Risk factors to predict the incidence of surgical adverse events following open or laparoscopic surgery for apparent early stage endometrial cancer: results from a randomised controlled trial

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Abstract

Aims: To identify risk factors for major Adverse Events (AEs) and to develop a nomogram to predict the probability of such AEs in individual patients who have surgery for apparent early stage endometrial cancer.

Methods: We used data from 753 patients who were randomized to either total laparoscopic hysterectomy or total abdominal hysterectomy in the LACE trial. Serious adverse events that prolonged hospital stay or postoperative adverse events (using common terminology criteria 3+, CTCAE V3) were considered major AEs. We analyzed pre-surgical characteristics that were associated with the risk of developing major AEs by multivariate logistic regression. We identified a parsimonious model by backward stepwise logistic regression. The six most significant or clinically important variables were included in the nomogram to predict the risk of major AEs within 6 weeks of surgery and the nomogram was internally validated.

Results: Overall, 132 (17.5%) patients had at least one major AE. An open surgical approach (laparotomy), higher Charlson's medical co-morbidities score, moderately differentiated tumours on curettings, higher baseline ECOG score, higher body mass index and low haemoglobin levels were associated with AE and were used in the nomogram. The bootstrap corrected concordance index of the nomogram was 0.63 and it showed good calibration.

Conclusions: Six pre-surgical factors independently predicted the risk of major AEs. This research might form the basis to develop risk reduction strategies to minimize the risk of AEs among patients undergoing surgery for apparent early stage endometrial cancer.

Clinical Trial Registration: NCT00096408

Keywords: Endometrial cancer; safety; surgery; risk factors

Introduction

Endometrial cancer represents a significant health issue for women in developed countries and its incidence is still rising (1). Advanced age and an oversupply of endogenous or exogenous oestrogen are the most common and well established risk factors for endometrial cancer and patients often receive treatment for obesity, diabetes mellitus and hypertension (2-5). Treatment of endometrial cancer is primarily surgical, generally yielding excellent survival outcomes (6).

Traditionally, surgery has been performed through a laparotomy (Total Abdominal Hysterectomy; TAH), which is associated with significant morbidity. Results from our randomized controlled trial comparing TAH with total laparoscopic hysterectomy (TLH) (the LACE trial) found that patients undergoing TLH reported significantly better postsurgical improvement in Quality of Life (QoL) compared to TAH (7). This improvement in QoL continued to favour a laparoscopic approach for up to 6 months post-surgery. Previous findings from the US Gynecologic Oncology Group (GOG) LAP2 trial suggest a lower incidence of surgical adverse events (AEs) in uterine cancer patients who received laparoscopic compared to open surgery (8). In contrast, the recently published Dutch TLH trial suggested a similar rate of surgical complications in laparoscopic and open surgery for early endometrial cancer and endometrial hyperplasia with atypia (9).

In this issue, we have reported that the incidence of AEs was significantly reduced in patients receiving TLH compared to TAH (Obermair et al, submitted for publication). The results suggest that the surgical approach is a potentially modifiable risk factor for AEs, but the risk factors leading to surgical complications are largely unknown.

Therefore, it was the aim of this manuscript to identify the risk factors associated with AEs in patients undergoing surgery for apparent early stage endometrial cancer. In addition, we

developed a nomogram to predict a patient's individual risk to develop a major AE based on pre-surgical characteristics.

Patients and Methods

Between October 2005 and June 2010, a total of 760 women with apparent stage I endometrial cancer was enrolled into the LACE trial (clinicaltrials.gov id: NCT00096408). Its study design, data on early surgical recovery and postoperative QoL as well as data on the surgical safety of TLH were reported previously (7, 10). In brief, patients were randomized to either TLH or TAH using stratified permuted blocks through a web-based system with concealment of the next allocated treatment to study staff. Ethical clearance was obtained from all the relevant hospitals where patients were recruited and all the patients had provided written informed consent.

Women were eligible if they had histologically confirmed endometrioid endometrial adenocarcinoma (irrespective of histological grade), disease apparently confined to the uterus and ECOG performance status of zero or one. Patients had to have medical imaging of the pelvis, abdomen and the chest to suggest the absence of extrauterine disease. Patients had a comprehensive surgical staging except those with grade 1 or grade 2 tumours with myometrial invasion up to the inner half, patients who were unfit for a lymph node dissection because of medical reasons or morbidly obese patients. All trial surgeons had to go through an accreditation process to ensure the highest possible surgical standard. The surgical technique was described in detail previously (11).

A comprehensive surgical and medical history was taken prior to surgery. Medical Co-morbidities were recorded, classified and scored according to Charlson et al (12). Patients also completed questionnaires on relevant social and demographic variables. Patients were

followed-up for at least 6 weeks for any adverse event. Post-operative adverse events (AEs) were recorded using the NCI Common Terminology Criteria for Adverse Events v3.0 (CTC AE). Serious AEs were defined as any event that resulted in death, was immediately life threatening, required inpatient hospitalization or prolongation of an existing hospitalization or that resulted in persistent or significant disability/incapacity. All serious AEs were reviewed by an independent safety committee. All the AEs were managed by respective clinicians/co-investigators as per their local guidelines and patients were followed-up until satisfactory resolution or until the principal investigator or co-investigator deemed the event to be chronic or the patient was assessed to be stable. A "major AE" was defined as either a postoperative AE of CTC Grade 3+ and/or a serious AE as defined above. For the aim of this analysis, the incidence of a "major AE" was considered an endpoint.

Statistical analyses

Patients who had completed at least 6 weeks of follow-up after surgery were included. Univariate logistic regression analysis was used to test for associations between the incidence of major AEs and relevant clinical and demographic factors. Due to the skewed distribution of CA-125, neutrophil count, bilirubin and alanine transaminase (ALT), these variables were log (natural) transformed and evaluated. Variables that showed significant association with major AEs were used in a multivariate logistic regression with stepwise model selection. Risk-factors were also evaluated for significant interactions. Height and or weight were missing for 27 patients (3.5%) and these patients were excluded in multivariate models that utilized body mass index as a predictor. No data were imputed. Treatment effects were analysed according to the intention to treat principle.

A nomogram was developed to predict the risk of major AEs within 6 weeks of surgery using the entire dataset. The following variables available prior to surgery formed part of the

nomogram: planned surgical approach (TAH vs TLH), Charlson's comorbidity score (12), grade of curettings ((International Federation of Gynecology and Obstetrics (FIGO) grades 1, 2 or 3), Eastern Cooperative Oncology Group (ECOG) score (0 vs 1), Body Mass Index (BMI) (<25, 25 to < 30, 30 to < 35, 35 to < 40 and 40+) and haemoglobin levels. The predicted probability was calculated for each patient based on the nomogram, which was then assessed for its ability to discriminate among patients, as quantified by the concordance index. This concordance index is equivalent to the area under the receiver operating characteristic (ROC) curve. A value of 0.5 indicates no discrimination ability and 1 represents perfect separation of patients with different outcomes. To correct for overestimation, bootstrapping was performed with 1000 replications and the nomogram was calibrated to improve predictions on external datasets. Statistical analyses were performed using SAS 9.2 or Stata version 11.2. Nomogram was generated using R version 2.13.2 (R Development Core Team, 2011) with 'rms' package added. Statistical significance was set at the level of 0.05.

Results

A total of 760 patients were enrolled in the LACE trial between 2005 and 2010. Of these, four patients withdrew after randomization but prior to surgery and an additional three patients withdrew from the trial one week after surgery. Of a total of 753 evaluable patients with at least 6 weeks of follow-up, 349 were randomly allocated to treatment with TAH, and 404 to treatment with TLH. Treatment groups were balanced in terms of relevant demographic and clinical factors and descriptive AE data are also shown elsewhere (Obermair et al, submitted for publication in this issue). A total of 117 (15%) patients had at least one post-operative AE with CTC Grade 3+, and 83 (11%) patients had at least one serious AE. One hundred and thirty two patients (17%) had a major AE.

Univariate logistic regression analysis showed that allocation to TAH, increasing Charlson's comorbidity score, increasing BMI, increasing ECOG performance score, higher grade of curettings, low baseline haemoglobin levels and elevated aspartate transaminase levels were associated with risk of a major AE, while age at diagnosis, and other blood status factors did not attain statistical significance (Table 2).

On multivariable analysis, treatment allocation to TAH, increasing Charlson's medical co-morbidity score, poor grade of differentiation on curettings (FIGO grade 2 or 3), high BMI and low preoperative haemoglobin level remained independently significant for major AEs ($p<0.05$). Figure 1 shows the nomogram to predict major AEs. To allow risk prediction, points were allocated to each of the predictor variables. The sum of all the points for a patient corresponds to a predicted probability of a major AE. Initial modelling showed a concordance index of 0.68. Internal validation with 1000 bootstrap resamples showed our model to over-predict by 4.5%. The model was recalibrated and achieved a bias-corrected concordance index of 0.65 for predicting a major AE.

Figure 2 shows in a graphical format, how closely the predictions from the nomogram compare with actual outcomes for patients in this study. Values on the x-axis represent the prediction calculated with use of the nomogram and those on the y-axis represent the actual data for our patients. The dashed diagonal line represents the performance of an ideal nomogram, where predicted outcome perfectly matches with actual outcome.

Discussion

We present a simple algorithm in the form of a nomogram to estimate an individual patient's risk of developing a major surgical AE following TLH or TAH for apparent early endometrial cancer prior to surgery. Parameters available before surgery and found to be

independently associated with an increased risk of major AE in patients presenting with apparently stage I endometrial cancer include an open surgical approach through laparotomy, a higher Charlson's medical co-morbidity score at baseline, advanced FIGO grade of curettings, higher BMI and low haemoglobin levels prior to surgery.

Adverse events during or following a surgical procedure are not uncommon, especially in high risk specialties such as surgical oncology. The published incidence of adverse events among patients with gynaecological cancer varies from 26% to 54% (13, 14) and some studies suggest that a significant portion of AEs are preventable (15-17).

The present manuscript suggests that major AEs are partly predictable. The planned surgical approach was one of the potentially modifiable risk factors. Choosing a laparoscopic approach to surgery for endometrial cancer reduced the risk of major surgical AEs by at least 46% after adjusting for other prognostic factors. Moderately differentiated curettings and low preoperative haemoglobin independently contributed to the risk of major AEs. The preoperative ECOG performance status was also included in the model but only scarce literature is available on the role of ECOG performance status and its impact on the risk of surgical adverse events in endometrial cancer. However, performance status has been shown to be related to clinical outcomes including survival in other cancers (18-24).

Obesity was reported to be a risk factor for postoperative AEs previously, especially in patients who require a laparotomy (25, 26). In the Dutch TLH trial (9), increasing age and BMI were significantly associated with an increased risk of major complications regardless of the surgical approach. In the LACE trial, higher BMI increased the risk for major AEs. However, age was not an important factor for major AEs.

The Charlson's index is a weighted index that considers the number and severity of medical co-morbid conditions. It was developed on a cohort of 559 medical patients in 1987 (12) and

was shown to estimate the risk of death from those medical co-morbidities. Previously we described the influence of the presence of malignancy, complexity of surgery, American Association of Anaesthetists score and BMI on the risk of AEs in a heterogeneous patient population with proven or suspected gynaecological cancer (14). In contrast, the present work describes the influence of the Charlson's index as a standardised tool to quantify the impact of co-morbid conditions on a large number of homogenous patients who had surgery for apparent early-stage endometrial cancer. With every increase in Charlson's index by 1 point, the risk of a major AE rises by 15%.

The nomogram, as presented already accounts for the impact of surgical technique in the estimation of the risk of a major surgical AE. To provide a worked example, if a patient presents with a BMI of 32 kg/m^2 (40 points) and a Charlson's score of 6 (50 points), with grade 2 endometrioid adenocarcinoma on curettings (30 points), and ECOG functional score of 1 (30 points), with haemoglobin levels of 110 g/L (70 points), the total points are 210 for a patients receiving a TLH, and 248 for a patient receiving TAH. This reflects a risk of major AE of 30% compared to 50% for this patient if surgery is conducted by TLH compared to TAH, respectively. Thus, everything else being equal, the nomogram (as presented) can used to guide treatment choice if risk of surgical AE is a major factor.

Some limitations to the present analysis are acknowledged. In the LACE trial, surgical AEs were a predefined secondary endpoint. While we collected data on some important risk factors leading to surgical AEs, other potential confounding factors, such as history of previous abdominal/pelvic surgery, surgeon's experience, and organizational factors were not collected. Patients enrolled in the LACE trial had to have clinical early-stage disease, uterus size less than 10 weeks gestation and had to be fit for surgery with an ECOG score of not higher than 1. Therefore, our prediction model is not applicable to patients presenting with advanced stage endometrial cancer or to patients with poor preoperative ECOG performance

score, and also needs to be validated on an independent dataset to confirm its utility. Finally, the risk prediction tool developed within the present study still needs to be validated on an independent sample.

In summary, our manuscript offers a new approach to quantifying the risk for major AEs in individual patients who require surgery for apparent early-stage endometrial cancer. These findings may allow gynecological oncologists to better predict the probability of major AEs in individual patients. In the future, the nomogram may also be used for comparison of risk adjusted adverse outcomes between health care institutions and also over time within the same institution.

Conflict of interest statement:

AMcC had shares and stock ownership of Gynetech. He had received occasional consultancy honoraria from Gate Healthcare. AO has been an occasional adviser for Genzyme, with honoraria for presentations. AO has received research support from Bristol-Myers Squibb. SKC and AO have received research support from Abbott Australia. All other authors have declared that there no conflicts of interest.

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Table 1: Patient characteristics (reproduced from Obermair et al submission)

	TLH n=404	TAH n=349
Age < 50 years n(%)	35 (8.7)	32 (9.2)
BMI, kg/m^2		
Normal (<25 kg/m^2), n(%)	47 (12.1)	46 (13.6)
Overweight (25 to <30kg/m^2), n(%)	97 (25.0)	72 (21.3)
Obesity Class I (30 to <35 kg/m^2), n(%)	77 (19.8)	86 (25.4)
Obesity Class II (35 to <40 $kg/m^{2)}$, n(%)	81 (20.9)	61 (18.1)
Obesity Class III (40+ kg/m^2), n(%)	86 (22.2)	73 (21.6)
Charlson's Index (mean, SD)	3.0 (1.8)	2.9 (1.8)
Nodal dissection, n (%)		
Any	161/404 (39.9)	210/349 (60.2)
Pelvic	147/161 (91.3)	205/210 (97.6)
Aortic	11/161 (6.8)	43/210 (20.5)
Other (not specified)	13/161 (8.1)	16/210 (7.6)
Grade on curettings, n(%)		
1	258 (63.8)	220 (63.0)
2	119 (29.5)	106 (30.4)
3	27 (6.7)	23 (6.6)
ECOG, n(%)		
0	349 (86.4)	299 (85.7)
1	55 (13.6)	50 (14.3)
Blood tests, mean (SD)		
Haemoglobin, g/dL	135.9 (11.8)	134.4 (12.9)
Platelet count, $10^9/L$	278.5 (71.6)	280.5 (69.7)
Neutrophil count, $10^9/L$[a]	1.5 (0.37)	1.5 (0.33)
White cell count, $10^9/L$	7.8 (2.1)	7.9 (2.1)
Haematocrit	0.41 (0.04)	0.41 (0.04)
CA-125, U/ml[a]	2.9 (0.83)	2.8 (0.86)

Abbreviations: TLH = total laparoscopic hysterectomy; TAH=total abdominal hysterectomy; BMI: Body Mass Index; ECOG: Eastern Cooperative Oncology Group;
Results are log(natural) transformed.

Table 2: Pre-surgical factors associated with risk of developing major AEs after surgery for apparently early stage endometrial cancer

		Odds ratio	95% confidence interval		p-value
			Lower limit	Upper limit	
Planned surgical approach					
	TLH	Ref			
	TAH	1.73	1.18	2.53	0.01
Age at diagnosis		1.01	0.99	1.03	0.48
BMI					
Normal (<25 kg/m^2)		Ref			
Overweight (25 to <30kg/m^2)		1.40	0.61	3.17	0.43
Obesity Class I (30 to <35 kg/m^2)		2.11	0.95	4.65	0.07
Obesity Class II (35 to <40 kg/m^2)		2.29	1.03	5.11	0.04
Obesity Class III (40+ kg/m^2)		2.73	1.25	5.97	0.01
Charlson's Index		1.17	1.05	1.30	0.01
Grade of differentiation on curettings					
	1	Ref			
	2	1.60	1.07	2.39	0.02
	3	1.81	0.90	3.63	0.10
ECOG					
	0	Ref	-	-	-
	1	2.40	1.51	3.83	0.01
Blood tests (prior to surgery)					
Haemoglobin, g/dL		0.98	0.97	1.00	0.01
Haematocrit < 40%		1.46	0.99	2.14	0.06
Platelet count < 150 X 10^9/L		1.35	0.28	6.57	0.71
Aspartate transaminase > 34 IU/L		1.80	1.08	3.00	0.02
Alkaline Phosphatase, > 140 IU/L		0.99	0.33	2.96	0.99
White cell count X 10^9/L		1.03	0.94	1.13	0.54
Creatinine		1.01	1.00	1.01	0.19
Bilirubin[a]		0.97	0.71	1.31	0.82
Albumin		0.99	0.98	1.01	0.38

Abbreviations: BMI: Body Mass Index; ECOG: Eastern Cooperative Oncology Group; a Log(natural) transformed

Table 3. Multivariate model predicting major AEs after surgery for apparently early stage endometrial cancer

	Odds Ratio	95% CI		p-value
Laparotomy vs laparoscopy	1.88	1.25	2.81	0.01
Charlson's score	1.15	1.02	1.29	0.02
Grade of differentiation on curettings				
Grade 1	Ref			
Grade 2	1.67	1.08	2.58	0.02
Grade 3	1.98	0.93	4.23	0.08
ECOG (1 vs 0)	1.64	0.97	2.78	0.07
BMI				
Normal (<25 kg/m^2)	Ref			
Overweight (25 to <30kg/m^2)	1.41	0.61	3.28	0.42
Obesity Class I (30 to <35 kg/m^2)	1.95	0.86	4.42	0.11
Obesity Class II (35 to <40 kg/m^2)	2.45	1.06	5.64	0.04
Obesity Class III (40+ kg/m^2)	2.69	1.19	6.09	0.02
Haemoglobin	0.98	0.97	1.00	0.03

Abbreviations: ECOG=Eastern Cooperative Oncology Group. BMI=Body Mass Index.

Figure 1. Nomogram to predict the risk of a major surgical adverse event after surgery for apparent early stage endometrial cancer

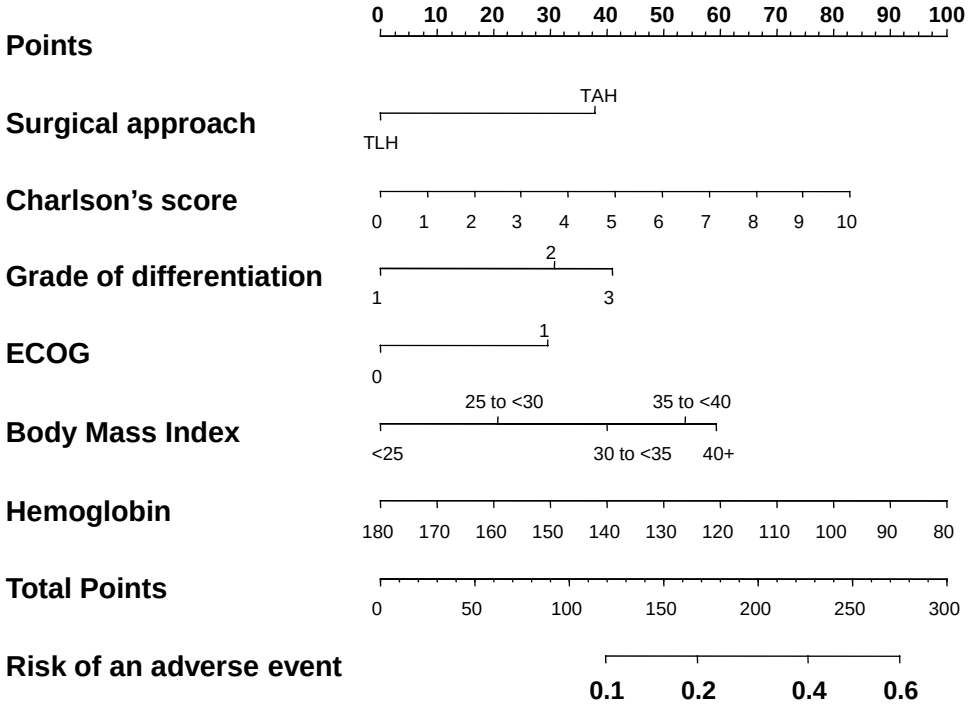
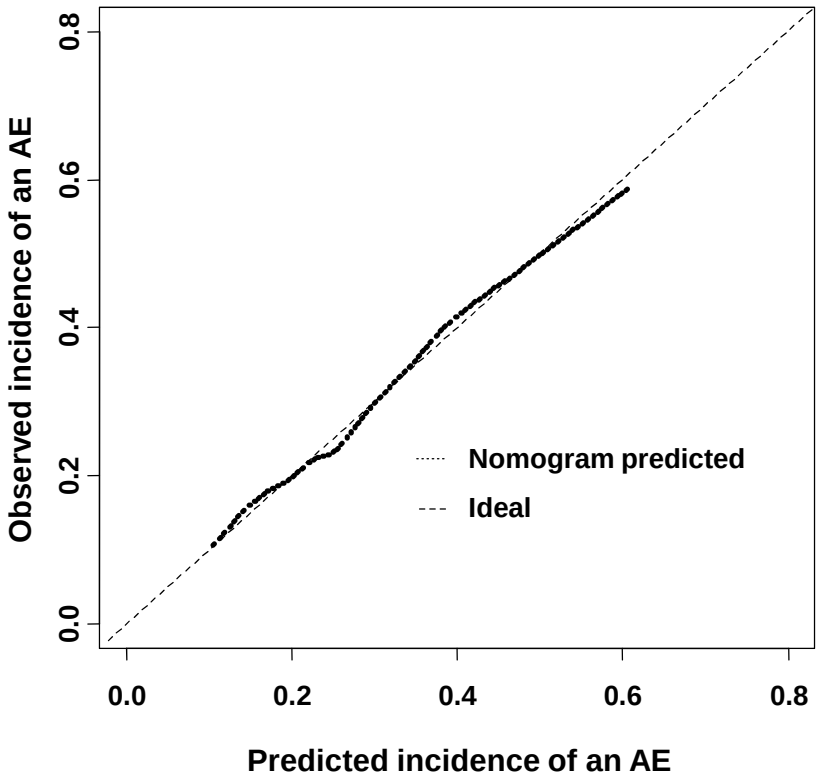


Figure 2. Calibration plot showing predicted probabilities and observed incidence of major adverse events



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