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External validation of non-imaging models for predicting distant metastasis in patients with endometrial cancer☆

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HIGHLIGHTS

- We evaluated the validity of two non-imaging scores to predict distant metastasis.
- The scores do not accurately predict metastasis in endometrial cancer.
- Using CA125, preoperative histology and tumoral size shows similar performances.

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ABSTRACT

Objective. To evaluate two non-imaging models designed to predict distant metastasis (stages IIIC–IV) in endometrial carcinoma (EC). Both used preoperative histological and biological findings. One used primary tumoral size, the other did not.

Methods. 374 patients operated on for EC by hysterectomy and at least bilateral pelvic lymphadenectomy were included. Patient's characteristics, preoperative histological, biological findings and primary tumoral size were used to calculate for each patient two scores (one for each model) for distant metastasis. The accuracy of the models was evaluated in terms of areas under the receiver operating characteristic curves (AUCs), rates of false negatives, and number of patients in the group at low risk to predict stages IIIC–IV.

Results. 309 and 65 patients had FIGO stages IA–IIIB and IIIC–IV respectively. Thrombocytosis and leukocytosis were not significantly different between patients who had distant metastasis and those who did not. CA125 serum level was significantly higher in patients who had distant metastasis (71.2 vs 32.0 U/mL, $p < 0.001$). High-risk preoperative histology and primary tumor diameter > 3 cm were more frequently observed in patients who had distant metastasis (55.4% and 39.9%, $p = 0.02$ and 21.3% and 8.5%, $p = 0.003$). The AUC were 0.65 [0.63–0.67] and 0.68 [0.63–0.67] with 54% and 93.4% sensitivity, 64% 19.1% specificity. Two hundred and twenty nine patients (61.2%) and 62 (17.0%) were classified as low risk; among them, 30 patients (13.2%) and 4 (6.4%) had final stage IIIC or IV.

Conclusion. Both models turned out to have a low discrimination power in our population. However, the score using primary tumoral size permits to identify a subgroup of patients in whom metastatic probability is low and lymphadenectomy unnecessary. Preoperative CA125 level, histological findings and primary tumoral size remain prognostic factors of stages IIIC–IV and should be included in predictive models.

1. Introduction

In North America and Europe, endometrial cancer (EC) is the most frequent cancer of the female genital tract and the fourth most common cancer site [1]. The main prognostic factors at diagnosis are: stage, grade, histological subtype, myometrial depth invasion [2] and lymphovascular space involvement (LVSI) [3]. Five year overall survival is 83% for endometrioid carcinoma, 62% for clear cell carcinoma and 53% for serous papillary carcinoma [2].

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The standard surgical treatment for stage I EC is total hysterectomy with bilateral salpingo oophorectomy with or without lymphadenectomy. Systematic lymphadenectomy does not improve overall survival or disease-free survival [4,5] and is not recommended in low risk EC, for whom the prevalence of lymph node (LN) metastasis is 5% [6,7]. For the high risk group (type 1 grade 3 stage I, stage II, or type 2 or in presence of LVSI), lymphadenectomy is often recommended because it has been suggested to improve overall survival [8,9]. Nonetheless, preoperative histology cannot predict accurately final histological type and grade [10] and preoperative Magnetic Resonance Imaging (MRI) [11] or PET-FDG [12] are less effective than lymphadenectomy to diagnose LN metastasis.

Considering the inability of a single tool to identify LN metastasis in EC, statistical models combining preoperative characteristics have been developed to accurately predict this risk. Recently, predictive models based on preoperative criteria such as CA125 level and MRI [13] and histological grade [14] have been described to identify a low risk group of LN metastasis. A score based on preoperative volume index, serum CA125 level and tumor grade/histology enabled to determine the risk of LN metastasis encompassing the risk of para-aortic LN metastasis with a good accuracy in patients with EC [15].

Luomaranta et al. developed a promising predictive model, combining preoperative biological factors (thrombocytosis, leukocytosis and CA125 serum level) and histological factors to identify patients who may not benefit from lymphadenectomy with an AUC of 0.81 and a negative predictive value of 95.7% [16]. More recently, Tuomi et al. developed a similar risk scoring system including biological factors (thrombocytosis and CA125 serum level), preoperative histology and primary tumoral size [17]. To dispense with MRI for prediction of LN and distant metastasis in EC could be cost effective and useful in institutions without MRI accessibility. Several guidelines (including the American College of Radiologists (ACR)) does not systematically recommend preoperative MRI for EC [18]. At the contrary, preoperative leukocyte count, platelet count and CA125 serum level could be easily accessible through blood sample analysis, which is systematically performed before surgery as part of the preoperative anesthetic evaluation.

The aim of this study was to evaluate the scores described by Luomaranta et al. [16] and Tuomi et al. [17] to predict LN and distant metastasis against an independent external dataset.

2. Material and methods

2.1. Study population

From January 1995 to December 2014, data on 435 patients with EC from Gasthuisberg Hospital (Leuven, Belgium) were retrospectively recorded into a database by three different researchers (AV, JU and MK).

Patient's characteristics, preoperative tumoral and histological findings as well as final tumoral characteristics were extracted from the report of the patient file.

Only patients with presumed early stage EC (stages I/II) who underwent at least pelvic lymphadenectomy were screened for inclusion in the study. Patients who received neoadjuvant chemotherapy, who had concomitant ovarian or cervical carcinoma, clinical stage IV or recurrent diseases were excluded.

The decision to perform lymphadenectomy was based on preoperative tumoral characteristics and avoided in low risk EC during the last decade [4,5]. Consequently, most patients who had grade 1 or 2 endometrioid corpus cancer with greatest surface dimension ≤2 cm, myometrial invasion ≤50%, and no intraoperative evidence of macroscopic disease were treated with hysterectomy only [19]. Pelvic and para-aortic lymphadenectomy were performed as previously described [20]. Pelvic lymphadenectomy comprised at least resection of the external iliac and obturator LNs. Para-aortic lymphadenectomy included resection of all nodes from the precaval, laterocaval, interaortocaval, preaortic, and lateroaortic areas up to the renal veins. Based on these criteria, we finally included 374 patients in this study.

2.2. Score establishment

Score calculation was based on methodologies previously described [16,17]. Preoperative biological data (leukocyte count, platelet count and CA125 serum level) were recorded and divided in two groups: leukocytosis was defined as a leukocyte count $>8.2 \times 10^9$/L, thrombocytosis was defined as a platelet count $>360 \times 10^9$/L and high CA125 serum level was defined as >35 U/mL. Preoperative histological findings obtained with either biopsy, curettage or polyp resection by hysteroscopy were divided in two risk groups: high risk histology group encompassing grade 3 endometrioid carcinoma, carcinosarcoma, clear cell carcinoma and serous carcinoma and low risk histology group encompassing grade 1 or 2 endometrioid carcinoma. Primary tumor diameter of 3 cm was chosen as the cut-off value [17]. A score of 0 was attributed if leukocyte count were $<8.2 \times 10^9$/L or platelet count were $<360 \times 10^9$/L or CA125 serum level were <35 U/mL or for low risk histology group or for primary tumor diameter <3 cm. A score of 1 was attributed in other cases.

Then, for the Luomaranta et al. model we applied the formula previously described [16]: 2× leukocytosis + 3× thrombocytosis + 7× × elevated CA125 + 4× high risk histology.

For the Tuomi et al. model we applied the formula previously described [17]: 1× thrombocytosis + 3× elevated CA125 + 2× high risk histology + 2× large tumor.

For each model, we built the area under the receiver operating characteristic (ROC) curve (AUC). Since the correspondence between the score and LN or distant metastasis was not reported, it was not possible to build calibration curve for the Luomarata et al. model. As described by Luomarata et al., we used 6 as a cut-point to establish FN rate. For the Tuomi et al. model, calibration curve was built and as described by the authors, we used 1 as a cut-point to establish FN rate.

2.3. Evaluation of the models

2.3.1. Discrimination

Discrimination was quantified with the area under the receiver operating characteristic (ROC) curve (AUC). The AUC reflects the ability of a test to discriminate between a diseased and a non-diseased subject across all possible levels of positivity. A 95% CI was calculated for each AUC. AUC ranges from 0 to 1, with 1 indicating perfect concordance, 0.5 indicating no better concordance than chance, and 0 indicating perfect discordance.

2.3.2. FN rate

For prediction model, cutoff values reported by the scores of Luomaranta et al. and Tuomi et al. were considered to define the subgroup of patients with a low predicted probability of LN or distant metastasis. For both scores, positive and negative predictions were compared with observed issues.

2.3.3. Clinical utility

One of the main aims of models is to identify the largest subgroup of patients with a low risk of LN or distant metastasis. For both models, we report the number of patients predicted as being negative or having a low probability of distant metastasis.

The numeric variables were analysed using Student's *t*-test. A p value < 0.05 was considered statistically significant.

3. Results

Biological data including preoperative leukocyte count, platelet count and CA125 serum level were not available for 61 patients. For the remaining 374 patients, biological data were recorded. Delay between blood sample and surgery was < 30 days for all patients.