific survival in both the whole population (P < 0.001) (Figure 1C) and the group with low-risk curettage histology (P = 0.04) (Figure 1D). sL1CAM level in plasma did not have independent prognostic impact when adjusting for age, FIGO stage, histologic type and grade (data not shown).

Patients with high sL1CAM plasma levels had significantly higher occurrence of lymph node metastases compared with patients with low sL1CAM level (23% vs 9% respectively, P = 0.003) when including the whole population, but not within the subgroup with low-risk histology classification (Supplementary Table 2). In a univariate model both high-risk histology in curettage and high plasma levels of sL1CAM were predictive of lymph node metastases. In addition, when correcting for curettage histology in a multivariate model, sL1CAM level in plasma was a predictor of lymph node metastases with OR 2.25 (95% CI 1.01–5.02, P = 0.048) (Table 4).

### Discussion

**Table 2. Prediction of lymph node metastases based on curettage histology, status of L1CAM and ER/PR in curettage specimen in 763 lymph node sampled endometrial cancer patients**

| Variable | N | Uni-variate OR | 95% CI | P | Multivariate OR | 95% CI | P | Sensitivity | Specificity | PPV | NPV |
|----------|---|----------------|--------|---|----------------|--------|---|-------------|------------|-----|-----|
| **Curettage histology**<sup>b</sup> | | | | | | | | | | | |
| Low risk | 590 | 1 | | | | | | | | | |
| High risk | 173 | 3.39 | 2.19–5.23 | <0.001 | 1.94 | 1.16–3.25 | 0.011 | 0.49 | 0.75 | 0.22 | 0.91 |
| **L1CAM expression** | | | | | | | | | | | |
| Low | 681 | 1 | | | | | | | | | |
| High | 82 | 4.49 | 2.69–7.50 | <0.001 | 2.51 | 1.41–4.64 | 0.002 | 0.28 | 0.92 | 0.33 | 0.90 |
| **ER/PR expression** | | | | | | | | | | | |
| Normal | 606 | 1 | 3.26 | 2.10–5.07 | <0.001 | 1 | 1.15–3.17 | 0.013 | 0.42 | 0.82 | 0.26 | 0.90 |
| Loss<sup>a</sup> | 157 | 1 | | | | | | | | | |

**Abbreviations:** CI = confidence interval; ER = estrogen receptor; L1CAM = L1 cell adhesion molecule; NPV = negative predictive value; OR = odds ratio; PPV = positive predictive value; PR = progesterone receptor.

<sup>a</sup>Only patients with data available for all variables included in the multivariate logistic regression analysis are included in the univariate analysis (N = 763).

<sup>b</sup>Curettage histological classification, low risk (benign, hyperplasia or endometrioid grades 1–2) or high risk (non-endometrioid or endometrioid grade 3).

<sup>c</sup>Patients with double loss of ER/PR expression.

Expression of L1CAM in hysterectomy specimen validates to be a strong predictor of poor outcome in endometrial cancer. Several studies have identified L1CAM as a strong prognostic marker when examining hysterectomy specimens in endometrial cancer. In this study we investigated expression of L1CAM in 795 primary tumours. In 14% of the cases (n = 110), expression of L1CAM was high whereas 86% (n = 685) of the cases showed low L1CAM levels. There was a significant association between L1CAM protein levels and L1CAM mRNA levels (Supplementary Figure 3). We identified that high expression of L1CAM in hysterectomy samples is associated with features of aggressive endometrial cancer (Supplementary Table 3) and poor survival (Figure 1E). Expression of L1CAM also showed independent prognostic impact in Cox survival analysis when adjusting for age, FIGO stage, histologic subtype and grade with HR 2.7 (95% CI 1.8–4.3, P < 0.001) (Supplementary Table 4). Within the subgroup of stage I endometrioid endometrial cancer, 5% of the cases expressed high L1CAM. In addition, within this subgroup, expression of L1CAM was associated with characteristics of aggressive endometrial cancer (Supplementary Table 5) and poor survival (Figure 1F), but it did not have independent prognostic impact when adjusting for age and histologic grade (data not shown).
sections, and should be used with caution, and depending on the research question. Although three tissue cores were used for each patient in this study, L1CAM-positive areas of the tumour might be missed that may result in underestimation of L1CAM expression. This is however also a challenge using full sections, and validation of markers is crucial before applied in a clinical setting.

In endometrial cancer the tumour is easily accessible for biopsy before surgery. Histologic type and grade are routinely investigated in the preoperative biopsies, and this provides prognostic information relevant for the extent of the surgery. However, the correlation between preoperative assessment of curettage and postoperative evaluation of hysterectomy specimens varies (Lampe et al, 1995; Frumovitz et al, 2004; Eltabbakh et al, 2005; Leitao et al, 2008; Werner et al, 2013). Therefore, identification of reliable markers in curettage material that could predict lymph node metastases would provide a better basis for treatment selection. There are different molecular markers that have been studied in preoperative biopsies, and could serve as predictive markers for metastatic disease (Salvesen et al, 2012). One example is combined loss of ER and PR for prediction of lymph node metastases and poor survival in endometrial cancer (Trovik et al, 2013). Its usefulness in tailoring surgical treatment is currently tested in a clinical trial (Momatec2, NCT02543710), where the decision to perform lymphadenectomy in low- and intermediate-risk patients is dependent on the preoperative hormone receptor status. In the present study we investigate L1CAM level in curettage and preoperative blood samples, and its potential for predicting lymph node metastases and poor prognosis. Only few studies have previously investigated the expression of L1CAM in curettage samples. Bosse et al (2014) compared expression of L1CAM in curettage and hysterectomy samples from 42 patients and Fogel et al (2003) from 14 patients. Both studies reported a good concordance between staining in curettage and hysterectomy samples (Fogel et al, 2003; Bosse et al, 2014). We here confirm that the L1CAM staining in the curettage and hysterectomy sample is significantly associated. More importantly, we report the novel finding that high L1CAM expression in curettage samples is a significant predictor of lymph node metastases in both a univariate analysis and a multivariate analysis correcting for curettage histology and preoperative ER/PR expression. Our large study shows that L1CAM expression in curettage specimens is associated with features of aggressive endometrial cancer disease and poor survival in both the whole patient population and within the subgroup of patients with a preoperative low-risk histology classification. These findings suggest that evaluation of L1CAM in curettage samples could be a valuable supplement to the currently performed preoperative assessment for determination of surgical extent. However, this is the first study investigating L1CAM as a predictive marker for lymph node metastases and its prognostic impact in curettage specimens, and these findings would have to be validated in other studies before its place in the preoperative assessment can be determined.

The soluble form of L1CAM has earlier shown to be present in sera of endometrial cancer patients. In a study by Fogel et al (2003),
9 out of 10 patients with L1CAM-positive endometrial tumours also had detectable concentrations of sL1CAM in preoperative serum samples. A recent study investigating serum levels of sL1CAM in 35 endometrial cancer patients found it to be lower in patients compared with healthy controls, and no correlations between soluble L1CAM concentration and histopathology, stage or grade were found (Wojciechowski et al., 2017). The latter is contradictory to our results as we find that the level of sL1CAM is significantly increased in endometrial cancer patients compared with healthy controls, and that a high level of sL1CAM is associated with aggressive disease characteristics and poor survival. In addition, we report that a high level of sL1CAM in preoperative blood samples predicts lymph node metastasis in both a univariate analysis and a multivariate analysis correcting for preoperative histology. Increased level of sL1CAM has also been found to be associated with poor prognosis in other cancer types, such as in gastrointestinal stromal tumours (Zander et al., 2011) and ovarian cancer (Bondong et al., 2012). Whether the soluble form of L1CAM, in addition to serving as a prognostic biomarker, also has a role in tumour development and progression is not clear, but studies investigating its function have suggested that sL1CAM is involved in stimulating cell motility and contributes to cell survival through activating anti-apoptotic pathways (Mechtersheimer et al., 2001; Bondong et al., 2012).

The primary treatment for endometrial cancer patients is surgical that typically includes hysterectomy and bilateral salpingo-oophorectomy with or without lymphadenectomy. Although lymphadenectomy is part of the complete staging procedure and important for risk stratification of endometrial cancer patients, no survival benefit is shown in randomised clinical trials, and it is associated with increased complication rates and prolonged operation time in a comorbid and obese patient population (Benedetti Panici et al., 2008; Pecorelli, 2009; Wright et al., 2012; Morice et al., 2016). Identifying markers that can preoperatively predict prognosis and lymph node metastases is important. Biomarkers can aid in tailoring the surgical treatment through identifying those patients with advanced disease who would benefit from extensive surgery, but also aid in preventing overtreatment in low-risk patients. Both L1CAM expression evaluated by IHC in curettage and the level of sL1CAM evaluated by ELISA in plasma seem to be promising biomarkers in endometrial cancer. Although L1CAM expression in curettage is a stronger predictor of both lymph node metastases and disease-specific survival in multivariate analysis compared with sL1CAM in plasma, and may be the preferred method, the fact that no tissue and only a blood sample is necessary for the sL1CAM analysis is an advantage. However, additional studies and in particular prospective randomised trials would be important to evaluate the effect of implementing L1CAM expression in curettage samples and sL1CAM level in blood samples into routine clinical practice.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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L1CAM as biomarker in endometrial cancer

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