Gynecologic Oncology 129 (2013) 28–32

Contents lists available at SciVerse ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Prediction of lymph node and distant metastasis in patients with endometrial carcinoma: A new model based on demographics, biochemical factors, and tumor histology

Anna Luomaranta *, Arto Leminen, Mikko Loukovaara

Department of Obstetrics and Gynecology, Helsinki University Central Hospital, Helsinki, Finland

HIGHLIGHTS

- A model that predicts the probability of stage IIIC–IV tumor in patients with endometrial carcinoma was developed.
- The model is based on demographics, biochemical factors, and preoperative tumor characteristics.
- The model could be applied for identifying patients who may not benefit from lymphadenectomy for the staging of endometrial carcinoma.

ARTICLE INFO

Article history:
Received 16 November 2012
Accepted 10 January 2013
Available online 15 January 2013

Keywords:
Endometrial carcinoma
Complete blood count
CA125
Demographics
Lymph node metastasis

ABSTRACT

Objective. To develop a model that might predict the probability of lymph node and distant metastasis (stages IIIC–IV) in endometrial carcinoma.

Methods. We studied 774 patients with endometrial carcinoma treated in a single institution. Demographic factors, biochemical factors and preoperative tumor characteristics, identified as potential risk factors for advanced carcinoma in unadjusted analyses, were used to create a logistic regression model with lymph node and distant metastasis as the dependent variable. Statistically significant odds ratios in the regression model were rounded to the nearest whole number. These rounded values were the estimated weights for each factor that were summed to generate a score that might predict the probability of stage IIIC–IV carcinoma.

Results. Biochemical factors and preoperative tumor characteristics predicted lymph node and distant metastasis in the regression model, whereas demographic factors were without effect. The score combining weighted risk factors was: (2×leukocytosis)+(3×thrombocytosis)+(7×elevated CA125)+(4×high-risk histology). The area under curve (AUC) for this total score was 0.823, with 71.6% sensitivity, 75.2% specificity, 25.9% positive predictive value, and 95.7% negative predictive value, using 6 as cut-point. After excluding stage IV carcinomas from the dataset, the AUC was 0.813 for the total score in predicting nodal involvement ($P = 0.82$ vs. total score in predicting stage IIIC–IV carcinomas in the complete dataset).

Conclusions. Based on the high negative predictive value, this prediction model could be applied for identifying patients who may not benefit from lymphadenectomy for endometrial carcinoma staging.

Introduction

Endometrial carcinoma is the most common gynecologic malignancy in developed countries and the sixth most common cancer among women worldwide [1]. Its incidence is constantly growing with estimated 47,130 new cases in the United States in 2012 [2]. It is likely that increasing prevalence of obesity and aging population contributes to the growing incidence [3]. Endometrial carcinoma usually presents early with uterine bleeding, and at diagnosis it is confined to the uterine corpus in more than two thirds of women [4,5]. Spread beyond the uterus and poor prognosis can be predicted by uterine risk factors, most importantly grade 3 endometrioid and nonendometrioid histology, deep myometrial invasion, and cervical stromal invasion [6–9].

The cornerstone of the treatment for endometrial carcinoma is surgery. Comprehensive surgical staging includes total hysterectomy, bilateral salpingo-oophorectomy, retroperitoneal lymph node dissection, and peritoneal washings. However, the role of lymph node dissection, in terms of the extent of the procedure and patient selection, remains under debate. According to the current opinion, routine lymphadenectomy can safely be omitted in women with low-risk carcinomas (superficial grade 1–2 endometrioid carcinomas) without detrimental effect on prognosis but with fewer complications, such as vascular and neural injuries, lymphedema, and lymphocysts [10,11]. In women with intermediate and high-risk carcinomas (superficial grade 1–2 endometrioid carcinomas with lymphovascular invasion,

* Corresponding author at: Department of Obstetrics and Gynecology, Helsinki University Central Hospital, PL 140, 00029 HUS, Helsinki, Finland. Tel.: +358 504271176.
E-mail address: anna.luomaranta@fimnet.fi (A. Luomaranta).

0090-8258/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.ygyno.2013.01.008

superficial grade 3 endometrioid and nonendometrioid carcinomas, and all deeply invasive carcinomas), a combined pelvic and para-aortic lymphadenectomy may improve survival [12].

The therapeutic challenge with presumed early stage endometrial carcinoma lies in balancing between surgical over- and undertreatment. It would be beneficial for the clinician to have a feasible method that could accurately assess the patient's individual risk for lymph node and distant metastasis preoperatively. Magnetic resonance imaging [13–16] and transvaginal ultrasound [17,18] are widely used to assess myometrial invasion. Their value is limited in the detection of lymph node involvement [18,19], which is more reliably discovered by fludeoxyglucose positron emission tomography/computerized tomography (FDG PET/CT) [20–24] and sentinel lymph node biopsy [25–28]. However, the utilization of these techniques is complicated by high cost and restricted availability. Further, sentinel lymph node biopsy has feasibility problems that arise from the widespread uterine lymphatic drainage and the site of the lesion that is not easily accessible for injection.

It has earlier been reported that advanced age predicts poor outcome in women with endometrial carcinoma [29–32], and normal weight women have tumors with aggressive histopathologic features, including high stage, more often than obese women [33–35]. Further, pretreatment anemia and thrombocytosis are associated with poor prognosis in endometrial carcinoma [36,37]. Leukocytosis is a common finding in patients with solid tumors [38], and in endometrial carcinoma it is independently associated with an increased risk of death [39]. An elevated serum CA125 level predicts lymph node involvement and other detrimental prognostic factors in endometrial carcinoma [40–43]. The aim of this study was to evaluate whether age, body mass index (BMI) and endometrial thickness as demographic factors, biochemical variables with prognostic significance, and preoperative tumor characteristics have utility in predicting lymph node and distant metastasis in endometrial carcinoma, either alone or in combinations.

Materials and methods

Using a retrospective database at the Department of Obstetrics and Gynecology, Helsinki University Central Hospital, we identified all women with surgically treated endometrial carcinoma between January 2008 and November 2012 (n = 780). Institutional review board approval was obtained for the study. Patients with comorbidities affecting complete blood count variables were excluded; i.e. 2 for active peptic ulcer, 1 for hepatic cirrhosis, 1 for chronic lymphatic leukemia, 1 for idiopathic thrombocytopenic purpura and pernicious anemia, 1 for myelodysplastic syndrome. Six patients with a concomitant primary ovarian or fallopian tube cancer and 1 patient with an appendiceal mixed adenoneuroendocrine cancer were not excluded. Thus, a total of 774 women met the inclusion criteria.

Demographic data included age, BMI, and endometrial thickness measured preoperatively by transvaginal ultrasound. Reliable measurement of the endometrial thickness was not possible in 6 women. Pathologic data collected were the histology, grade, and FIGO 2009 stage of the tumor.

Endometrial histology was assessed preoperatively in tissue samples obtained by uterine curettage or biopsy. Endometrial sample was not taken or it was nondiagnostic in 11 patients. Grade 3 endometrioid, clear cell, serous, undifferentiated, and neuroendocrine carcinomas were considered high-risk histologic type carcinomas; others were considered low-risk. Seventy-two (11.1%) low-risk cases according to the preoperative evaluation were shifted to the high-risk category in the pathologic evaluation after surgery, and 21 (18.4%) high-risk cases were shifted to the low-risk category.

Chest X-ray and upper abdominal ultrasound were obtained for the detection of distant metastases preoperatively. Bilateral pelvic lymphadenectomy was performed for patients with superficial grade 1–2 endometrioid carcinomas. For other patients, both pelvic and para-aortic lymphadenectomies were performed. There was some variation in practice patterns because the decision to perform lymphadenectomy and the extent of the procedure depended primarily on an intraoperative assessment of the depth of myometrial invasion, and surgical risks. Pertinent patient characteristics and surgical data are shown in Table 1.

Pretreatment serum CA125 concentration was quantitated with a chemiluminescent microparticle immunoassay on the Abbott Architect 2000i Analyzer (Abbott Diagnostics, Abbott Park, IL). The concentration was considered increased when >35 U/mL [44]. CA125 value was not available for 79 patients. Variables of the last pretreatment complete blood count were analyzed by photometric measurement (hemoglobin) and electrical impedance technology and flow cytometry (cells). Anemia was defined as blood hemoglobin concentration <117 g/L, leukocytosis as a leukocyte count $>8.2\times10^9$/L, and thrombocytosis as a platelet count $>360\times10^9$/L. These values represent the reference intervals for the Finnish adult female population [45].

Pearson χ^2 analyses were used to compute odds ratios along with 95% confidence intervals for the associations between each risk factor and lymph node and distant metastasis (stage IIIC–IV carcinoma) in our cohort. Factors identified as potential risk factors in unadjusted analyses ($P<0.05$) were used to create a logistic regression model with lymph node and distant metastasis as the dependent variable. Statistically significant odds ratios in the multivariable model were rounded to the nearest whole number. These rounded values were the estimated weights for each factor that were summed to generate a total score that might predict the probability of stage IIIC–IV carcinoma. Additional models were created with the elimination of individual factors from the model. The areas under curve (AUC) of the models were compared with the statistical receiver–operator curve area comparison test. $P<0.05$ was considered statistically significant.

Results

In unadjusted analyses, normal weight (BMI <25 kg/m^2), thick endometrium (>10 mm), anemia, leukocytosis, thrombocytosis, elevated serum CA125 concentration (>35 U/mL), and high-risk histology were associated with an increased risk for lymph node and distant metastasis

Table 1
Demographic and clinicopathologic data (n = 774).

Age (years) (mean ± SD)	67.5 ± 10.5
Body mass index (kg/m^2) (mean ± SD)	28.5 ± 6.2
Pelvic lymphadenectomy (number of cases, percent)	433 (55.9%)
Pelvic and para-aortic lymphadenectomy (number of cases, percent)	100 (12.9%)
Lymph node yield (mean ± SD)[1]	17.4 ± 9.6
Histology (number of cases, percent)	
Endometrioid carcinoma[2]	716 (92.5%)
Clear cell carcinoma	26 (3.4%)
Serous carcinoma	16 (2.1%)
Undifferentiated carcinoma	12 (1.6%)
Neuroendocrine carcinoma	2 (0.3%)
Adenosquamous carcinoma	1 (0.1%)
Epidermoid carcinoma	1 (0.1%)
Grade (number of cases, percent) (for endometrioid only, n = 716)	
Grade 1	427 (59.6%)
Grade 2	174 (24.3%)
Grade 3[2]	115 (16.1%)
FIGO stage (number of cases, percent)	
IA[3]	459 (59.3%)
IB	147 (19.0%)
II	50 (6.5%)
IIIA	34 (4.4%)
IIIB	6 (0.8%)
IIIC1–2	58 (7.5%)
IVA	0 (0%)
IVB	20 (2.6%)

[1]Number of cases 523 (lymph node yield was not available for 10 patients); [2]including 13 carcinosarcomas; [3]including 1 serous carcinoma in situ.