Original Research

Uterine Cancer Normogram to Predict Lymph Node Metastasis: Comparison to the Mayo Algorithm and an External Validation of a Model in a North American Population

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Summary

Objective: We sought to compare two intraoperative uterine cancer normograms for prediction of lymph node (LN) metastasis. We used the widely known Mayo criteria, comparing it to an algorithm provided by Koskas *et al.* to predict likelihood of LN metastasis. *Design*: 490 uterine cancer patients from a single practice provider were included in the review. Data was abstracted to include age, race, stage, tumor size, grade, histologic subtype, depth of invasion, cervical involvement, lymphovascular space involvement (LVSI), and microsatellite instability (MSI). Patient comorbidities were analyzed to include body mass index (BMI), diabetes, and hypertension. Laboratories for these comorbidities were included. Those patients staged 1, 2, and 3 were included in final analysis. *Results*: The receiver operator curve (ROC) for the Koskas normogram was 0.78 when 4% was used as the cutoff for LN metastasis, with a sensitivity of 78% and specificity of 60%. When a 5% cutoff was used, the ROC was 0.71. For every percentage point that the French score rose, the chance of being LN positive increased by 0.8% ($p < 0.001$). The three point Mayo criteria odds ratio (OR) was 7.4 and the ROC was 0.57. Lymph node metastasis also correlated with MSI as seen on immunohistochemistry (IHC) testing. *Conclusions*: The Koskas normogram provided a better predictive algorithm for risk assessment of LN metastasis. Our results are comparable with those previously published by Koskas *et al.* providing an external validation of this normogram previously used in an European population. These intraoperative variables can be incorporated into real time risk assessment for LN metastasis and operative decision making. Mayo criteria, not using tumor size, could spare an additional 40% of patients an unnecessary LND compared to standard 3 point Mayo criteria–with better predictive value.

Key words: Uterine cancer; Endometrial cancer; Lymph node metastasis; Mayo; Algorithm; Prediction.

Introduction

Uterine cancer is the most commonly diagnosed gynecologic cancer in North American women. There are estimated to be 65,620 patients diagnosed with uterine cancer in the United States in 2020 and 12,590 deaths [1]. Patients with uterine cancer are recommended definitive surgical management if found to be surgical candidates. Comprehensive surgical staging, to include hysterectomy, removal of the fallopian tubes and ovaries, lymph node dissection (LND) and further biopsies, is often based on tumor histology and other pathologic risk factors [2]. These risk factors for endometrial cancer are often headlined under the Mayo criteria to include tumor size $\geq$ 2 cm, depth of tumor invasion (DOI) into the myometrium ($\geq$ 50%), and tumor grade (1, 2 *vs.* 3) [3]. An algorithm developed by Koskas *et al.* [4] was also developed to predict lymph node metastasis in endometrial cancer. The variables for the Koskas algorithm include: patient race, patient age, tumor characteristics to include histology, DOI, grade, and primary tumoral extension. We undertook this study in endometrial cancer patients to evaluate the predictive ability of this algorithm to evaluate lymph node (LN) metastasis, elimination of tumor size as a pathologic risk factor, and compared it to the widely known Mayo criteria.

Expanding the Koskas algorithm to a wider population would allow a universal application of this algorithm. We sought to validate this algorithm in the United States within a major urban city and in a community practice population (compared to an academic referral center). We wanted to extend this validation to a current practice population in North America to ensure the outcomes and were reproducible. This would make the algorithm comprehensively applicable as regional population differences and genetic representations can vary globally.

Materials and Methods

490 uterine cancer patients from a single practice provider were included in the review. All patients had TH BSO and lymph node dissection and those with type II tumors had additional staging biopsies and omental biopsy. Lymph node dissection (LND) was to the level of the inferior mesenteric artery for all, and for type II patients the LND extended above this level to the renal vessels. Route of surgery was identified in all patients, and a minimally invasive approach was attempted for all candidates as no difference in outcomes has been reported [5]. Route was

chosen for laparotomy based on uterine size > 12 cm, pelvic bony dimensions assessed on exam, proven pelvis by childbirth, or evidence of extrauterine spread on preoperative imaging. Data was abstracted from a Washington state health maintenance organization's electronic medical record. Variables included: age, stage, tumor size, grade, histologic subtype, depth of invasion into myometrium, cervical involvement, lymphovascular space invasion (LVSI), and microsatellite instability immunohistochemistry (MSI). Patient comorbidities were also analyzed to include: body mass index (BMI), diabetes, hypothyroidism, and hypertension. Laboratories for these comorbidities included Hemoglobin A1c and TSH. All patients staged 1, 2, and 3 were included in final analysis. Patients with stage 4 endometrial cancers were excluded as lymph node status is not predictive of overall survival (OS) or adjuvant treatment algorithms [6]. Type I tumors were designated as endometrioid histology, and type II tumors were classified as serous, clear cell, and carcinosarcoma [7]. Uterine sarcomas were also excluded from the final analysis in this review. MSI was evaluated using immunohistochemistry (IHC) starting in 2016 per National Comprehensive Cancer Network (NCCN) guideline change for universal testing in endometrial cancers [8]. This project was approved by the institutional IRB.

Variables for the Mayo algorithm included: tumor size (<, ≥ 2 cm), DOI (<, ≥ ½), and grades 1, 2. Variables for the French algorithm included: age (continuous), race (Caucasian, black, others), primary site tumoral extension (endometrium only, depth of invasion <, ≥ half, cervical stromal invasion), histology (adenocarcinoma, serous, clear cell, carcinosarcoma) [9].

Statistics were calculated using SPSS 26.0 and goodcalculators.com. A receiver operator curve (ROC) was computed for predictive value of LN metastasis using each algorithm and outcomes were compared.

Results

490 patients were included in the study. 460 patients had comprehensive data available for final review. Patients were reviewed from January 2012 to July 2018. The average age was 63.7 years. The average BMI was 34.7, 225 (48.9%) patients had hypertension, 72 (15.6%) were hypothyroid, 119 (25.9%) were diabetic. The average HgA1c for all patients was 6.0% and was 7.4% in the diabetic population. The average TSH was 2.52 mIU/L (Table 1). Eighty patients (17.4%) had a type II tumor. Route of surgery was minimally invasive for 350 (76.1%) and laparotomy for 110 (23.9%).

283 patients were found to be FIGO 2018 stage 1A (61.5%), 66 1B (14.3%), 24 stage II (5.2%), 58 stage III (12.4%) [17 stage IIIA (3.7%), 3 stage IIIB (0.7%), and 38 IIIC (8.2%)], and 21 (4.6%) stage 4 patients. The stage 4 patients were excluded from analysis as were 8 additional sarcoma patients (Table 2). Lymph node pathology was evaluated for endometrial cancer metastasis: 91.4% of patients

(373) were negative for LN metastasis, 7.9% (38) were LN positive. There were 63 type II cancers, of which 14 (22%) were found to be LN positive.

Table 1. — *Demographics of the study population.*

Average age	63.7
Average BMI	34.7
Comorbidities	Patients (%)
Hypothyroid	72 (15.6)
Diabetes	119 (25.9)
Hypertension	225 (48.9)

Table 2. — *Patients Categorized by Tumor Characteristics.*

Stage	Patients N (%)
Stage 1A	283 (61.5)
Stage 1B	66 (14.3)
Stage 2	24 (5.2)
Stage 3A	17 (3.7)
Stage 3B	3 (0.7)
Stage 3C	38 (8.2)
Stage 4*	21 (4.5)
Sarcoma*	8 (1.7)
Grade	
Grade 1	259
Grade 2	82
Grade 3	90
Tumor Type	
Type 1	389 (84.5)
Type 2	63 (13.7)

* Subjects with stage 4 tumors or tumors with sarcoma histology were excluded from final analysis.

Microsatellite instability immunohistochemistry (MSI IHC) testing was instituted in 2016 when NCCN guidelines recommended universal testing (per HMO approval); 27 of 99 (27.2%) patients who were tested for MSI showed a loss in protein expression. Twenty-two were deficient in MLH1/PMS2 and 5 were deficient in MSH6. Twenty-six were found to have varying degrees of hypermethylation on further study, and 1 patient (MSH6) was identified to have a genetic mutation when gene panel tested, and she had a known personal history of colon cancer. Five (22.7%) of the MLH1/PMS2 deficient patients had stage 3 cancer, 17 were stage 1 (77.3%). One patient with a MSH6 deficiency was stage 3c (20%), the remaining were stage 1. Ten and a half percent of all the stage 3 patients were found to have an IHC protein expression deficiency.

We reviewed medical comorbidities and cancer characteristics. There was no association identified between med-
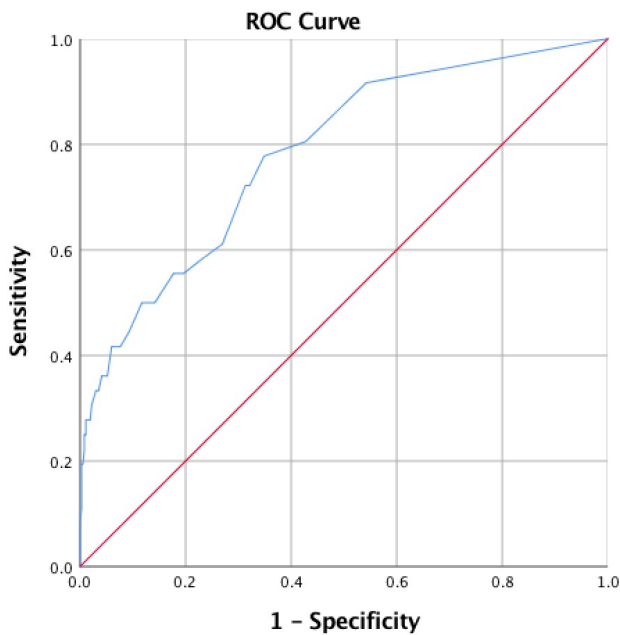
Figure 1. — ROC Curve using the Koskas nomogram. Area under the curve (AOC) of 1.0 indicates perfect concordance while AOC of 0.5 indicates no relationship.
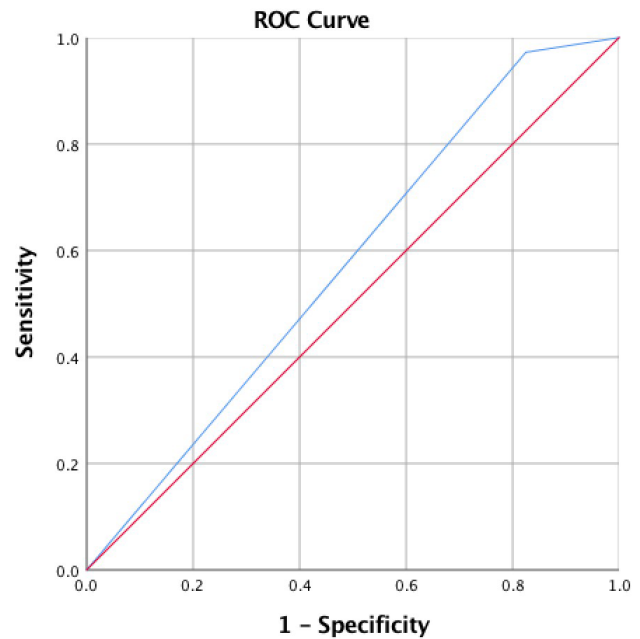

Figure 2. — ROC Curve using the Mayo criteria. Area under the curve (AOC) of 1.0 indicates perfect concordance while AOC of 0.5 indicates no relationship.

ical comorbidities, BMI, stage of cancer, LN metastasis, or high risk pathologic factors (ANOVA $p = 0.75$).

We then evaluated final pathology for high risk pathologic risk factors to include tumor size, depth of invasion, grade, cervical stromal invasion, lymphovascular space invasion, and histology. Pre and intraoperative risk factors were evaluated separately as well to include: tumor size, histology, depth of invasion, grade, and cervical involvement. The percentage of each group who were coded as high risk and recommend to have LND were retrospectively stratified by the two different algorithms. Per the Mayo criteria: 83% (382) patients were found to need LND using all three criteria; and 53.5% (246) were dispositioned to LND when tumor size was excluded; and 42.6% (196) of patients were stratified to need LND by tumor size alone. When using the French algorithm: 41.7% (192) of patients were dispositioned to LND using Koskas criteria.

The area under the curve (AOC) of the ROC for the Koskas normogram was 0.78 (95% CI 0.70-0.87) when 4% was used as the cutoff for LN metastasis, with a sensitivity of 78% and specificity of 60%. When a 5% cutoff was used, the ROC was 0.72 (95% CI 0.63-0.80). For every percentage point that the score rose, the chance of being LN positive increased by 0.8% ($p < 0.001$). The three-point Mayo criteria OR was 7.4 and the AOC was 0.57 (95% CI 0.49-0.66). (Figures 1 and 2)

Comment

Endometrial cancer is the most common gynecologic cancer in the United States. Prediction of LN metastasis has been proposed to stratify patients to undergo compre-

hensive cancer staging procedures. Documentation of node metastasis can effect recommendations for adjuvant therapies. There have also been concerns of clinical sequela and cost effectiveness from LND, should it be performed [10-12].

An interesting finding was that 10.5% of the IHC tested patients with a MLH1/PMS2 or MSH6 deficiency identified on IHC had stage 3 cancer. The rate may be more, as IHC testing was done on only 20% of the total study population based on timing of NCCN guideline recommendations. There may then be an association between advanced stage disease with lymph node involvement and microsatellite instability. Preoperative biopsy evaluation has been shown to correlate with surgical specimen IHC [13]. Perhaps IHC deficiency information from preoperative endometrial sampling may be an additional variable to include in risk stratifying algorithms for comprehensive surgical staging and lymph node sampling [14].

The Koskas normogram provided a better prediction algorithm for risk assessment of LN metastasis. Our results are comparable with those previously published by Koskas *et al.* providing an external validation of this normogram previously validated in an European population [9]. These intraoperative variables can be incorporated into real time risk assessment for LN metastasis and operative decision making. Mayo criteria not using tumor size could spare an additional 40% of patients an unnecessary LND compared to standard 3 point Mayo criteria with better predictive value, validating prior reports as well [15].

We have then validated the algorithm by Koskas *et al.* in a North American practice population. We support the

wider application of this algorithm in all patient populations. We have confirmed the superior functionality of this algorithm in our diverse cohort, which is different genetically than the French population, and thus it is applicable. If the use of this nomogram is expanded within the United States, we may see a decreased need for LND in endometrial cancer patients.

Ethics Approval and Consent to Participate

This study was IRB approved as a retrospective and quality improvement review and performed in accordance with institutional guidelines.

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Conflict of Interest

The authors report no conflicts of interest.

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