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GYNECOLOGIC ONCOLOGY

A nomogram for decision-making of completion surgery in endometrial cancer diagnosed after hysterectomy

Selen Bozkurt[1,2] · Tayfun Toptas[3] · Hulya Ayik Aydin[4] · Tayup Simsek[4] · Yasemin Yavuz[5]

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Abstract

Objective Extrauterine tumor spread is one of the essential determinants of disease outcome in endometrial cancer. However; more than 30% of patients still undergo incomplete surgery at the initial attempt. Strategies regarding the management of patients with incompletely staged early-stage disease or patients with undebulked advanced-stage disease remain controversial. Depending on postoperative uterine features and findings on imaging, patients may be put on observation or receive adjuvant therapy or undergo re-staging or debulking surgery followed by adjuvant therapy. To identify patients who would most benefit from a completion surgery, either for restaging or for cytoreduction, we developed a nomogram for estimation of extrauterine disease based on findings of final hysterectomy specimen.

Methods Data of 336 patients whose extrauterine disease status was known were analyzed. A nomogram was constructed using patient characteristics including age, grade, myometrial invasion, lymphovascular space involvement, cervical involvement, and peritoneal cytology. The nomogram was internally validated in terms of discrimination, calibration and overall performance.

Results The nomogram showed good performance accuracy with an area under the receiver operating characteristic curve of 0.870, a specificity of 95.5%, and a positive predictive value of 73.9%. Decision curve analysis revealed that the use of the nomogram in decision-making for completion surgery leads to the equivalent of a net 18 true-positive results per 100 patients without an increase in the number of false-positive results.

Conclusions Estimation of extrauterine disease from final hysterectomy specimen is possible with high predictive performance using the nomogram developed. The nomogram may help clinicians in decision-making for management of incomplete surgeries.

Keywords Endometrial cancer · Completion surgery · Nomogram · Decision analysis · Extrauterine disease

Introduction

Extrauterine tumor spread is one of the essential determinants of disease outcome in endometrial cancer (EC). The value of a staging surgery including sentinel lymph node (LN) biopsy or systematic lymphadenectomy in early-stage disease is its ability to provide prognostic information by identification of extrauterine disease. Although the results of two randomized controlled trials (RCTs) revealed no significant survival benefit of a lymphadenectomy in patients with presumed early-stage disease [1, 2], studies that examined patients who underwent combined pelvic and paraaortic LN dissection have indicated a survival benefit of lymphadenectomy, particularly in patients with node-positive disease [3, 4]. Moreover, a meta-analysis of fourteen retrospective cohorts revealed that a comprehensive surgery consisting

Selen Bozkurt and Tayfun Toptas contributed equally to this manuscript and are co-first authors.

✉ Tayfun Toptas
drttoptas@gmail.com

1 Department of Biomedical Data Science, Stanford University School of Medicine, Stanford, CA, USA

2 Department of Biostatistics and Medical Informatics, Akdeniz University School of Medicine, Antalya, Turkey

3 Department of Gynecologic Oncology, Saglik Bilimleri University Antalya Research and Training Hospital, C-Blok, K:2, 07100 Antalya, Turkey

4 Department of Gynecologic Oncology, Akdeniz University School of Medicine, Antalya, Turkey

5 Department of Biostatistics, Ankara University School of Medicine, Ankara, Turkey

of cytoreduction of all visible tumor foci provides survival benefit in patients with advanced (stage IV) or recurrent EC [5]. However; a National Cancer Database report of surgery trends for EC from 2003 to 2012 demonstrated that 32% of patients underwent incomplete surgery (total hysterectomy ± bilateral salpingo-oophorectomy [TH/BSO alone]), ranging a peak of 40% in 2003 to a low of 29% in 2008 [6].

Although no specific data exist in the literature, the main reason of the incomplete surgeries might be due to the fact that the likelihood of nodal metastasis in EC is significantly related with uterine risk factors; and according to the widely accepted concept, lymphadenectomy may be omitted in patients considered to be at "low-risk" for lymphatic dissemination (tumors with grade 1–2, endometrioid histology, depth of myometrial invasion ≤ 50%, and tumor size ≤ 2 cm) without a negative impact on prognosis [7]. However, preoperative and intraoperative identification of low–risk features may be somewhat problematic. The true risk may be greater than that of estimated due to the variability between preoperative biopsy, frozen-section examination and final pathology. The results of preoperative biopsy and intraoperative frozen-section examination have been shown to be prone to underestimation of final grade and myometrial invasion in approximately 25% of patients initially considered to be low-risk [8]. Unexpected postoperative diagnosis of EC, surgeries performed without an endometrial biopsy, and unavailability of a gynecologic oncologist or frozen-section analysis might be the other potential causes of high rates of incomplete surgeries.

Currently, the strategies regarding the management of patients with incompletely staged early-stage disease or patients with undebulked advanced-stage disease mostly rely on low levels of evidence, and thus, remain unclear. Depending on postoperative uterine features including grade, depth of myometrial invasion, lymphovascular space involvement (LVSI) and tumor size, and findings on postoperative imaging, patients may be put on observation or receive adjuvant therapy or undergo re-staging or debulking surgery followed by adjuvant therapy [9, 10].

A nomogram is a graphic chart that provides outcome probabilities for individual patients. It allows the integration of multiple variables and draws on the natural history of a large cohort of previously treated patients. In the current study, in order to accurately identify patients who would most benefit from a completion surgery, either for re-staging purposes or for cytoreduction, we developed a nomogram for estimation of the presence of extrauterine disease based on pathologic findings of final hysterectomy specimen. The term "extrauterine disease" was defined as any extension, infiltration or dissemination of the endometrial tumor outside the corpus and cervix uteri via direct, lymphatic or hematogenous routes. We also performed a decision curve analysis to establish the net benefits of using this nomogram over "completion surgery for all patients" and "completion surgery for none" strategies. The benefit was defined as identification of true positive cases in terms of extrauterine disease without an increase in the number of false-positive results.

Materials and methods

Approval for this study was granted by the Ethics Committee of the Akdeniz University School of Medicine. A single-institutional database of all EC patients ($N = 405$) undergoing primary surgery between August 2005 and November 2014 was reviewed. Patients who underwent incomplete surgery (TH/BSO alone) or those with primary synchronous malignancy were excluded ($N = 69$). Thus, analyses were performed on the clinicopathologic dataset of 336 patients whose extrauterine disease status was known.

The surgical algorithm routinely used at our institution for patients with clinically uterine-confined disease included a staging surgery consisting of TH/BSO, systematic pelvic lymphadenectomy, omental biopsy, peritoneal cytology, and visual evaluation of the peritoneal surfaces and abdominal viscera with biopsy of any suspicious lesions. Although not a standard practice worldwide, a systematic pelvic lymphadenectomy was performed in all patients regardless of any predefined risk factor for LN involvement. This was aimed to prevent missing of any nodal metastasis. A paraaortic LN dissection was added to pelvic lymphadenectomy if patients had at least one of the following features: (1) non-endometrioid histotype, (2) FIGO grade 3 endometrioid tumor, and (3) myometrial invasion ≥ 50% on frozen-section examination.

The strategy used for patients with apparent extrauterine disease included a cytoreductive surgery aiming at the removal of all visible tumor foci. In patients undergoing cytoreductive surgery, a combined pelvic and paraaortic lymphadenectomy was performed only if the cytoreduction was optimal (residual tumor size < 1 cm). Several studies have shown a significant improvement in survival when complete cytoreduction to no gross residual disease can be achieved in patients with advanced EC [5]. However, the definition of optimal cytoreduction in advanced EC is still not clear and settled. While some authors suggested a threshold of < 2 cm for residual disease, others proposed that optimal resection should be defined as a procedure leaving a maximum residual tumor ≤ 1 cm in diameter [10, 11].

For the purpose of this study, a primary surgery involving TH/BSO alone with or without evaluation of peritoneal cytology was considered incomplete surgery.

Development of the nomogram

Clinicopathologic characteristics including age, histologic type, grade, depth of myometrial invasion, tumor size, LVSI, cervical involvement, and positive peritoneal cytology were assigned as potential covariates. Univariate and multivariate logistic regression analyses were performed to investigate the associations between potential covariates and extrauterine disease. Variables were included in the multivariate models on the basis of a liberal significance level of 0.2. Tumor size was excluded from the multivariate analyses due to the large number of missing values. Correlations, variance inflation factors and eigenvalues were assessed to avoid multicollinearity. All possible pair-wise interactions between extrauterine disease and potential covariates were tested, and finally, three different models were developed.

The accuracies of the models were internally validated in terms of their discrimination (ability to differentiate between patients with and without extrauterine disease), calibration (agreement between observed and estimated outcomes) and overall performance. Area under the receiver operating characteristics curve (ROC-AUC) was used as the measure of discriminative performance. The value of ROC-AUC ranges from 0.5 to 1.0, with 0.5 indicating lack of discrimination and 1.0 indicating perfect discrimination [12]. The calibration performances of the models were evaluated by calibration plot and Hosmer–Lemeshow goodness-of-fit test. The calibration slope β of 1 and intercept α of zero are the parameters required for a well-calibrated model [13]. The overall performances of the models were assessed using Nagelkerke's R^2 measure and Brier Score. Brier score is a number between 0 (perfect) and 1, and a model with a Brier score greater than 0.25 is considered worthless [14]. Additionally, tenfold cross-validation and bootstrap techniques were utilized to test the models for overfitting and accuracy of the classification.

As the internal validation of models revealed similar performance accuracies, the proposed model was selected based on the authors' opinion, and graphically represented as a nomogram.

Clinical usefulness of the nomogram

A decision curve analysis was performed to quantify the clinical usefulness of the proposed model. Decision curve analysis presents the clinical net benefit of the model: one sums the benefits (true positives) and subtracts the harms (false positives) at each threshold probability of the outcome [15]. The reduction in the number of unnecessary surgeries per 100 patients was calculated as: *net benefit of the nomogram – net benefit of* "*completion surgery for all patients*" *strategy* / (*Pt* / (*1*− *Pt*)) × *100*.

All analyses were performed in R version 3.2.4 (https://www.r-project.org/), using the rms, pROC, PredictABEL and DecisionCurve packages.

Results

Of the 336 patients, 67 (19.9%) had extrauterine disease. Retroperitoneal LNs were the most common site of extrauterine disease, involved in 16.1% of patients (Table 1). Patients with extrauterine disease had significantly older age ($p = 0.007$), greater tumor size ($p < 0.001$), higher grade ($p < 0.001$), and greater proportion of deep myometrial invasion ($p < 0.001$), LVSI ($p < 0.001$), cervical involvement ($p < 0.001$), positive peritoneal cytology ($p < 0.001$), and non-endometrioid histotype ($p < 0.001$) (Table 2).

Model development phase of the study was presented in Table 3. The final (proposed) model included age, grade, depth of myometrial invasion, LVSI, cervical involvement, and positive peritoneal cytology. The performance values of the proposed model were as follows: ROC-AUC, 0.870 ($p < 0.001$); calibration slope β, 1.0; calibration intercept α, 0; and Brier score, 0.101. The difference between the probabilities predicted by the proposed model and the observed

Table 1 Characteristics of patients

Variables	Values
Age, median (range), years	58.5 (24–88)
Pelvic lymphadenectomy alone, *N* (%)	164 (48.8)
Combined pelvic and paraaortic lymphadenectomy, *N* (%)	172 (51.2)
Number of LNs removed, median (range)	34 (6–107)
$FIGO_{2009}$ stage, *N* (%)	
IA	157 (46.7)
IB	88 (26.2)
II	24 (7.1)
IIIA	8 (2.4)
IIIB	1 (0.3)
$IIIC_1$	23 (6.8)
$IIIC_2$	23 (6.8)
IVB	12 (3.8)
Extrauterine disease, *N* (%)	67 (19.9)
Parametrial involvement	1 (0.3)
Adnexal involvement (tube and/or ovary)	31 (9.2)
Retroperitoneal lymph node involvement	54 (16.1)
Peritoneal involvement	9 (2.7)
Omental involvement	10 (2.9)
Extra-abdominal and or parenchymal liver metastasis (detected via imaging modalities)	8 (2.4)
Multiple sites of extrauterine involvement	19 (5.6)

LN, lymph node; *FIGO*, International Federation of Gynecology and Obstetrics

Table 2 Comparison of uterine characteristics between patients with and without extrauterine disease

Variables	Extrauterine disease		*p*
	No (*N* = 269)	Yes (*N* = 67)	
Age, median (range), years	57 (24–82)	62 (27–88)	0.007
Tumor grade, *N* (%)			
Grade 1	161 (59.9)	9 (13.4)	< 0.001
Grade 2	59 (21.9)	22 (32.8)	
Grade 3	49 (18.2)	36 (53.7)	
Tumor size, median (range), cm	3 (0.1–18)	4.5 (1–15)	< 0.001
Deep (≥ 50%) myometrial invasion, *N* (%)	98 (36.4)	53 (79.1)	< 0.001
Lymphovascular space involvement, *N* (%)	30 (11.2)	30 (44.8)	< 0.001
Cervical involvement, *N* (%)	24 (8.9)	30 (44.8)	< 0.001
Positive peritoneal cytology, *N* (%)	4 (1.5)	14 (20.9)	< 0.001
Histologic type, *N* (%)			
Endometrioid	235 (87.4)	42 (62.7)	< 0.001
Serous	10 (3.7)	8 (11.9)	
Clear cell	8 (3.0)	4 (6.0)	
Carcinosarcoma	12 (4.5)	9 (13.4)	
Others*	4 (1.5)	4 (6.0)	

*Undifferentiated, small cell

probabilities was insignificant ($p = 0.671$). The ROC-AUC value of the nomogram indicated that 87% of patients with extrauterine disease were correctly identified. Ten-fold cross-validated test results regarding the discriminative accuracy of the nomogram revealed a specificity of 95.5% and a positive predictive value of 73.9%. The proposed model was shown as a nomogram in Fig. 1, and its discrimination and calibration plots were presented in Fig. 2a, b.

Decision curve analysis

Figure 2c shows the decision curve for the nomogram. The grey lines represent "completion surgery for all patients" strategy with its confidence intervals; the horizontal black line indicates "completion surgery for none"strategy; and the red curves show the net benefit of the nomogram at each threshold probabilities along with its confidence intervals. Decision curve analysis revealed that the use of the nomogram, compared with "completion surgery for all patients" strategy, provides net clinical benefit when threshold probability was ≥ 2%, and this benefit continues to increase as threshold probability increases

The benefit calculations of decision curve analysis for threshold probabilities between 1 and 5% were given in Table 4. The net benefit of 0.185 at threshold probability of 2% can be interpreted that the use of the nomogram in decision-making for completion surgery leads to the equivalent of a net 18 true-positive results per 100 patients without an increase in the number of false-positive results when compared with ''completion surgery for none" strategy. Moreover, only performing completion surgery on patients with a 2% or greater risk from the nomogram may result in at least 10% fewer surgeries when compared with "completion surgery for all patients" strategy.

Discussion

The management of patients with EC found after hysterectomy remains controversial. It is widely agreed that a group of patients with grade 1 or 2 endometrioid histotype, tumor size ≤ 2 cm, and myometrial invasion ≤ 50%—the so called low-risk patients—has a relatively negligible risk for extrauterine tumor spread [7]. Both the National Comprehensive Cancer Network (NCCN) and the joint European Society for Medical Oncology (ESMO), European Society for Radiotherapy & Oncology (ESTRO) and European Society of Gynaecological Oncology (ESGO) clinical practice guidelines recommend observation without any additional treatment for patients with low-risk uterine features [9, 10]. However, for patients with intermediate- to high-risk features, while the NCCN states that "imaging is recommended, but a surgical re-staging, including LN dissection can also be done", the joint consensus conference guideline suggests that "a lymphadenectomy to complete staging could be considered to tailor adjuvant therapy". The main reason for these equivocal recommendations is the lack of accurate evidence on the roles of completion surgery and imaging-based management in patients with incomplete surgery.

The available data on outcomes of patients with incomplete surgery are mostly based on retrospective studies, with

Table 3 Univariate and multivariate logistic regression analyses

Variables	Univariate analysis			Multivariate analysis (full model)			Multivariate analysis (backward selection model)			Stepwise multivariate analysis (proposed model)		
	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Age	1.03	1.01–1.06	0.010	1.01	0.97–1.04	0.744	–			1.01	0.97–1.04	0.824
Tumor grade												
Grade 1	1			1			1			1		
Grade 2	6.67	2.91–15.31	< 0.001	4.07	1.62–10.23	0.003	4.11	1.64–10.31	0.003	4.09	1.63–10.26	0.003
Grade 3	13.14	5.92–29.17	< 0.001	4.94	1.53–16.00	0.008	4.54	1.82–11.32	0.001	4.48	1.79–11.25	0.001
Myometrial invasion												
No	1			1			1			1		
< 50%	2.99	0.38–23.72	0.299	1.60	0.18–14.25	0.673	1.58	0.18–13.75	0.681	1.60	0.18–14.19	0.671
≥ 50%	17.31	2.30–130.23	0.006	4.56	0.54–38.73	0.165	4.48	0.54–37.33	0.165	4.47	0.53–37.47	0.168
LVSI												
No	1			1			1			1		
Yes	6.46	3.50–11.93	< 0.001	2.23	1.04–4.77	0.040	2.23	1.05–4.74	0.038	2.22	1.04–4.73	0.038
Cervical involvement												
No	1			1			1			1		
Yes	8.28	4.37–15.67	< 0.001	5.50	2.56–11.82	< 0.001	5.53	2.61–11.69	< 0.001	5.59	2.63–11.91	< 0.001
Positive peritoneal cytology												
No	1			1			1			1		
Yes	17.50	5.54–55.25	< 0.001	10.17	2.50–41.36	0.001	8.81	2.37–32.74	0.001	8.70	2.34–32.43	0.001
Histologic type												
Endometrioid	1			1			–			–		
Serous	4.48	1.67–12.00	0.003	1.31	0.29–5.95	0.725						
Clear cell	2.80	0.81–9.71	0.105	0.49	0.09–2.82	0.425						
Carcinosarcoma	4.20	1.67–10.58	0.002	0.75	0.17–3.24	0.698						
Others*	5.60	1.35–23.25	0.018	0.89	0.14–5.53	0.899						

*Undifferentiated, small cell

LVSI, lymphovascular space involvement; *OR*, Odd's ratio; *CI*, confidential interval

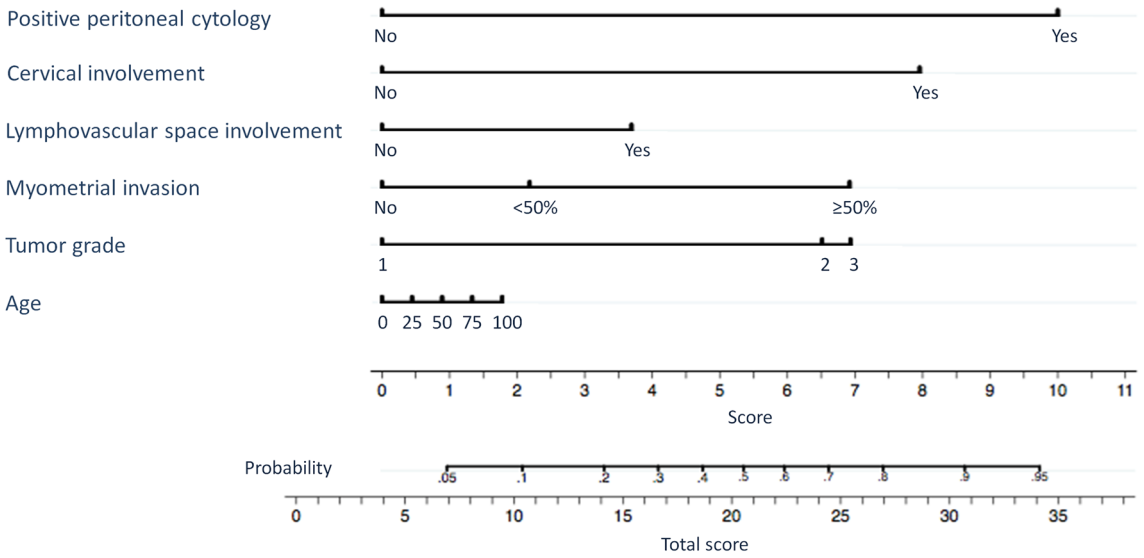

Fig. 1 Proposed nomogram for estimation of extrauterine disease

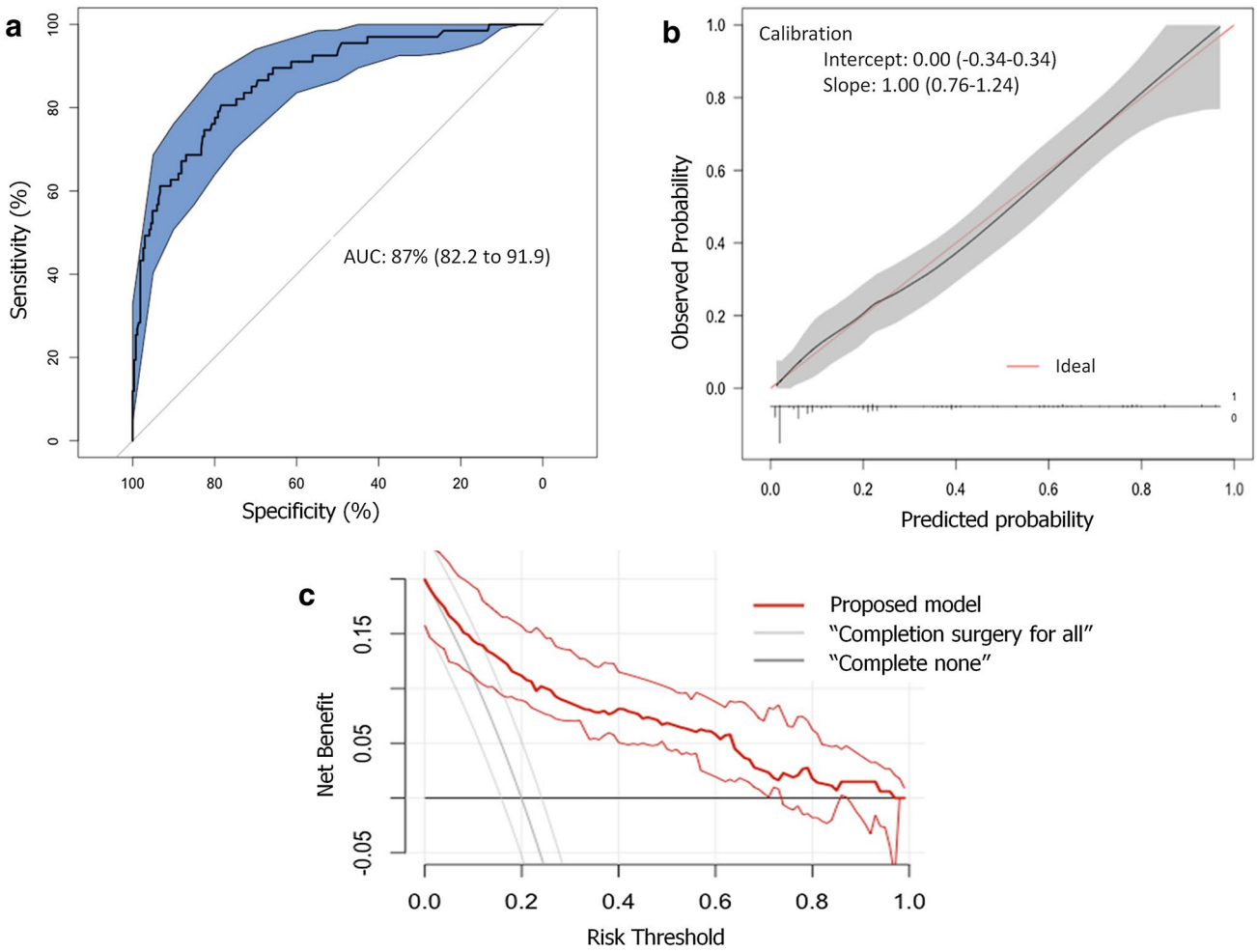

Fig. 2 **a** Discrimination plot of the nomogram. **b** Calibration plot of the nomogram. **c** Decision curve for the nomogram

Table 4 Results of the benefit calculations

P_t (%)	Net benefit over "completion surgery for none" strategy		Advantage of nomogram over "completion surgery for all" strategy
	"Completion surgery for all" strategy	Proposed nomogram	Reduction in unnecessary surgeries per 100 patients (*N*)
1	0.191	0.191	0
2	0.183	0.185	10
3	0.175	0.179	13
4	0.166	0.174	19
5	0.157	0.167	19

P_t threshold probability

the exception of two RCTs. In the largest series, Chan et al. [16] compared outcomes of 27.063 patients with incomplete surgery with those of 12.333 patients who had a comprehensive surgery including lymphadenectomy. The authors reported that patients with stage I grade 3 or stages II to IV disease that underwent lymphadenectomy had a significantly better 5-year disease-specific survival than those that underwent incomplete surgery; however, no benefit for lymphadenectomy was evident for patients with stage I grade 1 and grade 2 disease. Nevertheless, the results of two RCTs exclusively addressing the outcome of patients with presumed stage I disease revealed no evidence that surgical staging including systematic lymphadenectomy decreases risk of recurrence or death compared with no staging surgery [1, 2]. On the other hand, certain concerns regarding these RCTs have been raised, including selection of patients, the number of LNs removed, extent of lymphadenectomy, adjuvant therapies given, and the lack of central pathology review. In particular, in the ASTEC trial [2], the lymphadenectomy group consisted more patients with high-risk and advanced disease, whereas radiotherapy was administered to an equal number of patients in each group.

Another issue complicating a thoroughly evaluation of the role of staging lymphadenectomy in EC is the lack of standardization of adjuvant therapies. External beam radiotherapy (EBRT) for patients with uterine-confined disease has been demonstrated to significantly increase local–regional control but has no impact on overall survival [17]. Increasing concerns regarding toxicity of EBRT has led to increase in use of vaginal brachytherapy alone as adjuvant therapy in uterine-confined disease. The PORTEC-2 trial demonstrated that brachytherapy alone is associated with significantly fewer gastrointestinal toxicity than with EBRT, but with similar disease outcomes [18]. However, it should be noted that the PORTEC-2 trial specifically excluded patients with stage IB and II, grade 3 patients. Thus, the role of brachytherapy alone in the highest risk uterine-confined EC remains undetermined. The therapeutic benefit of adjuvant EBRT, chemotherapy or sequential combination of both modalities in patients with extrauterine disease were also investigated in several but mostly retrospective studies. However, optimal form of adjuvant therapy has yet to be determined. In the recent RCT (The PORTEC-3 trial) comparing chemo-irradiation with EBRT in high-risk stage I to III disease, chemo-irradiation improved failure-free survival though there was no difference in overall survival. Moreover, chemo-irradiation was significantly associated with any grade 3–4 adverse effects [18]. The preliminary results of another RCT (The GOG-258 trial) which compared chemo-irradiation versus chemotherapy alone in patients with stages III to IVA disease and non-endometrioid histotypes regardless of stage was presented as an abstract [19]. The study reported no significant difference in survival, while significantly more local–regional recurrences were reported in the chemotherapy alone group.

Despite the several studies regarding the role of lymphadenectomy during primary surgery for EC, only a few studies specifically focused on the feasibility and outcomes of completion surgery. In the sole comparative study to date, Ayhan et al. [20] investigated the outcomes of 40 patients with EC found after hysterectomy. Of the patients, 21 underwent completion surgery including systematic pelvic and paraaortic lymphadenectomy and 19 were managed non-surgically with observation or radiotherapy according to the uterine risk factors and imaging findings. A surgical complication was reported in only one patient (4.7%), which was an intestinal injury. While extrauterine disease following completion surgery was found in 19% of patients, adjuvant radiotherapy was given to 42% and 73% of patients with and without completion surgery, respectively. The authors reported that disease-free survival rates were 95% in the completion surgery group versus 87% in the non-surgical management group ($p > 0.05$). When considering the patients who received adjuvant radiotherapy, there was also a statistically non-significant slight trend for improved disease-free survival in the completion surgery group (88.8% vs 84.6%).

Imaging is a non-invasive way of identification of extrauterine disease in patients with EC diagnosed after hysterectomy. Similar to the studies of surgical staging, however, evidence regarding the role of imaging in EC relies on trials

performed in the preoperative or recurrence settings. Extrauterine soft tissue involvement can be detected by magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography combined with computed tomography (PET/CT). Detection of LN metastases with MRI is comparable to a CT scan with variable sensitivity ranging from 38 to 89% and specificity ranging from 78 to 99% [21]. Though rather high predictive accuracies have been demonstrated with the use of PET/CT, sensitivity rates are largely affected by the size of metastatic LNs, which have been reported as low as 12.5% in diagnosing lesions ≤ 4 mm [22]. Although MRI is the preferred method in evaluating primary tumor and local–regional tumor extent, a high-quality CT scan has better multiplanar spatial resolution that is useful in visualizing the entire abdominal cavity for enlarged nodes, omental and peritoneal disease as well as distant metastases [23]. NCCN recommends contrast enhanced CT of the abdomen and thorax to evaluate metastatic disease in patients who underwent hysterectomy with incidental finding of EC or incompletely staged with uterine risk factors; and whole body PET/CT in select patients who may be candidates for surgery/local–regional therapy [9].

In light of the current literature, it is not possible to draw definitive conclusions on the optimal management of patients with incomplete surgery. Patients may face either the risks of surgical complications and overtreatment from "completion surgery for all patients" strategy or the risks of undertreatment due to underestimation of disease extent from "imaging-based" strategy. A non-surgical management may also lead to overuse of adjuvant therapy, and thus overtreatment. It is obvious that there is a need for well-designed prospective studies evaluating the benefits and harms of the strategies recommended. Until sufficient data are available, however, advanced statistical tools indicating risk thresholds for the presence of extrauterine tumor spread may help clinicians in decision-making for treatment planning. Based on our nomogram, for example: a 50-year-old woman (1 points) with myometrial invasion ≥ 50% (7 points), grade 3 tumor (7 points), positive LVSI (4 points) and no cervical invasion (0 points) has a total of 19 points, which corresponds to a probability of approximately 4%. In addition, decision curve analysis shows (Table 4) that our nomogram is clinically useful at a threshold approximately 2% and above, since it has a higher net benefit than "completion surgery for all" and "completion surgery for none" strategies [24]. Similarly, if 4% is accepted as a threshold probability for performing completion surgery, our model reveals 17.4% net benefit for detection of extrauterine disease without an increase in the number of false-positive results. This also means that using our model with a 4% might provide a reduction of 19 patients in unnecessary surgeries per 100 patients.

Conclusion

In the present study, we demonstrated that estimation of extrauterine disease from final hysterectomy specimen is possible with high predictive performance using the nomogram developed. We also presented the potential clinical impact of the nomogram by decision curve analysis. However, our study is limited by its single-institutional retrospective nature with inherent problems of selection and referral bias. Although cross-validation and bootstrapping are sample reuse methods that prevent against over-interpretation of current data, they cannot ensure external applicability. Therefore, it is necessary to assess external applicability of the nomogram by validating the results in an external patient population.

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Author contributions SB: protocol/project development, data collection or management, data analysis, manuscript writing. TT: protocol/project development, data collection or management, data analysis, manuscript writing. HAA: data collection or management, manuscript editing. TS: manuscript editing, supervision. YY: protocol/project development, methodology, manuscript editing.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest and nothing to disclose.

Ethical approval This study has been approved by the Ethics Committee of the Akdeniz University School of Medicine. This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent of patients was not obtained due to the nature of study and the obtained data.

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